Advances in Experimental Medicine and Biology 1228

Junjie Xiao *Editor*

Physical Exercise for Human Health

Springer

Advances in Experimental Medicine and Biology

Volume 1228

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2018 Impact Factor: 2.126.

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Junjie Xiao
Editor

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Editor
Junjie Xiao
Cardiac Regeneration and Ageing Lab
Institute of Cardiovascular Sciences
School of Life Science
Shanghai University
Shanghai, China

ISSN 0065-2598 ISSN 2214-8019 (electronic)
Advances in Experimental Medicine and Biology
ISBN 978-981-15-1791-4 ISBN 978-981-15-1792-1 (eBook)
https://doi.org/10.1007/978-981-15-1792-1

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

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About the Editor

Junjie Xiao is the Vice Dean of the School of Life Science and also of the Medical School (in preparation) at Shanghai University. He is the Associate Editor of the *Journal of Cardiovascular Translational Research, BMC Sports and Science, Medicine & Rehabilitation*, and a member of the editorial board of *BMC Medicine*. He is the author or co-author of numerous scientific articles in various journals, including *Cell Metabolism, Nature Communications, Annual Review of Genomics* and Human Genetics, Circulation, and Theranostics. His major research interest is exercise and myocardial protection, especially using exercise as a platform to identify novel targets for enhancing cardiac regeneration and combating heart failure.

Part I

Overview

An Overview of the Beneficial Effects of Exercise on Health and Performance

1

Andreas Kramer

Abstract

Life expectancy is steadily increasing in modern societies, and so are noncommunicable diseases such as cardiovascular diseases, diabetes, obesity, and cancer, accounting for more than 70% of all deaths globally. The costs associated with these diseases are enormous, but it has been estimated that the majority of these noncommunicable diseases are preventable. In addition to an unhealthy diet, tobacco use, and harmful use of alcohol, physical inactivity is a key risk factor. Consequently, physical activity is a logical remedy, and in this chapter an overview of the numerous beneficial effects of physical activity on health and performance is given.

The chapter is divided into three parts: First, the basics of physical activity and exercise are discussed, for instance exercise classification, exercise intensity operationalization, energy supply, and the acute effects of exercise such as blood flow redistribution and increased cardiac output. In the second part, the effects of exercise on physical performance are summarized. Specifically, it is discussed how endurance, strength, power, and balance can be improved. This discussion includes recommendations regarding the type, intensity, and duration of the exercise leading to improvements in one of these aspects of physical performance, as well as the mechanisms causing these adaptations. In the third part, the beneficial effects of physical activity on physical and mental health are outlined, with particular attention to cardiovascular diseases, the metabolic syndrome, musculoskeletal diseases, mood, anxiety, depression, and dementia.

It can be concluded that with adequate programming, regular physical activity is an effective way to improve physical performance, improve physical and mental health, and reduce the risk factors for many noncommunicable diseases such as cardiovascular diseases, metabolic syndrome, sarcopenia, osteoporosis, and depression. In contrast to medication, physical exercise has no negative side effects, costs very little, and targets many health issues at once. If the multitude of beneficial effects of regular exercise were to be combined in a single low-cost drug, it would be prescribed for almost all types of physical and mental health issues.

A. Kramer (✉)
Sensorimotor Performance Lab, Department of Sport Science, University of Konstanz, Konstanz, Germany

FG Sports Science, University of Konstanz, Konstanz, Germany
e-mail: andreas.kramer@uni-konstanz.de

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_1

Keywords

Physical activity · Physical performance · Exercise · Medicine · Public health

1.1 Background

Living a long and healthy life is probably something everyone is hoping for. The first part—a long life—is becoming more and more probable, at least in most modern societies. Life expectancy is steadily increasing; during the last 160 years it has been increasing by almost 3 months per year for women, from a life expectancy of about 45 years in 1840 to almost 85 in 2000 in Japan [1]. The second part, however—a healthy life—is far from guaranteed. On the contrary, despite advances in modern medicine, noncommunicable diseases such as cardiovascular diseases, diabetes, obesity, and cancer are on the rise [2, 3]. The costs associated with these diseases are enormous [4]. For example, the costs of the diseases attributed to sedentary behavior alone have been estimated to be about 54 billion dollars per year [5].

Noncommunicable diseases (NCD) account for more than 70% of all deaths globally, killing about 41 million people in 2016 [6]. The majority of these deaths were attributed to the four main noncommunicable diseases: cardiovascular diseases (18 million deaths; accounting for 44% of all NCD deaths), cancer (9 million deaths; 22%), chronic respiratory disease (3.8 million deaths; 9%), and diabetes (1.6 million deaths; 4%) [6]. In addition to premature death, these diseases usually lead to a decreased quality of life, raising the question whether a long life in poor health is something to look forward to.

Key risk factors for NCDs are physical inactivity, unhealthy diet, tobacco use, harmful use of alcohol, and air pollution [6]. Fortunately, most of these risk factors are lifestyle related, that is, they are modifiable via adequate changes in lifestyle, in particular a change in physical activity levels. In this chapter, I will give an overview of the numerous beneficial effects of physical activity on health and performance, and the following chapters will examine the effects of physical exercise on a variety of diseases in more detail.

1.2 Basics of Physical Exercise

Throughout this book, we will mainly use the term "physical exercise" or just "exercise," but keep in mind that physical activity—that is, any movement requiring energy, such as walking, manual labor, or housework—will usually elicit similar benefits as physical exercise—that is, movement intended to maintain or increase physical health or performance—provided that the load is comparable. The load or demand of physical exercise is usually quantified by providing information on the type, duration, and intensity of the exercise; the number of series and repetitions; as well as the duration of rest in between repetitions and in between series. Based on these parameters, it is possible to estimate the energy expenditure of the exercise, either expressed as kilojoules (kJ), kilocalories (kcal, 1 kcal $\approx$ 4.2 kJ), or metabolic equivalent of task (MET, 1 MET is defined as the energy expenditure of 1 kcal per kg body mass per hour, roughly corresponding to the basal metabolism; moderate physical activity corresponds to 3–6 MET, and vigorous physical activity to more than 6 MET). MET is often used to compare the energy demand between different types of exercise and different individuals.

Whether exercise has an effect on health and the magnitude of this effect will depend primarily on the type, frequency, duration, and intensity of the exercise [7, 8]. As a rule of thumb, if many big muscles are involved, and the longer and more intense the exercise, the higher the energy expenditure will be, increasing the effects of the exercise [9]. There are several possibilities to classify the type of exercise; one useful categorization is the strength–endurance continuum: at one end of the continuum, heavy resistance strength exercises can be found, usually aimed at increasing maximal strength. A typical example would be barbell squats with near maximal additional weight, 1–6 repetitions per set and 3–6 sets [10]. At the other end of the continuum, aerobic training can be found, usually aimed at increasing

aerobic capacity or improving cardiovascular health. Typical examples include running or cycling at moderate intensities for 30 min to several hours. In between these two ends of the strength–endurance continuum, there are several intermediate types of exercise, such as resistance training with low loads and a high number of repetitions, or high-intensity interval training. The position of a specific exercise in this continuum will influence the adaptations to the exercise. Heavy resistance strength training will mainly elicit structural and functional changes in the muscles involved in the exercise, whereas aerobic training will mainly improve cardiovascular function. Therefore, it is important to have a good understanding of the body's acute and chronic response to different types of exercise. The physiological responses to acute exercise will be examined in detail in the next chapter, so I will only give an overview in the next section.

1.3 Acute Responses to Exercise

Exercise requires muscle contractions, and muscle contractions require energy. The only energy source the skeletal muscle can use is the energy stored in adenosine triphosphate (ATP). The hydrolysis or decomposition of ATP into adenosine diphosphate (ADP) and phosphate releases energy, which is used for muscle contractions (for details, see for example [11, 12]). As there is a limited amount of ATP present in the muscles, the ATP stores would be empty within seconds if the body did not reuse this ADP in a process called ATP resynthesis. This ATP resynthesis requires energy, and this energy is normally provided by phosphocreatine degradation, anaerobic glycolysis, aerobic glycolysis, and fat oxidation, that is, the breakdown of phosphocreatine, carbohydrates, and fat. For a review of the different energy systems, see for example [13].

In the muscle, there is a limited supply of these energy substrates. Thus, during prolonged exercise, energy substrates have to be transported to the working muscles. In addition, aerobic glycolysis and fat oxidation require oxygen, which also needs to be transported from the lungs to the muscles. Likewise, the by-products of the energy substrate breakdown (such as carbon dioxide or lactate) need to be removed from the muscle. The most important medium of transportation to and from the muscle is the blood. Oxygen, for example, binds to hemoglobin, a protein in erythrocytes, the red blood cells. The erythrocytes carry the oxygen from the lungs towards tissue of all kinds, including the brain and the muscles [14]. In exchange, carbon dioxide is transported back from the tissue towards the lungs and is then exhaled. During vigorous exercise, the working muscles' energy consumption can be increased more than 100-fold [15]. To accommodate this demand, more blood is redirected towards the working muscles. The mechanism that is primarily responsible for this perfusion regulation is the interplay of vasoconstriction and vasodilatation, that is, increasing or decreasing the blood vessels' blood flow primarily by relaxing or contracting the muscle tissue around arterioles and small arteries [16]. In addition to this redistribution of blood towards the working muscles, the overall blood flow is increased, that is, more blood is pumped through the cardiovascular system by the heart. This cardiac output is primarily increased by increasing the stroke volume—the blood volume that is pumped from the left ventricle of the heart per beat—and by increasing the heart rate. Assuming a resting heart rate of 60 beats per minute, a maximal heart rate of 180 beats per minute, a stroke volume of 70 mL at rest, and a maximal stroke volume of 120 mL [17] in a person, the cardiac output of the person can be increased about fivefold from the normal value at rest to the maximal value during very demanding exercise. Concurrent with this increase in blood flow, respiration is also increased to ensure a high respiratory gas exchange rate, meaning a high oxygen flow to the lungs and then to the blood, and a high carbon dioxide removal via expiration. Compared to resting values of about 6 L per minute in healthy adults, ventilation can be increased to about 100 L per minute during strenuous exercise [18], and much higher values have been reported for endurance trained athletes. In addition to the acute physiological responses to exercise outlined above—muscle contractions requiring energy; increase in energy and oxygen supply to meet the

increased energy demand; increased cardiac output, blood flow, and ventilation—there are, of course, many other responses, for example thermoregulation, hormonal responses, immune responses, or changes in mood. However, these will be reviewed in detail in the next chapter, and the basic cardiovascular responses we briefly discussed in this section should be sufficient to understand the effects of chronic exercise on performance and health, which will be discussed in the next sections.

1.4 Effects of Exercise on Performance

The effects of exercise can usually be viewed from two perspectives: on the one hand the effects on performance, such as strength or endurance, and on the other hand the effects on health, such as cardiovascular risk factors, mental health, or subjective well-being. The first perspective is particularly interesting for athletes, and we will review it in this section, followed by the health perspective in the next section.

Physical performance has many aspects, and someone with a high performance in one aspect does not necessarily show high performance in other aspect. For instance, a good sprinter might have poor marathon performance and vice versa. Usually, physical performance is divided into the following categories: strength, power, speed, endurance, flexibility, and coordination. While these categories can be helpful for structuring the field and linking the categories to physiological parameters—for instance muscle cross-sectional area to strength, muscle fiber type to speed, and mitochondrial content and function to endurance—it is clear that most motor actions require all of these categories, albeit with different emphases. For example, a basketball shot requires some amount of strength, power, and speed; limited amounts of endurance and flexibility; and a high amount of coordination. It follows that there is no general effect of exercise on all aspects of physical performance, but rather the effect will depend on the type, volume, intensity, and other characteristics of the exercise. According to the specificity principle, improving performance of a distinct motor action, skill, or task is to train this task as specifically as possible, be it a basketball shot, a 100 m dash, a clean and jerk, or walking on a slackline [19–21]. This principle has proven to be widely applicable, so if there is a clear specific aim for the training—which should be the case, otherwise it would just be exercise and not goal-oriented training—the athlete should train this task as specifically as possible, that is, with similar intensity, duration and work to rest ratio as during the competition.

If one does not want to specifically train for one specific task or sport but does want to improve a more general performance aspect, such as endurance or strength, an ample number of studies have been conducted that can help one choose the right exercise parameters.

1.4.1 Endurance

The term endurance can be used for the ability to maintain an activity for a long period of time. This general definition would also encompass wiggling one's toe for hours or performing a near maximal leg press for as many seconds or minutes as possible, but for this review, "activity" shall refer to physical activity that uses a considerable amount of muscle mass, as it is the case in running or cycling, and a "long" period of time shall usually refer to more than half an hour.

A good gross indicator of endurance performance in these cases is the maximal oxygen uptake capacity, $V'O_{2max}$ [22]. As the energy demand of sustained physical activity is primarily met aerobically [23], that is, via carbohydrate and fat oxidation, it follows that the delivery of oxygen to the muscle as well as the muscle's capacity to quickly use this oxygen can be a limiting factor of endurance performance. Oxygen is delivered to the muscle via the lungs and airways, and then the bloodstream. Studies have shown that the lungs and the airways are usually not the limiting factor in healthy people [24]. The oxygen delivery via the bloodstream can be limited by cardiac output as well as the oxygen transport capacity of the blood via red blood cells. It is estimated that cardiac output is one of the main limiting factors for maximal oxygen

uptake capacity [24, 25], notwithstanding the fact that blood doping or erythropoietin (EPO) doping, which increases the number of red blood cells, can increase oxygen transport capacity and endurance performance [26]. In addition to these limiting factors stemming from blood delivery, the muscle's capacity to quickly use the delivered oxygen needs to be mentioned: the first factor in this respect is capillarization or capillary density of the working muscle, which ensures a high oxygen extraction despite high rates of blood flow. Andersen and Henriksson [27] showed that endurance training increases capillary density, and other researchers demonstrated a correlation between the number of capillaries per muscle fiber $V'O_{2max}$ [28]. The second potential limiting factor on the muscular level is mitochondrial content and function, as the mitochondria are the muscle cell organelles processing the oxygen. However, despite the fact that mitochondrial content and function have been shown to greatly increase after endurance training [29], this increase does not translate to a pronounced increase in $V'O_{2max}$. It has been proposed that instead, this increase in mitochondrial content and function serves to allow for a slower utilization of muscle glycogen and blood glucose, and a greater reliance on fat as a source of energy, thus preserving glycogen and producing less lactate [30].

To sum up, the maximal oxygen uptake capacity $V'O_{2max}$ is an important indicator of endurance performance, as it reflects the efficacy of all the systems involved in oxygen delivery to the muscle. It is believed to be mainly limited by cardiac output and to a lesser extent by oxygen transport capacity in the blood, at least for whole-body exercise, but all parts of the oxygen pathway are important in order to achieve a high endurance performance. It has to be noted that even though $V'O_{2max}$ is a good overall indicator of endurance capacity—as witnessed for example by the strong correlation between $V'O_{2max}$ and the time in a 10-mile run [31]—it cannot be seen as a single variable that determines endurance performance. One illustration of this point is that two athletes with similar $V'O_{2max}$ can exhibit quite different endurance performance, for example in a marathon, due to differences for example in mitochondrial content and function and in running economy [32]. Ultimately, an athlete who is able to sustain a higher performance compared to another athlete for the duration of the competition will win, and this sustained submaximal higher performance does depend not only on $V'O_{2max}$ but also on the ability to maintain a high rate of oxidative ATP production. Similarly, exercise will normally increase endurance performance—for example, the time required to run or cycle a certain distance, or the maximal time that running or cycling can be sustained at a certain velocity or power output—to a greater extent than the concurrent increase in $V'O_{2max}$, sometimes even without any change in $V'O_{2max}$ [33, 34].

What is then the best way to improve endurance performance and/or maximal oxygen uptake capacity? There is a substantial amount of research in this area, and especially with the recent popularity of high-intensity interval training (HIT), it has become quite clear that there is no best way to do this, but several types of training are able to effectively improve endurance. Traditional endurance training consists of one long bout with moderate intensity, also termed MICT (moderate intensity continuous training). Typically, the duration of one exercise session ranges from 30 min to several hours, with an intensity of usually 65% of $V'O_{2max}$ or more [35]. Although it has been recommended that this type of endurance training should be for about 150 min per week [36], it is not very clear what the dose–response relationship looks like. It has been suggested that it follows an inverted U-shape, with moderate amounts of training yielding best results [37], but studies with lifelong endurance athletes performing regular endurance training with different training frequency and volume (from 2–3 times per week to more than six times per week) found the highest training volumes were associated with the best endurance performance [38]. Granted, this type of studies cannot establish causal relationships, but they should remind us that with adequate progression, high volumes of training are possible and also effective in improving performance beyond what is possible

with moderate amounts of training, even though the dose–response relationship might not be linear.

Irrespective of the optimal training dose, what are the effects on endurance performance that can be expected from traditional moderate intensity continuous endurance training? First, an effective endurance training with a duration of at least several weeks will increase $V'O_{2max}$, usually in the range of about 10% [39]. Improvements of more than 15% are normally only observed with very high training volumes and intensities [40]. Second, after an effective endurance training, endurance performance should improve, that is, the athlete should be able to run, cycle, row or ski for a longer duration at the same power output or velocity, or be able to increase his or her power output when exercising for the same duration as before the training. This improvement in endurance performance will normally be reflected in a rightward shift of the lactate threshold and the ventilatory threshold [35]. The threshold concept is discussed in detail elsewhere [41, 42]; in brief, the lactate threshold is defined as the exercise intensity that corresponds to an increase of blood lactate above resting levels. If the lactate threshold is shifted to the right, this means that the athlete can exercise at a higher intensity without a rise in lactate levels, presumably using predominantly fat oxidation and aerobic glycolysis.

As previously mentioned, traditional endurance training using moderate intensities and long durations is not the only way to improve endurance performance. One other training method in particular has gained a lot of attention in recent years, both in the scientific community and the general population: high intensity interval training, also referred to as HIIT or HIT. It can be defined as periods of high-intensity exercise—usually at more than 80% of maximal heart rate—interspersed with periods of active or passive rest. The duration of the work intervals can be as short as 20 s and in particularly strenuous forms of HIT can be coupled with rest intervals as short as 10 s (often referred to as "Tabata" exercise, after a Japanese scientist who first examined cycling HIT with 7–8 repetitions of 20 s work, 10 s rest [43]). This workout may sound too short to induce any adaptations, but keep in mind that the power output during the work intervals in that study was 170% of the power output generated at $V'O_{2max}$, so the athletes really had to push themselves. Other types of HIT use lower intensities but longer durations, for example 4 min at 90% of the velocity or power output generated at $V'O_{2max}$, with 2–4 min of rest in between. A variety of other work and rest durations as well as work to rest ratios have been successfully used to increase $V'O_{2max}$ and endurance performance (for a review see for example [44]). In most of these studies, HIT was conducted using running or cycling as the exercise mode, but a few studies also examined the potential of bodyweight exercises such as squats or jumps, concluding that intermittent bodyweight exercises might also be suitable as forms of HIT, provided that the rest intervals in between repetitions and in between sets are sufficiently short [45]. For an in-depth review of the mechanisms associated with HIT, see [46]. After it had been established that HIT is both an effective and an efficient type of endurance training [47], researchers began to compare HIT and MICT. This comparison is not always straightforward though, as MICT and especially HIT can be programmed in many different ways, using different intensities and work and rest intervals. To facilitate the comparison, some researchers match the work done during HIT to the work done during MICT: for instance, 60 min of continuous cycling at a power output of 60% could be matched to 10 times 4 min of cycling with 90% power output, interspersed with rest intervals of 4 min each. However, this comparison is not very realistic, as HIT is normally designed to be much shorter than MICT, requiring less work and less time. Depending on which type of comparison is used (work matched or not), the result tend to be a bit different: when HIT with shorter, more realistic durations is compared to MICT, it is normally found to be roughly as effective as MICT with respect to improvements in $V'O_{2max}$ and endurance performance [39, 48]. In work-matched comparisons, HIT tends to result in higher improvements than MICT [46, 49]. As for the physiologic adaptations to HIT vs. MICT, it seems as if HIT tends

to elicit mainly an increase in stroke volume and mitochondrial content and function, whereas MICT typically has an additional effect on vasculature and capillarization [46, 49–51]. With high training volumes, that is, more than 5–6× per week, as it is usually performed by endurance athletes, a polarized approached seems to be optimal, with the majority of the training being performed at low intensities and 10–15% of the training performed at high intensities, usually as some form of HIT [50, 52].

1.4.2 Strength and Power

Strength in the context of exercise is usually defined as the maximal voluntary contraction (MVC), which is the maximal force a person can exert with a certain muscle group. Typically, it is tested isometrically, meaning in a static position, and at defined joint angles, as muscles will change their force output depending on their length, a characteristic that is known as the force–length relationship. For example, MVC for knee extension is often assessed at a knee angle of 60–70°, where the knee extensors usually achieve their highest force output [53, 54]. Power is the product of force and velocity ($P = F * v$) and is often more important than maximal force, especially when the time period of force application is limited, for instance in throwing or jumping movements, or during quick postural adjustments to prevent falls. Rate of force development is the derivative of the force–time curve, in other words the slope of the force curve, and indicates how fast a given force can be developed, which is important for explosive movements. Strength and power are important for athletic performance (weightlifting, football, track and field, and martial arts, to name just a few) as well as for work and everyday activities (lifting heavy objects, quick postural adjustments); for elderly even stair climbing and chair rising can be considered activities requiring a high percentage of their maximal strength or power [55, 56].

Maximal strength mainly depends on muscle mass, volume, and cross-sectional area [57], which seem to be highly heritable [58], but substantial interindividual differences exist with respect to force per cross-sectional area [59]. While muscle power and rate of force development are also dependent on muscle size, a major additional determinant is the muscle's shortening velocity, which mainly depends on the muscle fiber type, with fast fiber types (IIa and IIx) exhibiting higher shortening velocity and peak power output than slow fibers (type I) [60, 61].

What type of exercise is suitable for increasing strength and power? The bad news is that endurance training, especially traditional high-volume endurance training with moderate intensity, does not increase maximal strength or power [62, 63], and combining endurance and strength training often blunts the effects of both types of training [62–65], although this blunting effect of concurrent training does not always apply or does only for explosive movements [66]. Traditional strength training consists of heavy resistance training, that is, moving weights such as dumbbells or loaded barbells, or pulling against a resistance provided for example by elastic straps. Much research has been conducted to establish the number of repetitions and sets as well as the training intensity that will elicit the highest gains in strength or power. For strength, mainly two approaches have emerged. The first one is primarily used to increase muscle mass and is known as hypertrophy strength training, a method that is often used by bodybuilders. A typical hypertrophy exercise session consists of 3–5 sets of 8–12 repetitions each, with a load of 70–80% of the one-repetition maximum (1 RM, the maximal weight an individual can lift during one repetition, for example 140 kg during a squat). The second one is primarily used to increase maximal strength, a method that is often used by powerlifters. A typical maximal strength exercise session consists of 3–6 sets of 1–6 repetitions each, with a load of 80–95% of 1 RM. However, there is no consensus in the literature whether the hypertrophy training is indeed superior with respect to increasing muscle mass [67], and if this increase in muscle mass is really functionally relevant for maximal contractions or more an increase in non-contractile muscle material such as sarcoplasmatic protein content and glycogen stores, lowering the force output relative

to the cross-sectional area [68]. However, maximal strength training with high intensities indeed seems to induce larger gains in maximal strength [67, 69, 70], which is in line with the training specificity principle, as this kind of training uses fewer repetitions with higher intensities, whereas the hypertrophy training uses more repetitions with lower intensities, resulting in better strength endurance performance, that is, increasing the maximal number of repetitions at lower percentages of 1RM, especially if even more than 8–12 repetitions per set are used [71]. When training for increased power instead of increased strength, lighter loads are used (usually 30–60% of 1 RM), with 3–5 sets of 1–5 repetitions each, enough rest in between sets, and a focus on movement speed, that is, as fast and explosive as possible [72]. When leg power is the training goal, an alternative to resistance training is plyometrics (different kinds of jump exercises such as drop jumps, countermovement jumps, or box jumps), which can increase power and jump height more than resistance training [73]. Last but not least, when exercising with the goal to increase strength or power, it is important to remember that large increases in the gym do not always transfer to large improvements in athletic performance or everyday activities [74]. To circumvent this issue, a good training regimen should always take into account the specific aim of the training and include as many specific exercises as possible, that is, exercises that mimic the target sport or everyday movement as close as possible with respect to the type of movement, movement velocity, and number of repetitions.

1.4.3 Balance

Balance will be shortly discussed here due to its relevance for fall prevention, a topic that is particularly relevant for the elderly and patients with balance disorders. Balance training—or sensorimotor or proprioceptive training as it is sometimes called—usually consists of exercises such as one-leg stance on instable surfaces, for instance tilt boards, air pads, or even slacklines, sometimes with additional motor or cognitive tasks (dual task training) or restrictions that make the balance task more challenging, such as closing one's eyes while balancing.

One question with respect to balance training is whether training one balance task will elicit improvements only in that balance task or if the training effects will transfer to other balance tasks. In other words, is balance a general ability or rather a set of skills? This is a fundamental question, as the answer will affect the way in which balance training programs should be designed in fall prevention: if balance were a general ability and training one balance task had improved performance in untrained balance tasks, it would not really matter which balance tasks were trained, as they would all be equally suitable for fall prevention. On the other hand, if balance were a set of skills and training, one balance task would only improve the task that was trained without any transfer to untrained balance tasks; coaches and therapists should carefully analyze which situations and tasks bear the highest fall risk and then have the patients or participants specifically train these tasks.

In the literature, the view that balance is rather a general ability seems to be the dominant one: the term balance training is used interchangeably for a wide variety of training programs, which are lumped together in reviews and meta-analyses, and generic tests such as one-leg stance are often used to measure balance capabilities. However, several studies that specifically aimed to answer this question challenge this view. Giboin and colleagues were the first to clearly show that short-term balance training seems to elicit highly task-specific effects, that is, improvements only in the balance task that was trained, without any transfer to untrained balance tasks [19]. A review and meta-analysis later confirmed these results [20]. A similar study but with three months of balance training instead of few weeks of training also reported similar task-specific results [21]. The potential objection that the balance training in these studies usually comprised only one balance task was refuted by studies using a variety of different balance tasks without any transfer to non-trained balance tasks [75, 76]. Ringhof and Stein added

to this line of evidence by demonstrating that the within-subject correlations of the performance in different balance tests was low and that gymnasts (with supposedly high balance capabilities) did not perform better than swimmers (with supposedly low balance capabilities) in most tests [77]. Taking into account all this recent evidence, it seems reasonable to conceptualize balance rather as a set of skills and to expect little or no transfer to untrained balance tasks. Therefore, coaches and therapists are advised to carefully analyze which situations bear the highest risk for falls or injuries and have the participants, athletes, or patients train these situations and tasks as specifically as possible. If deficits in strength and power are present, a tailored strength and conditioning training should also be taken into account [75, 76].

1.5 Effects of Exercise on Health

Health can be defined in several ways; the WHO states that health is "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." In that regard, improving one's physical performance as outlined above can improve one's well-being and therefore health, even when free from disease. Indeed, being able to perform all activities of daily living without help, that is, retaining one's autonomy, is an important aspect to quality of life, especially in old age, and regular physical activity plays an important role in this endeavor [78, 79]. Nevertheless, the first goal is usually to stay or get free from disease. Therefore, the most common physical and mental diseases, their risk factors as well as the role of exercises in preventing and treating these diseases will be outlined in the following sections and discussed in detail in the following chapters.

1.5.1 Physical Health

1.5.1.1 Cardiovascular Diseases

As mentioned in the introduction, noncommunicable diseases are responsible for more than 70% of all deaths worldwide, and cardiovascular diseases account for 44% of these deaths [6], which translates to about 30% of all deaths. Cardiovascular diseases include coronary artery diseases—also known as heart attacks—hypertensive heart diseases, stroke, or thrombosis. The causes for these diseases vary, but an important one is atherosclerosis, the buildup of plaque inside arteries. Risk factors for cardiovascular diseases include blood pressure, cholesterol profile, smoking, diabetes, excessive alcohol consumption, obesity, and lack of exercise [6, 80, 81]. For instance, physically inactive middle-aged women have been reported to have a 52% increase in all-cause mortality and a doubling in cardiovascular-related mortality [82]. On the other hand, being fit or active was associated with a risk reduction of more than 50% [83]. Lack of exercise and most of the other risk factors can be targeted by regular exercise. The question is which kind and which dose of exercise. Due to the diversity of cardiovascular diseases and also due to the fact that studies usually assess only some of the risk factors, it is hard to issue general recommendations. However, the consensus is that resistance training has fewer benefits than endurance training, which usually only affects insulin sensitivity, body fat, and physical performance but not plasma lipid levels, resting heart rate, or blood pressure [84]. Endurance training, however, affects all of these risk factors [84]. The optimal and sufficient doses of exercise are hard to establish, and while some studies and reviews suggest that a moderate amount is enough, with diminishing returns thereafter [37], others suggest that there is a linear relationship between physical activity and health status [85]. The American College of Sports Medicine suggests aerobic exercise of moderate intensity on five or more days per week with 30–60 min per session, or three or more vigorous intensity exercise sessions with 20–60 min per session [36]. These recommendations reflect growing body of evidence that high-intensity training can be as effective as traditional high-volume endurance training with moderate intensities, not only with respect to endurance performance improvements, but also with respect to health benefits, some of them even suggesting that high intensities might be superior [86, 87]. HIT is now even used

in cardiac rehabilitation [88], even though several years ago most physicians would be reluctant to prescribe high-intensity exercise.

1.5.1.2 Metabolic Syndrome

Another common disease in mostly sedentary societies is the metabolic syndrome, a term that has not been precisely defined but is usually used for the combination of at least three out of five of the following conditions: obesity (BMI of 30 or more), high blood pressure, high blood sugar, high serum triglycerides, and low serum high-density lipoprotein. Its prevalence is high and increases with age [89]. The metabolic syndrome is associated with cardiovascular diseases and diabetes, so in principle, the recommendations issued for cardiovascular diseases also apply to the metabolic syndrome. However, it has to be kept in mind that obesity will put some limitations on the type of exercise the affected individuals can perform without discomfort. For example, cycling or swimming might be more suitable than full weight bearing exercises such as running or plyometrics. In addition—just as it is the case with cardiovascular diseases—a healthy diet is a vital component of a lifestyle intervention that targets these diseases [90], even though this is a topic that is beyond the scope of this chapter. Similarly to cardiovascular diseases, it has been shown that cardiorespiratory fitness inversely correlates with the incidence of the metabolic syndrome [91, 92]. It has been reported that risk reductions are observed with as little as 30 min of moderate-intensity activity per day and that the mechanisms include the regulation of body mass; the reduction of insulin resistance, hypertension, and dyslipidemia; as well as the enhancement of insulin sensitivity and glycemic control [93]. Even though moderate-intensity exercise is effective in that regard, the results of several studies suggest that vigorous activity can yield even better results [94–96]. It has also been demonstrated that the effect of exercise is independent of weight loss, but a lifestyle intervention that reduces fat mass by combining physical activity with an appropriate diet is even more effective [97–99], that reducing visceral fat mass in particular might be an important goal [100]. Overall, the consensus can be simplified as "eat less, exercise more" [99].

1.5.1.3 Musculoskeletal Diseases

Diseases that normally manifest later in life but also seem to be linked to a lack of regular exercise are sarcopenia (loss of muscle mass, usually associated with aging), dynapenia (loss of muscle strength, usually associated with aging), and osteopenia (low bone mineral density, reduced by 1–2.5 standard deviations compared to a healthy young reference population) or osteoporosis (abnormally low bone mineral density, reduced by more than 2.5 standard deviations). It is not an easy task to disentangle the effects of aging from the effect of decreasing physical activity that often accompanies the aging process [101]. One possibility to gain some insight into this matter is studies comparing the physical performance of master athletes to the performance of age-matched individuals with a normal or sedentary lifestyle. These studies show that master athletes with high lifelong physical activity levels can maintain high levels of strength, power, endurance, and bone mineral density, even with old age [102–105]. Even though one could argue that these high levels of physical performance exhibited by master athletes might be partly the result of a selection bias, there is a plethora of training studies demonstrating that even at old age, exercise programs can substantially increase physical performance [106–109]. It follows that diseases such as sarcopenia and dynapenia can be prevented and treated with adequate training programs, usually involving heavy resistance training aimed at increasing muscle mass and function [110–113]. For specifics of effective training programs that increase muscle mass, strength, and power, the same principles apply for elderly as for the general population, as many studies have demonstrated that the training-induced relative performance improvements in elderly are usually comparable to the improvements observed in young and middle-aged populations [114–116]. Regarding the importance of sarcopenia and dynapenia—loss of muscle mass vs. loss of muscle strength and power—it has been argued that dynapenia is more important than sarcopenia from a functional point of view (e.g., for fall prevention or activities of daily living), and that

factors other than the loss of muscle mass also play an important role in the development of dynapenia, for instance neuronal changes or changes in contractile properties [117, 118].

While changes of muscle mass and function due to aging, physical activity and physical inactivity have been well investigated, changes in bone health and the effects of exercise on bone are not documented as well. The main cause for this discrepancy is probably that bones adapt much slower than muscles, with only small changes even after months of exercise or disuse. This makes studies assessing the effects of exercise on bone strength long and tedious. In addition, bone strength is very difficult to measure in vivo, so it is very rarely done and is done only in cross-sectional studies [119]. Therefore, only bone mineral content or bone mineral density are measured before and after training interventions, and the imaging techniques used to assess these effects have some limitations that should be taken into consideration when interpreting the effects. For example, dual-energy X-ray absorptiometry (DXA) supposedly measures bone mineral density, but it is a two-dimensional measurement, which is why it has been questioned as a valid measurement for a three-dimensional parameter such as bone mineral density [120–122]. Nevertheless, there are several good studies, sometimes using more sophisticated imaging techniques such as peripheral quantified computed tomography (pQCT), that have assessed the effects of different types of exercise on bone. The results from cross-sectional studies as well as longitudinal studies support the mechanostat model of bone adaptation, stating that bone adapts to the mechanical loads it is exposed to [123], and that it is mainly the magnitude of the load that drives the adaptation, with rate of loading adding to the effect [124, 125], in particular if it is a dynamic, unfamiliar form of loading [126]. In line with this model, high-impact exercises such as running and jumping have been associated with high bone mineral density, whereas low-impact exercises such as swimming or cycling do not increase bone mineral density [127–129]. The positive effects of high-impact exercise such as plyometrics on weight-bearing bone have been demonstrated not only in adults [130, 131] but also in children [132, 133]. Animal models suggest that as few as five jumps per day are sufficient to elicit these beneficial adaptations if the impact loading and thus the bone deformation (strain) is high enough [134]. Thus, low-volume high-impact exercise such as jumping is certainly not the only way to maintain bone mass and density and help to prevent osteopenia [135], but it seems to be the most efficient one.

An interesting line of evidence regarding the deconditioning effects of physical inactivity and potential countermeasures stems from space research as well as its terrestrial analogue, bed rest. The lack of gravitational loading experienced by astronauts leads to similar adaptations as physical inactivity, among others loss of muscle mass and function, loss of bone mass, and deconditioning of the cardiovascular system [136–138]. To prevent these adaptations and maintain astronaut health, the space agencies have tested many potential countermeasures, among others nutrition and various forms of exercise. While nutritional countermeasures—for example high-protein intake—were not successful [139], exercise has proven to be an effective countermeasure against this deconditioning caused by a lack of gravitational loading and reduced physical activity: for instance, in a recent study, intensive jump training was found to maintain bone mass and density, muscle mass and function as well as aerobic capacity after two months of bed rest, whereas the inactive control group exhibited significant losses of up to 40% [140–142]. These studies can help to gain insight into the mechanisms of physical inactivity as well as effective ways to combat the negative effects of physical inactivity. For a review, see [143].

1.5.2 Mental Health

Mental health is arguably more difficult to assess than physical health, and psychological diseases such as depression or anxiety remain stigmatized in many societies, possibly leading to a high number of unreported and untreated cases [144]. For these cases in particular, exercise might be an important treatment option. In this section, I will

give an overview of the benefits of exercise for diseases such as depression, anxiety, and Alzheimer's, but first I will discuss the positive effects of acute as well as chronic exercise on cognitive performance and mood in healthy populations. In general, the type and intensity of exercise has not been researched as well, but does not seem to matter as much for mental health as for physical health [145]. The doses required to elicit mental health benefits seem to be much lower than those required for physical health benefits [146], but, nevertheless, higher doses of exercise usually elicit larger effects [147], and for some aspects of mental health such as anxiety and dementia, endurance exercise has been found to be more effective than other types of exercise [148, 149].

1.5.2.1 Cognitive Performance, Mood, and Stress

Acute physical exercise can improve some aspects of cognitive performance, notably decision-making performance [150]. This effect has been attributed to increased arousal and adrenaline levels, but motivation and the saliency of the tested cognitive task also seems to play an important role [150]. In addition to this effect on cognitive performance, a single bout of exercise can increase mood [151, 152] in active populations as well as inactive populations [153, 154]. Regular physical exercise (at least 2–3 times per week) is associated with a number of measures of psychological well-being, among others less depression, anger, cynical distrust, and stress, as well as higher levels of sense of coherence and a stronger feeling of social integration [155]. Chronic stress in particular has received a lot of attention, maybe due to the high number of professional, social, and emotional stressors present in modern societies. It has been suggested that the body's stress response (among others increased secretion of glucocorticoids and catecholamines and the activation of the sympathetic nervous system) in combination with physical inactivity contribute to the development of the metabolic syndrome and cardiovascular diseases, whereas physical activity can make use of this increased stress arousal ("fight-or-flight" response) and prevent or ameliorate the negative effects of stress [156]. Indeed, several intervention studies demonstrated that in addition to the effects of exercise on physical health, regular exercise will reduce perceived stress [157], stress reactivity, and heart rate stress response [158].

1.5.2.2 Depression and Anxiety

Depression is the most common psychological health issue and can occur in mild, moderate, and severe forms [159]. Definitions vary, but a common one for major depressive disorder is as a clinical syndrome characterized by depressive mood or loss of interest in activities for two weeks or more, accompanied by several additional symptoms such as sleeping disturbances, changes in eating habits, fatigue, suicidal thoughts, or reduced ability to concentrate [160]. Physical activity has been found to be associated with decreased risk of depression [161], making it a useful tool in preventing the onset of depression [162].

When applied to clinical populations, meta-analyses quantified the effects of exercise interventions on depression symptoms as very large [163, 164], and exercise participants were more likely to recover from the illness than non-exercising counterparts [165]. For mild to moderate depression, the effect of exercise seems be comparable or even superior to antidepressant medication and psychotherapy [166–168], possibly due to its positive effects on body image, coping strategies, self-efficacy, and quality of life [166], and on a molecular level increased hippocampal brain-derived neurotrophic factor (BDNF) levels [169, 170] and serotonin availability [171]. In addition to treatment effects, relapse rates are reported to be lower for exercise compared to medication treatment [172]. There seems to be little influence of the type of exercise performed; both endurance and non-endurance exercise seems to be effective [173]. For severe forms of depression, exercise is recommended more as an addition than a replacement for medication or therapy [166], although some studies also found effects comparable to the effects of medication [174]. For medication it seems to be the other way round: for mild and moderate forms of depression, meta-analyses revealed that the effect of medication is minimal or nonexistent, whereas for

severe forms of depression antidepressants have a substantial effect [175]. Despite the efficacy of exercise in the prevention and treatment of depression, it is still underrepresented in physicians' recommendations [163].

Another frequently diagnosed psychological disease is anxiety, with depression and anxiety showing high comorbidity [176, 177] and considerable overlap [178], so many results from studies on depression potentially generalize to anxiety as well. Similar to depression, definitions of anxiety vary; generalized anxiety disorder is characterized by excessive, uncontrollable, and often irrational worry about events or activities, with a variety of symptoms, including headaches, muscle tension, breathing difficulty, irritability, and sleeping difficulties [160]. In line with the studies that found improved mood after acute exercise, it has also been reported that acute exercise can improve state anxiety and that regular endurance exercise with a duration of more than 20 min per session for at least ten weeks can improve trait anxiety, independent of age and health status [149]. Meta-analyses quantified the evidence for a positive effect of exercise interventions in anxiety reduction as low to moderate [179], making exercise—endurance exercise in particular—a viable part of anxiety prevention and treatment.

1.5.2.3 Dementia and Alzheimer's Disease

Dementia can be defined as a clinical syndrome characterized by difficulties in memory, disturbances in language and other cognitive functions, changes in behaviors, and impairments in activities of daily living. Alzheimer's disease is the most common cause of dementia, accounting for up to 75% of all dementia cases [180]. The mechanisms and risk factors involved in the development of Alzheimer's—other than old age and genetic predisposition—are still not well understood, but there is good evidence that controlling vascular risk factors, especially hypertension, is important in the prevention of the disease [181]. Consequently, physical activity has been recognized to be an important factor in this regard [182–184]. Links between diabetes, obesity, and Alzheimer's have also been proposed [185], making physical activity aimed at preventing and treating the metabolic syndrome as well as cardiovascular diseases an even more appealing prevention strategy. In addition, exercise, particularly aerobic exercise, can slow down the progression of Alzheimer's, possibly via increases in angiogenesis, neurogenesis, synaptogenesis, and neurotransmitter synthesis in the different cerebral areas involved in cognition [148]. Other protective factors seem to be mentally stimulating activities and social activity [180].

1.6 Conclusion

With adequate programming, regular physical activity is an effective way to improve physical performance (strength, power, and endurance), improve physical and mental health, and reduce the risk factors for many noncommunicable diseases such as cardiovascular diseases, metabolic syndrome, sarcopenia, osteoporosis, and depression. In contrast to medication, physical exercise usually has no negative side effects, costs very little, targets many health issues at once, and has additional potential benefits, for instance improved mood or improved cognitive abilities. Recent evidence also suggests that many health benefits of exercise can also achieved via short high-intensity exercise, which substantially decreases the time demand, thus weakening the most common reason for not exercising (lack of time). If the multitude of beneficial effects of regular exercise were to be combined in a single drug, it would be an instant bestseller. The challenge remains to convince sedentary populations that the numerous health benefits of exercise are worth the effort and that it is time to stop leaving their health to physicians and pharmaceutical companies, and instead take responsibility for their own health by choosing a lifestyle that incorporates regular physical activity, a healthy diet, and a healthy lifestyle in general.

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Part II

The Physiological Responses to Exercise

Type of Exercise Training and Training Methods

2

Sascha Ketelhut and Reinhard G. Ketelhut

Abstract

There is general agreement that exercise training leads to functional, morphological, and metabolic adaptations of different biological systems, thereby increasing overall physical performance and promoting good health. Thus, an active lifestyle is propagated in all age groups. However, not every exercise routine or workout is suitable for everyone. Inappropriate training can also pose risks, and too low or too high training intensity or volume often does not lead to the expected success. To ensure significant benefits, specific principles and strategies need to be considered and accustomed to the individual.

This chapter summarizes the key exercise variables and training principles to consider when developing a training program to improve or maintain performance and health. In addition, the various steps for creating an individual training program are described, and an overview of the different training methods and training strategies is given.

Keywords

Physical activity recommendations · Exercise methods · Training principles · Training variables

2.1 Background

Physical inactivity and sedentary lifestyle have become a growing public health problem in western lifestyle [1]. About 10% of annual deaths are attributed to physical inactivity [2]. A first approach to preventing the morbidity and mortality of various diseases is lifestyle modification, including regular physical activity as the main strategy for all ages.

There is no doubt that adequate regular physical activity has a beneficial effect and is associated with improvements to various health effects. Therefore, practical strategies to increase physical activity should become a public health priority. An active lifestyle is propagated in all age groups. In addition to the World Health Organization [3], numerous other associations and national governments have established evidence-based guidelines for physical activity.

S. Ketelhut (✉)
Institute of Sport Science, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Halle (Saale), Germany

Medical Center Berlin (MCB), Berlin, Germany

R. G. Ketelhut
Medical Center Berlin (MCB), Berlin, Germany

Charité-University Medicine, Berlin, Germany

Department of Sport Sciences, Humboldt-University, Berlin, Germany

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_2

Recently, the US Department of Health and Human Services (HHS) released a new edition of the Physical Activity Guidelines (PAG) for Americans, with recommendations on physical activity even for those starting as young as 3 years of age [4].

The guidelines provide general recommendations on the type, volume, intensity, and frequency of exercise required to maintain and promote good health. For a substantial health benefit, adults should be engaged in moderate-intensity exercise for at least 150 min per week, or in high-intensity physical activity for at least 75 min per week. The recommended 150-min exercise should consist of aerobic workouts that are spread over the week, as well as strength training, which is required for all major muscle groups at least 2 days per week. In addition, various stretching exercises and exercises with balance, flexibility and coordination should be regularly included. To obtain additional and more comprehensive health benefits, an increase to 300 min per week at moderate intensity or 150 min per week at vigorous intensity is recommended.

Physical activity is defined as movement of the body of any kind, which increases the energy consumption beyond the resting level. When physical activity is performed to improve or maintain health or physical fitness and is used in a planned, structured, and repetitive sense it is called exercise or exercise training [5].

There is general agreement that exercise training leads to functional, morphological, and metabolic adaptations of different biological systems, thereby increasing overall physical performance and promoting good health. Not every workout is suitable for everyone. Inappropriate exercise can also be risky, and too little or too much training intensity or volume often does not lead to the expected success. To ensure a significant benefit, specific principles and strategies need to be taken into account and accustomed to the individual.

This chapter summarizes the key exercise variables and training principles to consider when developing a training program to improve or maintain performance and health. In addition, the various steps for designing an individualized exercise program are described, and an overview of the different exercise methods and training strategies is given.

2.2 Training Variables

The favorable effect of exercise on human health is determined by three key factors:

- Training mode
- Training volume
- Training intensity

These training variables are used to characterize and control a training stimulus. The composition of the variables and their interplay decisively determine the exercise incentive and thus the development of athletic performance or health outcomes.

2.2.1 Training Mode

The training mode refers to the specific activity performed by the athlete or the patient. Different training modes lead to different adaption's in certain physiological systems of the body. If the goal of exercise training is to develop cardiorespiratory fitness, activities using large muscle groups continuously or intermittently, such as running or cycling, should be used. On the other hand, if the goal is to improve strength, resistance training would be the first choice. Selecting the appropriate exercise mode during training ensures that the systems to be improved are challenged. In addition to the goal of exercise training, the requirements of the person should be considered. Different risk factors, injuries, and diseases can be contraindications for certain kinds of exercise modes in patients.

In terms of compliance, personal preferences should be considered when determining the training mode. Whenever there is a chance, an exercise mode should be applied that is more attractive to the athlete or the patient. When selecting an exercise mode, it should also be considered how

easily the exercise intensity can be monitored and adjusted to ensure overload as the performance progresses.

2.2.2 Training Volume

The training volume is the amount of work that has been done during a defined period (training session, training day, training week). The training volume is often given as the distance covered (m, km, steps performed), the loads moved (kg, t), duty cycle (minutes, hours), and number of repetitions performed (number of intervals, number of sets, number of series).

For both athletes and patients, adequate exercise volume is crucial to improving exercise performance and health. Several studies have identified a dose–response relationship between exercise volume and health outcomes [6, 7]. Thereafter, a higher volume of physical exercise exerts higher effects on performance and health outcomes. However, it must be assumed that the benefits cease to occur at a certain level of physical exercise. It is likely that the shape of the dose–response curve is parabolic and may vary depending on the desired health outcome and baseline level of physical activity [8]. Lower volumes of exercise may have positive health effects in high-risk patients and those with very low levels of fitness [9], whereas those with high levels of fitness require much higher training volume to produce positive effects.

2.2.3 Training Intensity

Training intensity characterizes the amount of stress or effort during exercise. Typical measures of intensity are speed (m/s, km/h, min/km, mph), load (kg, N), mechanical power (watts), or height and width (cm, m). Commonly, intensity in percent of maximum power (% of maximum power, % of maximum speed) or biological load measurements (VO_{2max}, heart rate, lactate, etc.) is used to describe exercise intensity.

In addition to the training volume, the training intensity is a crucial factor for the adaptation of the body to the training. Adjustments in the body are specific to the intensity during the exercise session. An exercise intensity that is too low does not burden the body systems and therefore does not lead to the desired physiological adaptions, while too high an intensity can cause fatigue and premature termination of the training session. In either instance, the training session is poor and ineffective.

Recent position stands have supported the greater benefits of vigorous versus moderate exercise [8]. Furthermore, there is evidence of a minimum intensity threshold for the benefit that appears to be related to the subjects' initial fitness state [10]. Therefore, a threshold of exercise intensity may vary depending on fitness level, and it may be difficult to accurately define a precise threshold to improve fitness or performance. The intensity of physical activity should be adapted to the physical fitness level and any chronic diseases, injuries, or physical or mental limitations of the subject.

2.2.3.1 Methods of Assessing the Intensity

The most accurate methods of regulating exercise intensity are monitoring oxygen consumption during exercise to determine percentage of VO_{2max}. Since VO_{2max} assessment is not that operable, most exercise prescriptions use heart rate (HR), rating of perceived exertion (RPE), metabolic equivalents, and specific speeds or watts to monitor intensity during exercise.

If possible, a graded exercise test should be performed to assess the athlete's or the patient's aerobic capacity and cardiorespiratory fitness level. During the test, the parameters used later to monitor the exercise intensity (HR, RPE, watts, speeds, etc.) should be recorded throughout the test protocol. After determining the maximal exercise capacity, intensity recommendations can be derived.

Since the muscle mass involved during an activity affects the response of the parameters obtained, such as HR, VO_{2max}, and lactate levels. it is important to choose an exercise test that suits the training mode of the workout. If the exercise mode includes running exercises, the graded exercise test should be performed on a treadmill. If the training mode includes cycling, the exercise test should be performed on a bicycle ergometer. The use of common

conversion formulas is not recommended, since they are not that accurate.

Heart Rate Max

The maximum heart rate (HR_{max}) refers to the HR achieved in a sport-specific exercise test under maximum exertion. The HR_{max} indicates a current state of the cardiovascular system. Due to the high interindividual variability in every decade of life, the generally established formula HRmax = 220 – age is not recommended for the determination of HR_{max}. It is rather recommended to determine the HR_{max} in the preferred sport with a specific test procedure. Based on the HR_{max} as reference value, an intensity recommendation for different types of training can be derived. It should be noted that HR_{max} is influenced by factors such as performance, training age, age, gender, sport, and genetics.

Assessment of the Perceived Exertion (RPE) Scales

Another way to assess and regulate intensity during exercise is to use tools that measure the perceived effort of training. Athletes and patients use the Borg RPE scale [11] or the OMNI scales [12] to modulate exercise intensity through the subjective assessment of their effort. Both scales show moderate to strong validity compared to typical measures of exercise intensity such as $\%VO_{2max}$, $\%HR_{max}$, and blood lactate concentrations [13, 14]. This method is a very convenient way to access the intensity that does not require additional materials. However, this is not an objective measure and may therefore be influenced by external environmental factors and various subject characteristics such as age, sex, training status and fitness level [15, 16].

The Metabolic Equivalent

The metabolic equivalent can also be used to specify exercise intensity. One metabolic equivalent of task (MET) corresponds to 3.5 mL/kg/min of oxygen consumption and is considered to be the amount of oxygen needed by the body at rest [17]. METs have been set for a variety of physical activities (Table 2.1).

Table 2.1 Exercise intensity and METs

Intensity	MET	Activity
Light	<3.0	Walking at 2.0 miles per hour
Moderate	3.0–5.9	Walking at 3.0 miles per hour
Vigorous	≥6.0	Walking, jogging, running at ≥4,5 miles per hour

Adapted from American College of Sports Medicine [8]

2.3 Training Principles

In the health and fitness area there are numerous training methods and strategies. This makes it difficult to determine the best or most effective strategy or method, especially considering the various reactions an exercise can trigger in every human being. Nevertheless, specific training principles can be derived from our knowledge of the physiology of adaptive processes. A successful exercise program designed to improve physical fitness and health parameters should consider general principles for the organization and the systematic structure of exercises known as training principles.

2.3.1 Individuality

The training stimulus must correspond to the physiological capacity of the individual. Each individual is unique and reacts differently to an external stimulus. There are several factors that can lead to different responses to a particular training stimulus:

- Gender
- Maturation
- Conditioning
- Genetic predisposition
- Risk factors
- Diseases
- Constitution

Thus, an effective training program must include an exercise prescription specifically developed for the individual desires, goals, and requirements. Therefore, it is essential to collect and request information about the athlete or the patient and then apply that information to generate an

athlete-specific training program by manipulating the design variables of the main program.

2.3.2 Overload

The stress stimulus must exceed a certain biologically effective intensity threshold in order to trigger an adaptation reaction. The human body is a highly adaptable organism that continuously adapts to changing environmental stimuli. If the body is not subjected to increased or new demands, no adjustment processes will be performed. Therefore, during exercise training the body must be subjected to an abnormal stress or overload that exceeds the usual level of stress to induce a physical adjustment. Overload is the stimulus that induces adaption and can be achieved by changing the modifiable training variables. In appropriate dosages, overloading leads to short-term fatigue but ultimately improves performance [18].

For example, aerobic physical activity stresses the cardiorespiratory system and muscles, requiring the lungs to move more air and the heart to pump more blood and deliver it to the working muscles. This increased demand increases the performance and capacity of the lungs, the heart, the circulatory system and the exercising muscles. In the same way, muscle-strengthening and bone-strengthening activities overload muscles and bones, and make them stronger.

2.3.3 Specificity

All adjustments to the training are specific to the stimulus used. A training stimulus should be specially designed to trigger certain adaptation processes. Different training stimuli cause different physiological reactions and lead to various adaptations. This is known as the SAID principle (specific adaptation to an imposed demand). The training variables must be strategically manipulated to ensure the physical demand of exercise and the resulting adjustment. This reflects the training goal [19]. If the training goal is to improve cardiorespiratory fitness, the training stimulus should consist of exercises that stress the cardiovascular system, such as endurance training, rather than performing resistance training.

2.3.4 Progression

In order to achieve steady and continuous improvement in the fitness of athletes and patients, the physical demands must be gradually increased to overload their systems. If stress stimuli of the same intensity act on the organism for a long time, the biological systems have adapted to the respective load after some time whereby no further increase in performance is achieved. Exercise frequency, duration, and intensity or changes in resting intervals are the most commonly manipulated variables to progressively overload the system. Usually, the training frequency, intensity, or duration should not be increased more than 10% per week [20].

2.3.5 Variation

To guarantee that the training stimulus is effective and challenging, the training variables should be systematically changed throughout the training process. As already mentioned, the human organism responds to an overload stimulus with adaptation. To ensure progressive adaptation, the applied training stimulus must be adjusted. In mismanagement of training incentives, there may be an increased risk of injury and overtraining [21]. Variation can be achieved by modifying the training intensity and volume, the exercise order and training mode. In addition to the overload principle, variation in the training process due to injury prevention is also important. Applying the same stimulus for a longer period may overwhelm specific parts of the body.

2.3.6 Recovery

After an acute workout, a certain recovery time is required to restore performance before the next training stimulus is applied. Any training stimulus that exceeds an intensity threshold and triggers an adaptive response affects the functional

systems of the body. The organism must react with functional and morphological adaptations. The body cannot repair without recovering. The optimal recovery duration depends on the exercise used, the training status, and other internal and external circumstances. Normally, a rest period of at least 24–48 h is recommended.

High training stimuli that are used over a longer period without adequate regeneration may result in overtraining or overtraining syndrome, leading to stagnation or loss of performance. Apart from performance alterations, overtraining is often associated with fatigue, weariness, listlessness, loss of motivation, moodiness, and an increased risk for injuries and infections. Restoring the previous performance level can then take weeks and months even if a regeneration period is carried out. It is then necessary to schedule appropriate rest periods during the exercise program and to monitor the regeneration process. This is especially true for athletes who achieve high training volumes and intensities. Various physiological and psychological markers can be used to monitor the state of recovery (questionnaires, HR at rest, creatine kinase, urea, etc.). In recent years, heart rate variability (HRV) has become established as a sensitive indicator for recovery status and overtraining. Studies show that a good recovery status becomes visible through high vagal HRV parameters [22] and must be considered as a prerequisite for intensive training. Based on prospective randomized-controlled training studies, HRV monitoring can positively influence performance development in endurance sports [23]. In particular, the vagal HRV parameters are suitable for detecting overtraining [24].

Although the HRV analysis for recovery monitoring is mostly applied in athletes, it can be assumed that even ambitious recreational athletes can benefit from an HRV-controlled training. Different manufacturers offer special wearables with integrated HRV measuring that make them easy to use.

2.3.7 Reversibility

Unfortunately, the body and its tissues can not only adapt positively to applied overload stimuli by increasing their abilities. If no regular congestion stimuli are applied, the adjustments are declining again. Therefore, it is important to integrate the exercise training regularly and optimally over the entire lifetime.

2.4 Designing a Training Program

2.4.1 Screening and Baseline Assessments

A training program must include a training recipe that is specific to each athlete or patient to suit their needs, interests, and abilities. This requires a comprehensive baseline screening that monitors patient history, risk factors, lifestyle, physical fitness, and training experience, and identifies contraindications and preferences. In addition to screening questionnaires, various laboratory analyses and field tests can be used to identify strengths and weaknesses and assess individual performance. The test results can be classified according to established reference values, helping to develop a physical fitness and health profile of the athlete or the patient. Using this information precise exercise prescriptions can be derived, and realistic and achievable goals can be framed. In order to obtain reliable test results, standardized test procedures must be followed. Testing is not a one-time task but rather an ongoing mission that assesses the status of the athlete and the effectiveness of the prescribed exercise program. This allows fitness and health professionals to make objective decisions about the program. If a follow-up assessment is conducted, it is possible to evaluate the progress and adjust the program if necessary.

2.4.2 Setting the Goal

Based on the screening, specific training goals can be derived. These goals should be specific, realistic, achievable, and measurable. To formulate goals such as “achieve better fitness” or “lose body fat” are not very applicable. They are neither accurate

in terms of parameters to be changed nor are the magnitude of the change or the time frame defined. In order to apply an optimal training stimulus, an outcome parameter has to be selected which represents the target so that it can be measured (e.g., VO_{2max}). Furthermore, it is important to determine the extent to which this parameter needs to be changed (e.g., increased by 5 mL/kg/min) and the time frame for the change (e.g., 4 weeks). If training goals are formulated which are not feasible in the given time frame, this can negatively influence the motivation of the athlete or the patient.

2.4.3 Designing the Program

Exercise training consists of several factors, that can be manipulated and interact systemically. A successful training program requires a sound management of the adaptive and recovery response to specific structured exercise interventions [25].

A training plan is the structured description of the process and the methodology of a training program over a defined period, thus defining the direction and pace of performance development. When designing the training program, it is important to determine the temporal structure and periodization, the specific training mode and exercises, the order of the exercises and the training variables and determining the organizational forms and methods.

To design an effective exercise program, the basic training principles (individuality, overload, specificity, progression, variation, recovery, reversibility) as well as biological, psychological, behavioral, social, and environmental factors must be considered.

2.4.4 Implementation of the Training

After creating a training program, the actual training can begin. It is important to follow the training plan and applying the stimuli as indicated and adjusting only when needed. Throughout the training process, it is important to monitor the training and document changes in the training methods and variables. In addition, it is important to receive feedback from the athlete or the patient after each training session. This is especially important to assess how demanding the training is and to avoid too high or too low stimuli. The feedback should consist of frequent dialogues with the athlete, and simple questionnaires and physiological measures should be made (resting heart rate, HRV, blood samples, etc.).

If the training program does not have the expected effects, appropriate training variable adjustments should be made. Whenever there are significant changes in biological, psychological, behavioral, social, and environmental factors that may affect exercise performance, recovery or adaptive processes and training methods and variables should be adapted appropriately.

2.4.4.1 Start Low, Go Slow!

The greatest increase in fitness and health results from a change from previous inactivity with very few minutes increments to small amounts of physical activity, especially if activity is of moderate (brisk walking) or vigorous (jogging and running) intensity. Recreational athletes who start intensive endurance sports immediately after a long break should be careful. This group has a higher risk of cardiac events. Therefore, it is important, especially for newcomers or non-athletes, to start with low intensity and gradually increase the intensity and scope of training.

Because the body needs weeks, and in older people even months, to adapt from previous inactivity to a regular workout, only those who take their time can avoid overloads and injuries. The beginner often feels that the recommended training intensity is very low or even too low. Therefore, it is important for the beginner to develop a correct feeling of stress during exercise and to adjust the load accordingly.

In order to get a good feeling for a uniform given running speed, the so-called pendulum run is well suited at the beginning. One can easily run for 1 min in one direction, then turn and run back again. If one has not returned to the starting point after 2 min, the run was irregular, because the sections are the same, and obviously the first section was too fast. This should be repeated on the following days to get a feeling for a consistent

and tailored to the individual performance right running speed.

2.4.5 Re-assessment

After the training program has been used for a certain period, baseline assessments should be repeated to identify possible changes in the relevant parameters. In general re-assessment should be done after 6–8 weeks of training, as this is approximately the time the body needs for functional and morphological adjustments. The results of the baseline evaluations and reassessments are then compared to assess the effects and, if necessary, to make appropriate adjustments to the training program. It is very important to ensure the same test conditions as during the baseline assessments (Fig. 2.1).

2.5 Training Methods

Various types of training programs have been designed, varying in mode, frequency, duration, and intensity of the activity. This section tries to provide a short overview of common training methods that should be incorporated into a healthy workout routine.

2.5.1 Endurance Training

Typically, aerobic activities, also called endurance or cardio activities, are physical activities in which people move their large muscles in a rhythmic manner for a sustained period. Therefore, the activities depend heavily on aerobic metabolism, as opposed to being primarily governed by muscle strength or power or anaerobic metabolic systems [26].

Running, brisk walking, biking, cross-country skiing, swimming, and dancing are all examples for aerobic activities. Aerobic activity increases a person's heart and breathing rate to meet the demands of the body's movement. Over time, regular aerobic activity makes the cardiorespiratory system stronger and fitter.

To achieve general endurance training, a minimum of 5 min continuous training with at least 1/6–1/7 of total body muscle is required for the untrained, which is fulfilled by all classic endurance sports. However, the exercise intensity must be in an individual training-effective range. In completely untrained persons, a training effect can already be achieved through everyday activities such as walking, cycling, and climbing stairs.

Apart from traditional continuous exercises of longer durations, intermittent exercise protocols consisting of short exercise bouts that rely primarily on the anaerobic metabolism instead

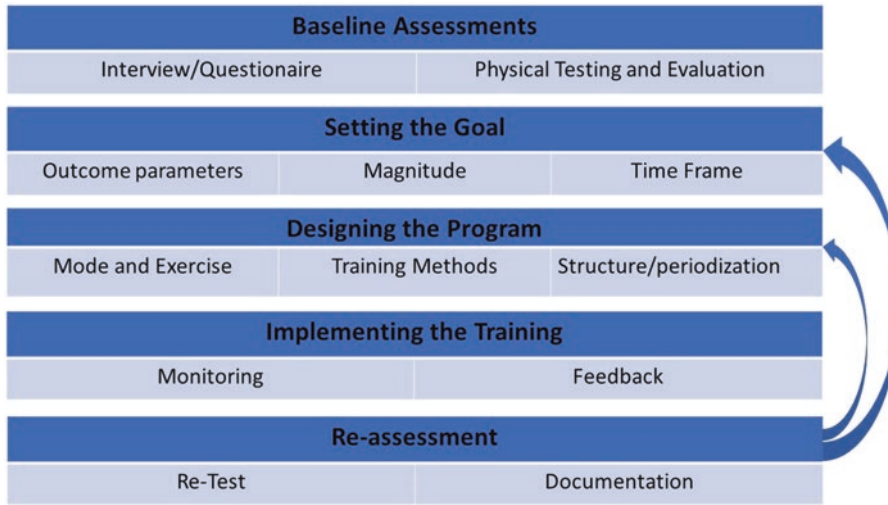

Fig. 2.1 General structure for designing a training program

of aerobic are also applied in endurance training.

Aerobic endurance exercise has been well documented to reduce body fat mass, increase insulin sensitivity [27], modulate cardiovascular risk profile [28], and reduce cardiovascular morbidity and mortality in physically active and sedentary subjects [29–31].

2.5.1.1 Long Slow Distance Training

Long, slow distance training (LSD) consists of a continuous exercise which is performed at a specific intensity for an extended period of time. In general, LSD refers to a moderate intensity that is often described as "conversation," where the individual is able to talk without respiratory distress [32]. The training intensity is set at approximately 70% of VO_{2max} [32]. This guarantees a high proportion of fat metabolism. The training volume or duration is relatively high and should be between 30 min and 3 h [33]. The goal of LSD training is the development of fat metabolism and basic stamina. The physiological benefits derived from LSD training include enhanced cardiovascular function and improved mitochondrial energy production and oxidative capacity of skeletal muscle, thus improving the lactate threshold intensity. LSD is a prerequisite for more intensive training.

2.5.1.2 Tempo Training

Tempo training consists of a shorter exercise duration than LSD training. Tempo training is also referred to as threshold training [33], as the intensity corresponds to the lactate threshold. Thus, the energy demand is ensured equally by the lipid and glycogen metabolism. The main goal of tempo training is to improve the endurance capacity, prepare for race pace, improve energy production for both aerobic and anaerobic metabolism, enhance the body systems ability to sustain exercises at a specific pace, and increase lactate threshold (Table 2.2). The volume or duration varies considerably in the different endurance sports and is determined by the training model.

2.5.1.3 Interval Training

Interval training is characterized by exercise that alternates between bouts of heavy or severe exercise intensities and bouts of rest or low to moderate exercise intensities [26]. The advantage of interval training is that it enables individuals to achieve greater total exercise time at intensities close to VO_{2max}, when compared to continuous training. The exercise protocols generally consist of exercise bouts lasting between 3 and 8 min with relative high intensities (Table 2.2). The exercise bouts are interspersed by active or passive rest periods of varying lengths and aims to increase VO_{2max} and enhance anaerobic metabolism.

2.5.1.4 High-Intensity Interval Training

HIIT is defined as repeated bouts of vigorous to maximal intensity exercise interspersed by periods of passive or active recovery at low intensity. The goal is to spend as much time at an intensity above 90% VO_{2max}. The work–rest interval range from 1:1 to 1:4 to guarantee a quality effort on subsequent exercise bout (Table 2.2).

HIIT needs a firm base of aerobic endurance training especially when applying exercise bouts with higher intensities. The main goal of HIIT is to improve VO_{2max}, improve running speed and economy.

2.5.1.5 HIIT Versus MICT

In earlier days endurance exercise prescriptions favored LSD, as it was assumed to induce more positive effects at a lower risk for adverse events. In the last years research has discovered that the relative intensity, not the duration, of exercise is of most importance in relation to all-cause mortality [34]. In this concern HIIT has been purposed as an effective alternative to traditional moderate-intensity continuous training (MICT) inducing similar or even superior changes in cardiorespiratory fitness and health-related markers in adults [35]. Despite a substantially lower time commitment and reduced total exercise volume HIIT stimulates physiological remodeling comparable with MICT [36]. The fact that lack of time is often stated as one of the barriers to regular exercise participation underlines the potential of HIIT [35]. Furthermore, a recent published study provides evidence that a single session of HIIT can be enjoyable and preferable as moderate-intensity

Table 2.2 Endurance training methods and training variables

Training type	Intensity	Duration	Mode	Goal
Long slow distance training	60–80% HR_{max} 9–12 RPE Moderate	30–180 min	Continuous	Enhancing cardiovascular function, improving mitochondrial energy production and oxidative capacity of skeletal muscle, and developing lipid metabolism
Tempo training	80–90% HR_{max}, 13–14 RPE Heavy	20–45 min	Continuous/ intermittent	Improving energy production from aerobic and anaerobic metabolism, developing sense of race pace, improving running economy, and increasing lactate threshold
Interval training	≈HR_{max} 15–17 RPE Heavy to severe	3–8 min	Intermittent	Increasing VO_{2max} and enhanced anaerobic metabolism
High-intensity interval training	≥HR_{max} 18–20 Severe	20–120 s	Intermittent	Increasing VO_{2max} and improving running speed and economy

Abbreviations: *RPE* rate of perceived exertion, HR_{max} maximal heart rate, *min* minutes, *s* seconds

continuous training (MICT) among inactive individuals [37].

From a physiological perspective HIIT has been shown to induce similar adaptions as MICT leading to an increase in resting glycogen content, an increased capacity for lipid oxidation, enhanced peripheral vascular structure and function, improved exercise performance, and an increased maximal oxygen uptake [35]. Furthermore, HIIT has been shown to improve endothelial dysfunction and reduces blood pressure [38]. These effects are documented not only in healthy adults but also in risk patients [38].

Thereafter, it can be stated that HIIT can serve as an effective alternative to traditional endurance training, inducing comparable and even superior alterations in different physiological, performance and health-related markers in healthy and diseased populations [35].

Apart from adults also children and youth seem to profit from HIIT in respect to endurance performance and hemodynamic parameters as an own study revealed [39]. HIIT seems to be an effective strategy delivering relevant benefits to the cardio metabolic profile in children and youths. Knowing that children habitual physical activity pattern consists of short bouts of high intensity exercises interspersed with rest periods suggests that HIIT is well suitable in this age group. Moreover, enjoyment of exercise and thus compliance could be higher compared to exercise regiments applying MICT. Furthermore, literature confirms that children seem to tolerate HIIT better than continuous exercise, displaying a higher fatigue resistance and a fast recovery after exercises with high to maximum intensities [40] (Box 2.1).

Box 2.1 Beneficial Effects of HIIT

- HIIT is an effective method to increase endurance performance
- Regular HIIT may lead to comparable or even superior blood pressure reductions than traditional MICT
- HIIT and MICT mediate similar cardioprotective effects, with HIIT achieving them with less time-consuming protocols
- HIIT consists of a more diversified exercise regimen and thus seems more appealing and enjoyable, which may enhance motivation and compliance
- If training variables are individually adjusted, HIIT can be safely applied to healthy and disease populations
- Especially children may profit from HIIT

2.5.1.6 Interval Training Protocols

There are numerous interval training protocols which differ in terms of the exercise variables (intensity, duration, number of intervals, length of rest intervals, etc.). Therefore, providing general recommendations for the most effective HIIT protocol is difficult.

Typical protocols in health promotion consist of 4–6 exercise bouts lasting 4 min with an intensity of 85–95% of VO_{2max}. These bouts are interspersed by 2–4 min of active rest. Apart from these relatively long protocols, shorter ones are also applied. These include exercise bouts of 30 s to 1 min, with intensity being increased accordingly. The exercise-to-rest ratio ranges from 1:1 to 1:5. In general, active rest should be applied where a moderate load (50–70% HR_{max}) should be maintained.

A recent study compared the effects of long (4×4 min) and short ($4 \times 8 \times 20$ s) HIIT bouts on running performance and on physiological and perceptual responses [41]. Cardiovascular and metabolic responses during exercise were found to be similar between short and long intervals of HIIT training, but blood lactate concentration tended to be lower during the short HIIT training, indicating that short-interval training was perceived to be easier than long HIIT.

It may be assumed that HIIT protocols with higher intensities that burden the body systems more lead to more pronounced physiological adaptations. Thereafter if performance enhancement is the training goal, shorter exercise bouts with higher intensities should be applied. In general protocols should aim for a total session volume that enables the athlete or the patient to spend between 5 and 10 min at VO_{2max} [42] (Fig. 2.2).

2.5.1.7 Safety of HIIT

Although the acute risk of cardiovascular events is slightly higher during HIIT than during moderate exercise, HIIT can be considered safe even in risk patients [43]. Nevertheless, specific recommendations should be followed both in healthy and in risk patients.

Before applying HIIT, a comprehensive medical examination and especially a stress ECG should be performed by a doctor. Additionally a vigilant surveillance of the patient during the protocol is advisable. Contraindications to HIIT include unstable angina pectoris, uncompensated heart failure, recent myocardial infarction, uncontrolled diabetes, heart disease that limits exercise, severe chronic obstructive pulmonary, cerebrovascular diseases, and hypertensive patients with blood pressure over 180/110 mmHg [43].

2.5.2 Resistance/Strength Training

Apart from endurance, muscular strength is an important component of health and physical fitness. Muscle mass, strength, and quality play a crucial role in maintaining independence and enhancing cardiometabolic and musculoskeletal health throughout the lifespan. Accordingly, current health-oriented physical activity guidelines for adults recommend not only endurance but also muscle strengthening activities [3]. Strength training may be referred to as a systematic program of exercise for the maintenance or development of the muscular system. Although the primary outcome is improved strength and muscular endurance, several health benefits are derived from this form of exercise as well.

Different studies have linked a higher level of muscular strength to a better cardiometabolic risk profile [44]. Moreover, fewer cardiovascular events [45], a lower risk of developing functional limitations, and a lower risk of all-cause mortality [45, 46] have been reported.

Regular resistance training has been shown to positively influence body composition [47], insulin sensitivity [48], blood pressure [49], and bone mineral density and content [50], which preserves bone mass and reduces the risk for osteoporosis. Resistance training is especially important for people over the age of 50 to prevent muscle deficiencies and to reverse the age-associated loss of muscle mass known as sarcopenia [51].

To develop a sound training program, different training variables must be manipulated in a systematic fashion to attain specific training goals. Commonly, training intensity is considered as the most critical variable of resistance training [52]. Training intensity is often expressed as load, which

refers to the amount of weight assigned to an exercise set. The load is generally described as a certain percentage of the greatest weight that can be lifted with proper technique for one repetition, the so-called one-repetition maximum (1RM) [53]. Apart from training load (% 1RM) rating of perceived exertion may also be applicable to monitor and control intensity.

Training intensity is closely linked to the number of times an exercise can be performed. Therefore, the number of repetitions represents another important training variable that determines the duration of the training stimulus applied. Since the duration of the training stimulus affects metabolic, neuronal, and cardiometabolic responses, a specific training goal implies the use of a certain load and repetition regimen [53].

A succession of repetitions completed before the athlete stops to rest is referred to as a training set [52]. Though a single-set training, comprising just one set per exercise may be enough in stimulating gains in muscle strength and hypertrophy in untrained individuals [54], multiple-set training seems advisable especially in more advanced resistance trained athletes [55].

Since the duration of the rest periods between sets not only affects the performance of the subsequent sets but also the metabolic [56], hormonal [57], and cardiovascular [58] responses, it plays a crucial role for training adaptions.

Furthermore, the contraction velocity must also be considered in resistance training, as it can affect the neural [59], metabolic [60], and hypertrophic [61] responses.

Most resistance exercises include dynamic repetitions, thus comprising concentric, eccentric, and isometric muscle action (stabilization, pauses between the concentric and eccentric actions). Eccentric muscle actions are proven to induce higher hypertrophic adaptions [62]. Therefore, it is recommended to emphasize the eccentric phase in resistance training programs aiming for hypertrophy.

The adjustment of the training variables is primarily based on the training goal. In Table 2.3 assignment of exercise variables is displayed for different training goals. In general, if muscular endurance is to be improved, then lower intensities, higher volumes, and shorter rest periods are applied.

If training aims to improve muscle hypertrophy, then light to moderate intensities are applied.

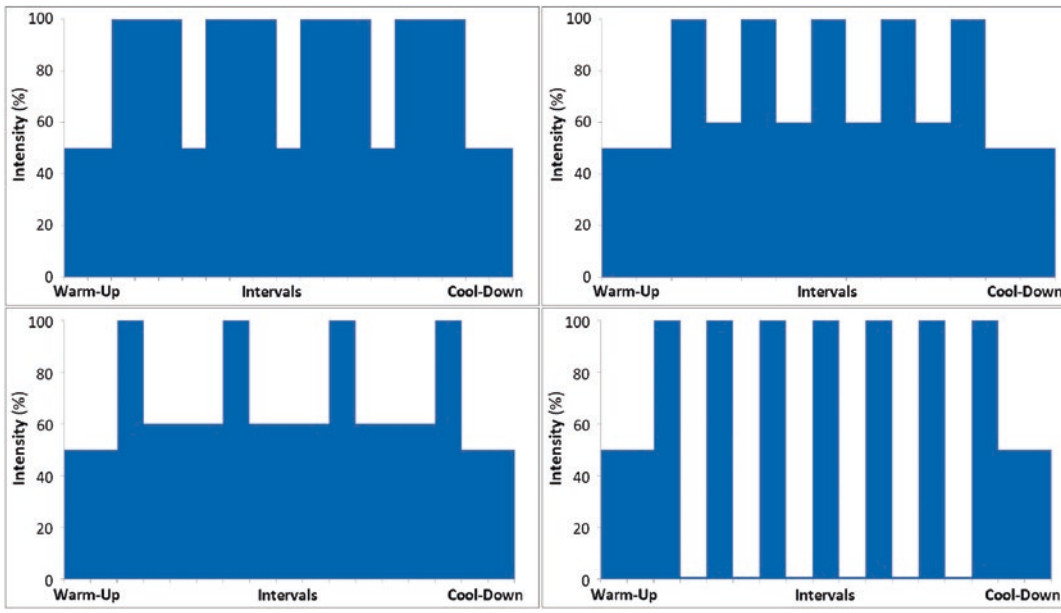

Fig. 2.2 Examples of different HIIT protocols

Usually intensities of 65% of 1 RM are recommended; nevertheless, current literature shows that also intensities of only 40% of 1 RM exert similar effects [63].

It must be stated that in untrained subjects almost any type of program and variable assignments will cause improvements in muscle strength and hypertrophy. Thus, it is advisable to start off with a muscular endurance program with relatively low loads and high repetitions in novice subjects. In this way, one avoids an overloading of the musculoskeletal system and has the chance to acquire the proper exercise technique by performing a larger number of repititions. In more advanced athletes, exercise variables should be adjusted according to the main training goal to guarantee optimal adaption (Table 2.4).

Whenever the training goal is to improve muscular performance opposed to maintaining the current level, a continuous progression in training variables is important to guarantee overload as performance increases.

2.5.2.1 General Training Recommendations

In general, a sound strength training program aiming to enhance health and fitness variables should comprise a multitude of different exercises targeting the major muscle groups. Protocols aiming for muscular endurance and hypertrophy are less strenuous on the body and are therefore recommended in health-orientated programs. If the athlete or the patient is familiar with the exercises performed and meets the technical recommendations, multijoint exercises should be preferred over single joint exercises. Concerning the muscle action, dynamic exercises combining concentric, eccentric, and isometric muscle actions are recommended. To prevent muscular imbalance, the opposing muscles should always be trained as well. Each repetition should be performed deliberately and in a controlled manner using a correct technique. When there are no physical restrictions, each repetition should be moved through the full range of motion of the joint. Proper breathing techniques should be used, meaning that the athlete/the patient exhales during the concentric phase and inhales during the eccentric phase to avoid an extreme peaking of the blood pressure. Advanced athletes whose primary goal is to increase strength rather than improve health can use the Valsalva maneuver on complex multijoint exercises (such as squats or deadlifts) to ensure a stable core and to prevent adverse loading on the spine.

2.5.3 Flexibility Exercise

Apart from endurance and strength exercises, flexibility exercises should be included in a healthy workout routine. The combination of insufficient muscle strength and lack of flexibility is often the cause of musculoskeletal injuries, lower back pain, and loss of functional independence especially in aging and sedentary individuals. Flexibility is referred to the ability of a joint, or series of joints, to move through a full range of motion without injury [64].

Different morphological, anatomical, and exercise-related factors affect flexibility and must be considered when developing an individual stretching program (Box 2.2).

Box 2.2 Factors Affecting Flexibility

- Age
- Sex
- Joint structure
- Muscle and connective tissue
- Level of physical activity
- Stretch tolerance
- Time of day
- Temperature

2.5.3.1 Different Forms of Stretching Exercises

Flexibility or stretching exercises are exercises that attempt to stretch/elongate specific muscle–tendon groups with the goal to improve joint range of motion. Stretching of the muscle–tendon group can either be performed actively or passively. In active stretching the stretched position is held by the strength of the contracting agonist muscle. In passive stretching a partner or a device provides the external force to cause the stretch.

Table 2.3 Assignment of exercise variables based on the training goal

Training goal	Load (% 1 RM)	Repetitions	Rest periods (s)	Muscle action
Muscular endurance	<65	>12	30–60	Slow to moderate
Muscular hypertrophy	65–90	6–12	60–90	Emphasizing eccentric action
Muscular strength	>90	<6	180–360	Fast to explosive

Abbreviations: *%RM1* percent of 1 repetition maximum, *s* seconds

There are different types of stretching exercises and techniques which are described in Table 2.5.

2.5.3.2 Effects of Stretching Exercises

Static and dynamic stretching exercises are effective in improving joint range of motion (ROM) and thus increasing the freedom of movement for everyday activities. Stretching exercises using proprioceptive neuromuscular facilitation methods may be superior to static and dynamic stretching, as they may positively influence muscle reflexes and thus muscle inhibition [65].

Self-myofascial release (SMR) has lately become a popular intervention in rehabilitation and fitness settings. Systematic reviews suggest that SMR may have positive effects on joint ROM without decreasing subsequent muscle performance [66, 67]. Furthermore, SMR has been shown to reduce the perceived pain after intense bouts of exercise and enhance recovery [67], making it a potent cooldown routine.

Regular flexibility exercises can enhance postural stability and balance [66]; furthermore, it may reduce muscle tone, may prevent muscular imbalances, and improves movement economization. Different studies could even detect positive effects of acute and regular static stretching exercises [68, 69] and after acute SMR training [70, 71] on arterial compliance, thus reducing cardiovascular risk profile.

Results assessing the acute and long-term effects of flexibility exercises on musculotendinous injuries are inconsistent [72]. No effects of stretching exercises before or after activity on delayed onset of muscle soreness have been detected [73].

Apart from the positive effects, flexibility exercises may also evoke adverse effects. Especially intensive static stretching may lead to immediate decrements in muscle strength expression [74, 75], which appears to be related to neuromuscular inhibition and decreased contractile force [76].

2.5.3.3 General Recommendations for Stretching Exercises

When applying stretching exercises, specific recommendations should be followed to guarantee optimal effects (Table 2.6). Since flexibility is highly joint specific, a stretch program should incorporate stretching all major muscle groups, as well as opposing muscle groups. Similar to endurance or resistance exercises, overload must also be applied in flexibility exercises. Thus, the muscle must be stretched beyond its normal resting length to increase range of motion. To guarantee progressive improvement, it is important to adapt exercise variables by increasing the time the stretch position is held, the number of repetitions of the exercise, and the intensity of the stretch. Stretching exercises should always precede a warm-up phase to increase the muscle temperature and elastic properties of collagen in muscles and tendons. Since intensive static stretching may have adverse effects on subsequent performance, stretching exercises routines should be performed following practice or competition.

During the stretching exercise, the muscle should be slowly elongated, and the stretch position should be held just before the point of discomfort. While holding the stretch, one should keep breathing slowly and rhythmically and avoid breath holding.

There are optimal ranges of flexibility for different sports and activities, and injury risk may be increased when an individual is unable to attain this range. It is important to note that both inflexibility and hyperflexibility can result in higher risks of injury [77]. Thereafter, the main goal of flexibility training should be to optimize flexibility in

relation to a specific activity or personal needs rather than simply maximizing flexibility [78].

2.6 Exercise During Pregnancy

Exercise during pregnancy has been discussed controversially in the past, especially as a a high volume and intensity of exercise, such as that in competitive sports, hardened the pelvic floor muscles and the birth could be more complicated. Even in early pregnancy, there are significant changes that can affect the mother's physical performance (Box 2.3).

It is therefore generally recommended to continue the physical activity during pregnancy and to reduce it successively in the second and third trimester. In addition to a pregnancy gymnastics sports with regular aerobic stress like swimming, walking or bike (ergometer) can be recommended. Swimming or water aerobics is especially recommended. The water temperature should not be below 20 °C and not above 35 °C.

Physical exertion should predominantly take place in the aerobic and submaximal range in order to avoid a larger increase in body temperature due to excessively high loads (potentially teratogenic). A performance-oriented sports or competitive sports should be avoided.

Women who are physically inactive before pregnancy but have the desire to do something for their fitness, such as aerobic exercise, should start with interval training at low intensity with 10-min intervals and breaks of 10 min between the exercises. After 2 weeks, the duration and intensity of the workout can be slowly increased to 30–45 min.

Box 2.3 Changes of the Maternal Organism During Pregnancy

- Increase in heart rate
- Increase in cardiac output
- Increased oxygen demand
- Increase in venous capacity
- Faster hypoglycemia
- Blood pressure variation
- Weight gain
- Loosening of tendons, ligaments, and joints
- Altered thermoregulation

2.7 Conclusion

Regular physical exercise that is adequately used is probably the most effective, safest, cheapest, and most easily assessable health promotion strategy. It can protect against many diseases, especially cardiovascular diseases and their risk factors.

Although endurance exercise seems most effective in eliciting health benefits, it is recommendable

Table 2.4 Recommendations for strength training for different training statuses to improve muscular performance

Training Status (training age)	Training Frequency (d•wk)	Exercises/ muscle group	Sets/ exercise	Training Intensity (%1RM)	Velocity of muscle action	Rest periods(min)	Repetitions
Beginner (3 months)	1–3	1–2	1–2	Low to moderate (60–70)	Slow to moderate	2–3	8–12
Intermediate (3–6 months)	2–4	2	2–3	Moderate (70–85)	Moderate	2–3	8–12
Advanced (>1 year)	4–7	2–4	3–6	High to very high (80–100)	Moderate to fast[a]	1–4[a]	1–12[a]

[a]Depending on training goal

Abbreviations: *d·wk* days per week, *%RM1* percent of 1 repetition maximum

to additionally incorporate strength, flexibility, and neuromuscular exercises into the training program to achieve the best possible effects. Furthermore, a growing body of literature confirms the effectiveness of higher exercise intensities on health and performance outcomes, thus underlining the importance of incorporating exercise programs like HIIT into the weekly exercise routine.

Numerous associations and national governments have established guidelines for physical activity. Although these guidelines are based on large, representative studies, they are very general in terms of differentiating between different age groups, sexes, risk patients, and individual circumstances. Furthermore, the recommendations are very broad regarding intensity and volume, providing hours per week, calories burned per week, the number of steps taken per day, and subjective rating of perceived exertion. Even if this form of exercise prescription seems very simple at first and applicable for everyday life, they are not very precise. Overloading and underloading can be the result, thus impairing the effectiveness of exercise training.

If one considers exercise as a medicine, the exercise suggestion has to be correctly defined and dosed. That does not mean following the "one size fits all" principle; rather, the intensity, duration, and frequency of the workload as well as the exercise mode must be individually determined and adjusted according to the state of fitness and health of the patient and should comply with his or her training goal, the personal circumstances, and opportunities (Box 2.3).

Therefore, it is the mission of health and fitness professionals to adapt these broad recommendations to the individual needs of their patients and to develop individually tailored programs. Furthermore, the training process has to

Table 2.5 Forms of stretching exercises

Static stretching	In static stretching a muscle–tendon group is slowly stretched and the end position is held for a certain period before it is released
Dynamic stretching	Dynamic stretching involves controlled active movements like bouncing or swinging during the stretch where the final stretch position is not held and the movements are repeated several times
PNF	PNF stretching is usually performed with a partner and involves an isometric contraction of the selected muscle–tendon group before a static stretch is performed
Self-myofascial release	Self-myofascial refers to a form of manual therapy that applies mechanical compression (often using a foam roller) to muscle and fascia to manipulate the myofascial system and improve mobility

Abbreviations: *PNF* proprioceptive neuromuscular facilitation stretching

Table 2.6 General recommendations for flexibility training

Exercise type	Static, dynamic, active, passive, PNF
Exercise duration	10–30 s
Exercise frequency	3–7 d·wk^{-1}
Exercise intensity	Mild discomfort
Exercise timing	After exercise training or during an individual session
Repetitions	2–4 times per exercise
Number of exercises	10–12
Preconditioning	When the muscular temperature is elevated through light-to-moderate exercise

Abbreviations: *PNF* proprioceptive neuromuscular facilitation stretching, *s* seconds, *d·wk.*$^{-1}$ days per week

Box 2.4 10 Rules for Healthy Sports

- Start slowly-increase slowly (start low!-go slow!)
- Adequate rest after exercise
- No sports during colds and illnesses
- Include a warm-up and cooldown in every exercise program
- Sports to adapt to climate and environment (height!)
- Pay attention to proper nutrition and sufficient amount of fluid
- Adapt sports to age and medication
- Individualize exercise program
- Sport should be fun!!!

be monitored and the program has to be adjusted whenever internal or external circumstances change. Only in this way is it possible to achieve optimal results and improve compliance.

Therefore, it would be advisable to use objective assessment methods to monitor exercise intensity and volume. In this concern, the deployment of wearables seems to be a good approach. Not only can exercise programs and performance progress be analyzed retrospectively, but they are also suitable for prospective stress control during physical activity (Box 2.4).

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3 Molecular Mechanisms Mediating Adaptation to Exercise

Zahra Gholamnezhad, Bruno Mégarbane, and Ramin Rezaee

Abstract

Several experimental and human studies documented the preventive and therapeutic effects of exercise on the normal physiological function of different body systems during aging as well as various diseases. Recent studies using cellular and molecular (biochemical, proteomics, and genomics) techniques indicated that exercise modifies intracellular and extracellular signaling and pathways. In addition, in vivo or in vitro experiments, particularly, using knockout and transgenic animals, helped to mimic physiological conditions during and after exercise. According to the findings of these studies, some important signaling pathways modulated by exercise are Ca^{2+}-dependent calcineurin/activated nuclear factor of activated T-cells, mammalian target of rapamycin, myostatin/Smad, and AMP-activated protein kinase regulation of peroxisome proliferator-activated receptor-gamma coactivator 1-alpha. Such modulations contribute to cell adaptation and remodeling of muscle fiber type in response to exercise. Despite great improvement in this field, there are still several unanswered questions as well as unfixed issues concerning clinical trials' biases and limitations. Nevertheless, designing multicenter standard clinical trials while considering individual variability and the exercise modality and duration will improve the perspective we have on the mechanisms mediating adaptation to exercise and final outcomes.

Keywords

Exercise · Physical activity · Molecular mechanism · Signal transduction · Molecular adaptation

3.1 Background

Several animal and human experiments (both in vivo and in vitro) as well as clinical evidence documented the beneficial effects of exercise and physical activity on disease prevention or rehabilitation. In addition, exercise and physical trainings are necessary to maintain normal physiological function of musculoskeletal, cardiovascular, nervous, endocrine, and respiratory

Z. Gholamnezhad (✉)
Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

Department of Physiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
e-mail: gholamnezhadz@mums.ac.ir

B. Mégarbane
Department of Medical and Toxicological Critical Care, Paris-Diderot University, Paris, France

R. Rezaee
Clinical Research Unit, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_3

systems in geriatrics, and influence the aging process [1]. During recent decades, various investigations described the biological adaptation and revealed modification of intra- and inter-organ communications after physical activity and training. Human studies indicated that these adaptational changes in biological system may differ based on physical/training activity type, severity, duration of each session, and acute or chronic nature as well as sex, age, disease state, genetics of the one who undertakes the practice, and environmental epigenetic factors (i.e., lifestyle, nutritional condition, and physical fitness) [2].

Exercise induces several physiological adaptive processes by modulating cellular and molecular regulatory mechanisms. Modification of molecular pathways including intracellular and extracellular signaling may be attributed to alteration of gene/protein expressions leading to cellular/tissue phenotypic changes. In addition, the role of immune and satellite cells in muscle regeneration and restoration as well as hereditary genetic differences are the most important factors affecting exercise-induced physiological adaptive processes.

Cellular and molecular investigation of exercise physiology started in 1962 by the examination of human skeletal muscle biopsies. Advances in proteomics, genomics, and bioinformatics investigations helped to reveal some cellular and molecular aspects of adaptations to exercise. Evaluation of the skeletal muscle gene expression using computational approaches resulted in identifying about 300 secretory proteins involved in cell signal transduction pathways [3]. Another study showed that 6-week endurance exercise affected the expression of about 800 human muscle genes, out of which 100 genes were related to greater aerobic exercise-induced molecular adaptation. Also, in training-responsive transcriptome, there were three overrepresented DNA sequence representing *PAX3*, *RUNX1*, and *SOX9* transcription factor binding sites, while miRNA targeting these genes were downregulated after aerobic exercise [4]. Moreover, different experimental diseases and knockout (KO) and transgenic animal models were employed to determine exercise-mediated signal transduction modifications.

Exercise-induced molecular adaptation resulted in supra-molecular changes in biological systems which are summarized in Fig. 3.1.

3.2 Skeletal Muscle Adaptations

Since locomotor system has a key role in movement and escape reaction, its status and function are important for human body hemostasis and survival. Although several organs take part in physical activity, muscles are key elements in motor performance and related adaptive responses. Muscle is the main target of exercise-induced mechanical, oxidative, and metabolic stress. Moreover, physical training induces homeostasis disturbance by enhancement of muscle energy storage consumption and increment of cell energy turnover [3]. In muscles, mitochondrial (and other organelles') production of nitrogen and oxygen species, as main intracellular messengers, and norepinephrine, epinephrine, growth hormone, cytokines, cortisol, and calcium, as main extracellular messengers, was shown to activate signaling pathways and compensatory mechanisms mediating adaptation [5, 6]. These messengers alter the biological action of cytoplasmic proteins and enzymes, membrane ion channels and receptors which consequently results in activation or inactivation of signal transduction pathways by phosphorylation or dephosphorylation of the related enzymes and proteins. Cellular and molecular investigations started from 1985 explained some effectors involved in these signaling network and adaptational response. The main proposed signaling pathways in muscles are Ca^{2+}-dependent calcineurin/activated nuclear factor of activated T-cells (NFAT) pathway, mammalian target of rapamycin (mTOR), myostatin/Smad, and AMP-activated protein kinase (AMPK) regulation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-α). The cross talk among these pathways was shown to modulate muscle adaptation and cause muscle fiber type remodeling in response to exercise.

During the last decade, transcriptomics, as an approach to examine RNA molecules changes in one or a group of cells, was employed to study

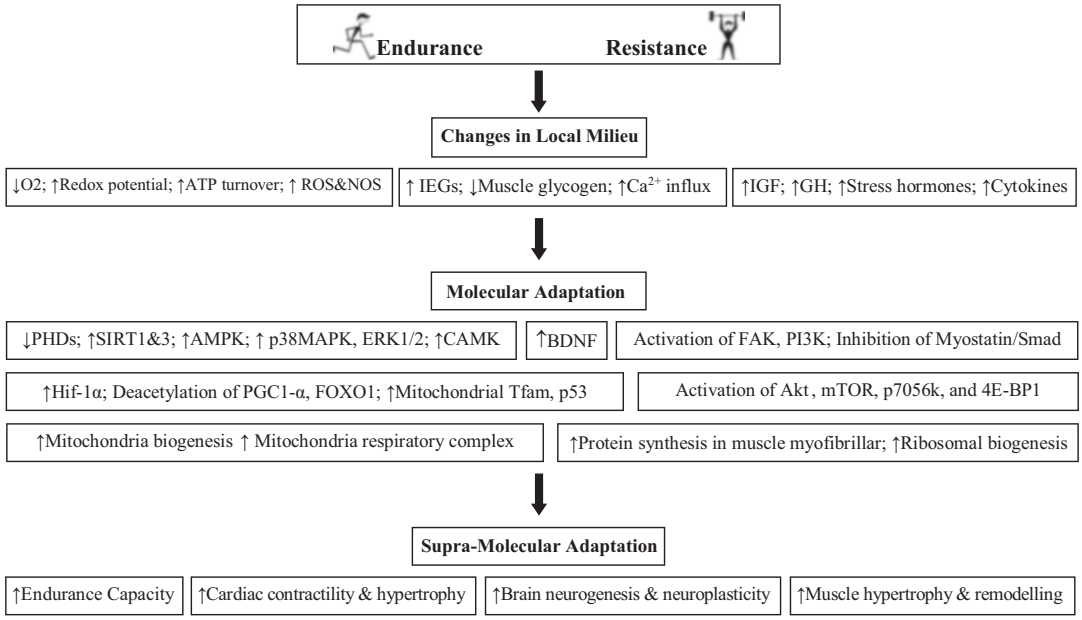

Fig. 3.1 Exercise-induced molecular adaptation resulted in supra-molecular changes in biological systems

the physiological adaptation of human muscle to acute or chronic exercise [7].

3.2.1 Exercise-Induced Signal Transduction Pathways

3.2.1.1 Ca^{2+}-Dependent Calcineurin/Activated NFAT Pathway

Elevation of intracellular Ca^{2+} concentration was demonstrated to result in muscle contraction and activation of calmodulin calcineurin/NFAT signal transduction which mediates transformation of muscle fiber type fast to slow. In adult skeletal muscle, this signaling pathway is necessary for maintenance of slow fibers. Phosphatase calcineurin regulates five transcription factors (NFATc1–4 and NFAT5) belonging to NFAT family proteins [8]. In adult muscle, the main NFAT isoform is NFATc1 [9]. Using NFATc1-null mice, the effect of exercise on muscle fiber remodeling was examined and the role of NFATc1 as a transcription factor that induces transformation of fast fiber to slow ones was indicated. In addition, it was demonstrated that NFATc1 might interact with the activation domain of MyoD which leads to blockage of the essential transcriptional coactivator p300 recruitment and inhibition of promoters of the MyoD-dependent fast fiber gene [10].

Ca^{2+} release from ryanodine receptor is required for normal muscle contraction during physical activity. Conformation of ryanodine receptor to leaky channels by protein kinase A (PKA) hyperphosphorylation, S-nitrosylation, and depletion of the phosphodiesterase (PDE4D3) and the ryanodine receptor stabilizing subunit calstabin 1 (FKBP12) would impair Ca^{2+} signaling and force generation, and decrease exercise capacity. It was shown that S107 (a small molecule) improved exercise capacity by prevention of depletion of calstabin 1 from the RyR1 complex, and reduction of plasma levels of creatine kinase and calpain (Ca^{2+}-dependent neutral protease) activity [11].

3.2.1.2 AMPK/PGC1-α Pathway

AMP-activated protein kinase (AMPK) is a key regulator of muscle metabolism and energy turnover. It regulates PGC-1α modification which in turn activates transcription factors involved in mitochondria biogenesis [12]. It was indicated that AMPK activation increases the *PGC-1α* gene expression and directly induces phosphorylation

of PGC1-α [13]. PGC-1α is a transcription coacttivator which activates nuclear respiratory factor (NRF) 1 and 2 that resulted in mitochondrial transcription factor A (mtTFA). It was demonstrated that transcription and replication of mitochondrial DNA are regulated by mtTFA [14]. Several studies showed impairment of training performance after knockout mutation in *PGC1-α* gene, and regulation of the expression of genes related to glucose and lipid metabolism by AMPK-activated sirtuin 1 (SIRT1)-induced PGC1-α deacetylation, revealing the regulatory role of PGC1-α [15]. Moreover, exercise-mediated decrease in acetyltransferase GCN5 (general control non-derepressible 5) may increase PGC1-α deacetylation and activity [16].

3.2.1.3 IGF-1/Akt/mTOR/p70s6K Pathway

Increases in muscle mass and protein synthesis were shown to be regulated by mammalian/mechanistic target of rapamycin (mTOR) [17]. IGF-1 induces mTOR activity and increases muscle growth through phosphatidylinositol 3-kinase (PI3K)/Akt pathway [18]. mTOR regulated initiation of the downstream substrates translation including p70s6K (ribosomal protein s6 p70 kinase) and translation elongation protein 4E-BP1 (eukaryotic initiation factor 4E-binding protein1). Since mTOR has a large molecular size, post-exercise evaluation of this protein by western blotting is difficult. Therefore, in human studies, phosphorylation of its downstream substrates was evaluated. In KO mice with mutated mTOR, the significance of this pathway in exercise-induced muscle growth was approved.

In resting muscle, mammalian target of rapamycin complex 1 (mTORC1) was indicated as a key regulator of mitochondrial protein expression. PGC1-α, the transcription factor Yin Yang 1, mTOR, and raptor are mTORC1 components in this regulation.

An in vitro study investigated this mechanism in chronic contractile activity (CCA) and rest. The effect of CCA on the response of myotubes of murine skeletal muscle cell culture was examined in the absence/presence of rapamycin (as an mTORC1 inhibitor). CCA increased cytochrome oxidase (COX) IV, COX, and mitochondrial transcription factor A (Tfam) activity, but rapamycin did not suppress these effects. Rapamycin alone decreased organelle state 3 respiration, while it increased COX IV and Tfam mitochondrial content. The authors of the study suggested that mTORC1 activity is necessary for mitochondrial function in resting conditions; however, it is not an integral factor for CCA-induced elevation of mitochondrial content [19].

3.2.1.4 Myostatin/Smad Pathway

Skeletal muscle disuse and mechanical unloading would result in muscle loss and atrophy.

Cachexia (muscle atrophy) is one the complications of disabling diseases like cancer, heart failure, renal failure, chronic obstructive pulmonary disease, and AIDS. Inadequate cytokine and inflammatory responses as well as muscle disuse would induce and initiate signaling pathways including myostatin/Smad, IGF1-Akt-mTOR, E3 ligases of the ubiquitin proteasome, and Atrogin-1/MAFbx and MuRF1 which mediate skeletal muscle protein adaptation to disuse and inflammation [20]. Myostatin (growth differentiation factor 8) belongs to transforming growth factor (TGF)β superfamily and is a ligand for activin receptors which regulate downstream Smad proteins [21]. It was shown that inhibition of Smads transcriptional activity would result in muscle hypertrophy [22].

Short and long lived skeletal muscle protein degradation is carried out through ubiquitin-proteasome pathway including E1, E2, and E3 ligases. Muscle Atrophy F-box (MAFbx/atrogin-1) and Muscle-specific RING Finger protein1 (MuRF1) are two main muscle E3 ligases that are controlled by Forkhead box O (FOXO) of transcription factors. Under normal conditions, activation of IGF-1-PI3K-Akt-mTOR pathway leads to Akt inhibition of FOXO which induces muscle growth and suppression of muscle atrophy [18, 20].

It was indicated that carbohydrate intake during aerobic physical activity inhibits the expression of proteolytic genes by skeletal muscle microRNA regulatory action on PI3K-Akt-FOXO1 pathway [23].

3.2.2 Exercise-Induced Adaptation in Muscle Fiber Type

In the skeletal muscle of adult human, slow and fast fiber types and their isoforms type including I/β (for slow fibers), and IIa, IId/x, and IIb (for fast fibers) were identified. The physiologic (morphological, biochemical, and functional) characteristics of these isoforms including fiber-specific gene expression patterns, strength, contraction speed, and fatigability are different [24, 25]. Aging, exercise, and pathological conditions were shown to modify transcription factors related to the muscle fiber isoform. Gene expression modifications which lead to muscle plasticity were not fully elucidated [26].

Estrogen-related receptor gamma (ERR-gamma) is a nuclear receptor that acts as constitutive transcriptional activator. The role of this receptor in modification of fiber type and oxidative metabolism was indicated in transgenic mice of muscle-specific VP16 ERR-gamma model. The results showed that exercise induced muscle type conversion and increased oxidative capacity (i.e., enhanced mitochondrial biogenesis and enzymatic activity) in this model. Nevertheless, exercise capacity and mitochondrial activity were decreased in mice missing one copy of ERR-gamma. In addition, muscle gene expression profile was shifted toward oxidative fiber (red) type muscle following ERR-gamma elevation. A small molecule agonist for ERR-beta/gamma produced a stimulatory effect on mouse myotubes' mitochondrial activity. The authors of the study concluded that ERR-gamma activation could have therapeutic effects on metabolic diseases with impaired oxidative metabolism and lower content of red type muscle fiber [27].

3.2.3 Exercise-Induced Metabolic Adaptation of Skeletal Muscle

Skeletal muscles are known as a key metabolic organ. In resting adults, 30% of basal metabolic rate is attributed to skeletal muscles [28]. When stimulated by insulin, skeletal muscles markedly contribute to glucose deposition and become the main organ for glycogen storage. Moreover, physical activity induces insulin-independent muscle glucose uptake. Therefore, skeletal muscles play critical roles in metabolic homeostasis, glycemic control, and prevention and management of metabolic disease. Because of these metabolic roles and the fact that skeletal muscle is the main organ affected by exercise training, human muscle biopsy was used to reveal molecular physiology of exercise. A main impact of exercise on skeletal muscle biochemistry and metabolic function is mediated through modification of mitochondrial biogenesis and function. It was well documented that exercise training induces mitochondrial remodeling (in terms of functional and molecular aspects) of skeletal muscles. Physical activity might result in two-fold increase in mitochondrial density and oxidative phosphorylation capacity [29].

One of the contributors to exercise-induced metabolic changes in muscles is the increase in fatty acid (FA) delivery and oxidation. It is well known that PPARδ [30], PGC-1α [31] and ERR-gamma [27] are involved in exercise-induced FA oxidation. It was thought that FA may enter the cell by simple diffusion and induce changes in biological machinery, mitochondrial enzymes and biogenesis [32]. However, recent findings showed that the fatty acid transporter CD36 might be a key regulator of FA membrane transport that modulates fatty acid oxidation in resting and active conditions [33].

3.2.3.1 Endurance Exercise Adaptation

The beneficial effects of aerobic endurance exercise on enhancement of cell oxidative capacity were shown to be mediated through enhancement of mitochondrial oxidative enzymes content [34] and cellular insulin sensitivity in geriatrics [35].

It was demonstrated that exercise could improve obesity and insulin resistance induced by cafeteria (low fat) diet. Swimming exercise ameliorated cafeteria-diet-induced decrease in insulin-stimulated glucose transport in red gastrocnemius muscle of the perfused hind limb of rats [36].

3.2.3.2 Resistance Exercise Adaptation

Chronic resistance exercise enhances mitochondrial respiration capacity of skeletal muscle both

quantitatively and qualitatively by modest increases in the mitochondrial gene expression and proteins content in young adults [37]. Resistance exercise also ameliorates age-induced skeletal muscle loss by restoration of the decline in synthesis rates of proteins and transcription of myosin heavy-chain gene of muscle [38].

Implementing resistance exercise upregulates the IGF-1-PI3-Akt-mTOR pathway gene expression in the muscle which increases the synthesis of muscle proteins and muscle mass [20]. Exercise and muscle loading increase both autocrine and endocrine IGF-1 levels [39].

Degradation pathways are essential for maintenance of skeletal muscles. Chaperone-assisted selective autophagy (CASA) is one of these pathways, and it increases after the muscle undergoes tension. After acute bout of strenuous resistance exercise, CASA induction was found to act as an adaptation mechanism for degradation of damaged proteins of muscle cytoskeleton. In addition, repeating resistance exercise bouts for 4 weeks increased the expression of CASA components [40].

3.2.3.3 Combined Exercise Adaptation

Combined exercise protocols of training such as high-intensity interval training (HIIT) or sprint interval training (SIT) were also demonstrated to possess the advantages of both endurance (aerobic) and resistance exercise, despite the fact that the intensity of resistance and endurance components of combined exercises is lower than that of each individual training [41]. In young healthy men and women, the effect of 6-week SIT was compared to that of endurance training. The results showed comparable improvement in muscle markers of oxidative capacity and mitochondrial enzymes, including pyruvate dehydrogenase E1alpha protein content, 3-hydroxyacyl CoA dehydrogenase maximal activity, and PGC-1α, after both types of training. In addition, after training, muscle consumption of phosphocreatine and glycogen decreased, while the rate of whole body lipid oxidation increased [42]. However, the intensity of training is an important determining factor of adaptation process as it was indicated that low-intensity training may restrict the mitochondrial response [43].

It was well documented that HIIT elevates the levels of proteins related to lactate transport, glycolysis, and glycogenesis which consequently lead to increment of muscle glycolytic capacity. Hypoxia-inducible factor-1 (Hif-1)α is one of the major regulators of expression of proteins that contribute to anaerobic metabolism. Six-week HIIT was shown to increase the glycolytic capacity in gastrocnemius muscles. The authors of the study concluded that Hif-1α acts as a main regulator of muscle metabolic adaptation after HIIT [44].

The evaluation the effect of 12 weeks of HIIT exercise in young adults indicated that increases in VO_2 peak and citrate synthase enzyme activity in the muscle were comparable to those induced by lower-intensity training following longer duration [45].

Transcriptional coactivators and corepressors are important elements in mitochondrial biogenesis modulation in skeletal muscles. Three weeks of high-intensity interval training in human volunteers decreased the levels of p107 protein which has a reciprocal correlation with mitochondrial oxidative phosphorylation [46].

The effect of intense intermittent cycle training on signaling pathways related to mitochondrial biogenesis was evaluated before and after (immediately and after 3-h recovery) collecting vastus lateralis biopsies from healthy subjects. Exercise induced immediate increases in phosphorylation of p38 mitogen-activated protein kinase (MAPK) and AMPK (α1 and α2 subunits) and later (after 3 h of recovery) elevation of PGC-1α mRNA. However, the level of PGC-1α protein was not changed. While the protein kinase B/Akt (Thr-308 and Ser-473) phosphorylation was decreased, results showed no changes in hypertrophy-related downstream targets (p70 ribosomal S6 kinase and 4E binding protein 1). These findings approved the role of AMPK and p38 MAPK in PGC-1α regulation in low-volume intense interval exercise-induced mitochondrial changes for effective metabolic remodeling and fatty acid/glucose oxidation [47].

The adaptive muscle response (i.e., mitochondrial capacity) to an acute bout of HIT was

evaluated in vastus lateralis muscle biopsies of healthy subjects. Samples were obtained before and after (immediately and after 3- and 24-hour recovery) exercise. In resting condition, PGC-1α was detected in cell lysate. AMPK and p38 MAPK were activated by training, and the expression of mitochondrial genes' mRNA and nuclear PGC-1α protein was increased. Moreover, 24 h after exercise, mitochondrial changes including increases in enzymatic activity and protein content were detected which reflect the key role of PGC-1α in muscle adaptation to HIT [48].

Analyzing the biopsies of skeletal muscle collected from untrained healthy males before and after a single bout of high-intensity exercise showed training-induced alterations in protein phosphorylation. Results showed 1004 unique phosphosites on 562 proteins that were regulated by exercise training. Among them, there were substrates of known kinases (i.e., mTOR, MAPK, PKA, AMPK, and calmodulin-dependent protein kinase (CaMK)), though most of them were unknown elements of exercise signaling. Moreover, AMPK-dependent A-Kinase Anchoring Protein 1 (AKAP1) phosphorylation showed to have an important role in exercise-induced mitochondrial alterations [49].

Miyamoto-Mikami et al. studied changes in skeletal muscle gene expression in young men after 6-week high-intensity intermittent exercise training. Induction of mitochondrial biogenesis after HIIT exercise could be attributed to changes in gene expression which was consistent with previous reports. Gene ontology analysis showed upregulation of exercise-related genes including *CARNS1*, *FGF6*, *MYLK4*, *PGK1*, *PPP1R3C*, and *SGK1*, as well as encoded protein genes *CARNS1*, *MYLK4*, *PPP1R3C*, and *SGK1* [50]. After HIIT exercise, signaling pathways related to mitochondrial biogenesis (such as PPARγ Coactivator 1 Alpha protein as a signaling molecule) [47, 48, 50] and mitochondrial enzymes (e.g., citrate synthase) were activated [42, 48, 50, 51].

3.2.3.4 Comparison of the Effects of Exercise Modalities on Adaptation

Exercise-induced mitochondrial and metabolic changes were shown to be affected by type (endurance and resistance), intensity, and duration of training bouts. Resistance training modulates myogenesis and ratio of muscle protein synthesis to degradation, while endurance training improves angiogenesis, biogenesis of mitochondria, and metabolism of fatty acid metabolism. Moreover, it was demonstrated that HIIT would lead to a combination of endurance and resistance training effects. So HIIT results indicated improved oxidative and glycolytic capacity, mitochondrial enzyme activities, intramuscular triglyceride and glycogen storage levels, and angiogenesis.

However, more investigation should be undertaken to reveal different adaptation changes induced by various types of training. Wang et al. investigated the influence of endurance and resistance exercise on mitochondrial components and their related signal transductions. In a randomized crossover study, healthy individuals trained only under endurance exercise program or endurance training followed by resistance training (ER) and the expression levels of mRNA of related mitochondrial genes were evaluated in muscle biopsies which sampled pre- and post-(1- and 3-h post-cycling) exercise training. The results showed elevation in mRNA of pyruvate dehydrogenase kinase-4, PGC-1α, and PGC-1-related coactivator (PRC) after both endurance and endurance plus resistance training; however, the mRNA expression levels of such genes were higher in ER (endurance + resistance) group. In addition, synthesis of ribosomal S6 kinase 1, eukaryotic elongation factor 2, and mTOR increased in post-training samples of the ER group. Moreover, the expression of genes related to mTOR signaling (i.e., cMyc and Rheb) increased after ER exercise. Additionally, 1-h post-cycling samples obtained from both endurance exercise and RT groups showed increased levels of acetyl-CoA carboxylase, AMP-activated protein kinase, and Akt protein phosphorylation. These findings approved the beneficial effects of combined endurance and resistance training on

mTOR-mediated mitochondrial biogenesis and adaptive increase with respect to oxidative capacity [52].

In Robinson et al.'s study, effects of different exercise modalities on old and young participants were investigated. It was postulated that aging-induced reduction of mitochondrial content is correlated with a decline in cardiorespiratory fitness in the elderly [53]. In addition, impaired mitochondrial ATP production in resting condition may facilitate progression of age-induced insulin resistance [54]. In this study, the correlation between insulin-resistant states and reduced mitochondrial oxidative capacity of skeletal muscle, and the role of exercise was examined in young and old subjects in resting and fasting conditions. At the beginning of the study, mitochondrial respiration of old subjects was lower compared to young individuals. Maximal mitochondrial oxygen consumption of both old and young individuals was increased after 12 weeks of HIIT training. However, this marker increased only in young subjects after combined training (CT), but resistance training (RT) had no effect on it in both groups. There were no differences in mitochondria intrinsic markers (reactive oxygen species (ROS) production, and coupling efficiency) between the two groups after HIIT, RT, and CT programs. Decrement of mitochondrial respiratory capacity in aged individuals might be due to alterations in mitochondrial protein levels which could be improved by physical training. The number of normalized mtDNA copy in old subjects was lower than young participants, and HIIT and RT significantly improved mtDNA; however, the increasing effect of CT on mtDNA was nonsignificant. HIIT was shown to combat age-induced downregulation of the expression of genes related to insulin signaling, mitochondrial function, and muscle hypertrophy. Among different exercise regimes, HIIT had better impacts on these signaling pathways, and the effects of HIIT were more marked in old individuals compared to young people. In old adults, after HIIT, the expression of 22 genes such as those related to regulation of translation (ribosomal MT-RNR1 and 2) and mitochondrial tRNA transferase for leucine (*MT-TL1*), valine (*MT-TV*), glycine (*MT-TG*), methionine (*MT-TG*), and arginine (*MT-TR*) was increased. The impact of RT and CT on gene expression was less than that of HIIT. These findings indicated that exercise's beneficial effects are associated with the type (or modality) of training as well as genetic and epigenetic factors. Taken together, in both old and young subjects, HIIT improved aerobic capacity markers (mitochondrial respiration and insulin sensitivity) but had no significant effect on anaerobic capacity. RT and CT exercise had a remarkable impact on muscle mass and strength elevation in both age groups, and it also enhanced performance and muscle metabolic storage by increasing non-oxidative glucose disposition index [2].

HIF-1 is a key factor in modulation of cell response to hypoxia and causes its effects via increasing the expression of genes regulated to oxygen delivery or glucose metabolism. Therefore, HIF-1 significantly contributes to adaptation to exercise-induced hypoxia. However, there is not enough evidence on changes in HIF-1 and its target genes after chronic exercise training. In addition, acute exercise-induced elevation in HIF-1 may be suppressed following long-term training. The negative regulatory effects of chronic exercise on HIF-1 might have beneficial impacts on muscle metabolism. HIF-1 inactivates pyruvate dehydrogenase complex by increasing pyruvate dehydrogenase kinase 1 and reducing the flux of pyruvate into the mitochondria resulting in endurance performance decline. Therefore, deletion of HIF-1 might lead to better training adaptation in muscles [55]. An epigenetic corepressor of HIF-1 is sirtuin 6 (SIRT6) which is a histone-3 lysine-9 deacetylase that could improve mitochondrial activity by targeting the glycolytic genes [56]. Based on such knowledge, the effect of long-term training on negative regulation of HIF-1 and related mechanisms were studied in two human investigations; a longitudinal before/after study on the effects of six-week training in individuals and a cross-sectional study on elite athletes and moderately trained subjects. The results showed a remarkable elevation of muscle HIF suppressors in elite athletes following endurance training protocols. The authors suggested that lower phosphoinositide-dependent protein

kinase-1 level in those athletes is a consequence of high activity of prolyl hydroxylase domain-containing protein 2, as its expression is probably regulated by its tricarboxylic acid cycle substrate, hypoxia, and HIF-1. In addition, the levels of HIF transcriptional factors inhibitors including factor-inhibiting HIF (FIH) and SIRT6 were increased in elite athletes [55]. It was shown that a single bout of running in sedentary individuals induced five-fold increase in p300/CBC which is a coactivator of HIF but decreased SIRT6 as an HIF inhibitor. However, in trained individuals, p300/CBC decreased, approving the hypothesis of HIF negative regulation in chronic exercise [57]. Therefore, the early phase of muscle adaptation to exercise might be quite different from the late phase. In early phase, HIF activation is necessary for elevation of vascular endothelial growth factor (VEGF) level and angiogenesis in muscle [58]. It seems that increases in the number of muscle capillaries occur before mitochondrial enzymatic changes and in muscles oxidative capacity increases supported by upregulation of pyruvate dehydrogenase complex activity in elite subjects [59].

3.3 Cardiovascular Adaptations

Cardiovascular benefits of exercise training and physical activity were emphasized in the literature, but molecular mechanisms and signal transduction related to those effects are poorly elaborated [60]. The effect of exercise on different human physiological systems and even within each system (e.g., cardiovascular system) may vary based on exercise modality (e.g., endurance vs resistance), training intensity, and duration and repetition of bouts [3]. The studies discussed below showed the therapeutic and preventive effects of different exercise modalities on cardiovascular diseases.

Pacemaker activity of SA (sinoatrial) node is mediated by f-channels (hyperpolarization-activated, nonselective cation current) which are regulated by cAMP. The findings of a study using mutant mice with hyperpolarization-activated cyclic nucleotide-activated (HCN) isoform channel (hHCN4-573X) showed that cAMP regulation is responsible for the determination of basal and maximal heart rate, and during exercise, other factors may have affect heart rate [61]. In addition, sympathetic stimulation by exercise would increase heart contractility by activation of beta-adrenergic receptors and protein kinase A. It was demonstrated that PKA phosphorylates the cardiomyocyte ryanodine receptor (RyR2) at Ser2808, resulting in more marked Ca^{2+} influx and contraction [62]. It was also demonstrated that chronic exercise could change isoforms of myosin light chain 1 subunit which may lead to alteration of molecular pathways of cardiac myocytes' contractile response. These findings showed that exercise produced force–length relationship changes, increased myocytes sensitivity to Ca^{2+}activation, and increased cardiac power output [63].

The effect of exercise on cardiac myocyte autophagic process was evaluated. The levels of autophagy-related proteins and microtubule-associated protein 1 light chain 3 (LC3)-II expression (autophagy indicator) were examined in left ventricle of control and single-bout-exercised rats. Samples were obtained immediately and 0.5, 1, and 3 h after a 30-min running exercise. In exercise group, there was a time-dependent change in LC3-II as it decreased immediately, increased 1 h after exercise, and returned to rest levels 3 h after exercise. Phosphorylation of AMPK alpha was increased immediately after exercise. In addition, exercise-induced changes in the mTOR phosphorylation (as an autophagy inhibitor) were opposite to LC3-II expression alterations. These findings showed a role for mTOR-mediated pathway in cardiac muscle autophagy changes after training exercise [64]. Myocardial mitochondrial function has a key role in regulation of cellular death and supplying energy. Pathological conditions such as ischemia may induce fragmentation and fission of cardiomyocyte mitochondria which results in mitophagy and cellular death. This hypothesis was questioned by recent investigations showing that suppression of mitochondrial fission may cause cardiac dysfunction. The adaptive role of mitochondrial fission and fragmentation in maintenance of cardiac optimal function during exercise was indicated. It was shown that

beta1-adrenergic receptor-mediated physiological mitochondrial fragmentation during submaximal training may improve mitochondrial function. In this type of fragmentation, dynamin-related protein 1 is also activated, but downregulation of mitophagy and maintenance of membrane potential by exercise, induce regulatory mechanisms which maintain normal mitochondrial function and cover energy demand [65]. The effects of ginsenoside Rg3 supplementation and aerobic exercise on mitochondrial function were investigated in rat cardiac muscle. In both groups (one received ginsenoside Rg3 and the other underwent aerobic exercise), cardiac muscle protein levels of PGC-1α and nuclear factor-E2-related factor 2 (Nrf2) were increased. PGC-1α activation resulted in elevation of Nrf1 expression and Tfam mRNA levels which led to increases in mitochondrial DNA and enhanced levels of proteins including quinone oxidoreductase 1 (NQO1), superoxide dismutase, catalase, and nicotinamide adenine dinucleotide phosphate. Exercise, similar to ginsenoside Rg3, increased expression of autophagy-related protein 7 (ATG7) and beclin1 as well as conversion of LC3-I to LC3-II. Therefore, both exercise and ginsenoside Rg3 could improve mitochondrial function and remodeling [66].

It was well documented that exercise-induced cardiac hypertrophy due to adaptive physiological changes may lead to higher power output and lower heart fibrosis. The key role of heat shock proteins and their related gene (heat shock transcription factor 1) in this process was indicated. Therefore, some of the protective effects of exercise against cardiovascular diseases might be mediated via increased expression of heat shock transcription factor 1 and synthesis of heat shock proteins [67].

Calcitonin gene-related peptide (CGRP) might act as a vasodilator agent and decrease the infarct size during cardiac ischemia. The effect of single-bout exhausting exercise and chronic aerobic training (8 weeks of swimming) on CGRP mRNA expression in rat cardiac muscle and aortic arch was evaluated. Single-bout exercise had no significant effect on this gene, while chronic exercise increased the expression of CGRP mRNA in cardiac muscle but had no adaptive impact on aorta [68].

Exercise beneficial effects in coronary heart disease patients were shown to be mediated by increased phosphorylation of endothelial NO synthase (eNOS) via protein kinase Akt pathway. However, in normal mice, this pathway might not act effectively. In this regard, it was indicated that the expressions of platelet endothelial cell adhesion molecule-1, phosphorylated eNOS at Ser1177, protein kinase Akt, phosphorylated Akt at ser473, and eNOS proteins, were not altered after 24 weeks of exercise in healthy mice [60]. The role of NOS1 in exercise-mediated beneficial effect on myocardial contractility was evaluated in mice after 8-week aerobic interval training. In trained mice, cardiac hypertrophy index, VO_2 max, level of NOS1 expression, and nitric oxide content were higher than the control animals. The effect of NOS1 on contractility might be mediated through increment of Ca^{2+} cycling and phosphorylation of phospholamban in cardiac myocytes [69].

One of the common complications of allogeneic hematopoietic stem cell transplantation is post-operative chronic graft-versus-host disease (cGVHD) which leads to morbidity and disability. The beneficial effects of 11 weeks of moderate exercise on cGVHD mice were indicated. In trained animals, cardiomyocyte markers of autophagy including Atg12, phospho-ULK1 (S555), SQSTM1/p62, and LC3BII were increased. Moreover, myocardial glutathione reductase, catalase, and alpha-tubulin contents were higher in exercise group compared to sham group. These results showed that exercise protects against debilitating cardiac disease [70].

The protecting effects of 5 weeks of moderate exercise on cardiomyopathy induced by obesity-associated type-2 diabetes (db/db) were demonstrated. Results of in vivo experiment showed improvement of ejection fraction and fractional shortening in exercised group. In isolated cardiomyocytes of exercise group, velocity of contraction and maximum contraction were increased. In addition, connexin 43 levels and markers of mitochondrial function including mitochondrial biogenesis regulators (Mfn2/Drp-1 levels),

mitochondrial trans-membrane potential and cytochrome c leakage were improved in exercised db/db mice. These finding showed the beneficial effects of moderate exercise on diabetes-induced cardiomyopathy [71].

Cachexia is one of disabling complications of cancer which is characterized by muscle and adipose tissue loss, fatigue and suppressed cardiac function. The molecular mechanism mediating decrease in myocardial function of left ventricular mass and the role of exercise were investigated in a tumor-bearing animal model. Exercise could prevent or modulate inflammatory and oxidative signaling pathways which were activated by inflammatory cytokines and ROS [72]. It was indicated that although exercise could not prevent cancer-induced remodeling in the heart, disorganization of myofibers, interstitial fibrosis, and cardiomyocyte enlargement decreased in trained animal [73].

3.4 Adaptations Observed in Other Physiological Systems

Most of investigations documented the metabolic and biochemical effects of exercise in skeletal muscle, heart, vascular, liver, adipose, endocrine, and brain tissues; however, few studies were done using other tissues such as kidney, lung, pancreas, colon, and immune.

3.4.1 Central Nervous System Adaptations

Neuroendocrine and immune system have direct and indirect critical roles in exercise-induced adaptation response. The central nervous system coordinates neuroendocrine signaling for cardiovascular, respiratory, and metabolic responses to exercise and controls the quality of exercise (initiation, intensity, duration, and termination) [74]. In different models of memory deficit and cognitive disorders, the neuromodulatory effects of exercise on brain molecular pathways were demonstrated. These beneficial effects are increases in immediate-early gene c-Fos expression in dentate gyrus; enhanced Wnt3 expression; suppressed glycogen synthase kinase 3 expression; increased numbers of bromodeoxyuridine-positive and doublecortin (DCX)-positive cells; increased levels of astrocytes glial fibrillary acidic protein and decreased levels of S100B protein, enhanced BBB integrity; prevention of oxidative stress injury, induction of morphological changes in astrocytes of the stratum radiatum of CA1 area; increased cell proliferation and suppressed apoptosis in dentate gyrus; increased levels of brain-derived neurotrophic factor (BDNF) and tropomyosin receptor kinase B (TrkB) expressions; and enhanced levels of glycogen and normalized expression of monocarboxylate transporter 2 [75].

3.4.2 Nervous System and Skeletal Muscle Cross Talk

Despite the growing evidence on the ameliorating effect of exercise on cognitive, neurodegenerative, and chronic inflammatory disease, the nature of neuroendocrine, immune, and metabolic system cross talk during exercise is not yet fully elucidated. During muscle contraction, myocytes release cytokine and myokines which exert autocrine, paracrine, and endocrine effects in muscle and remote tissues including liver, adipose and brain tissue [76]. Exercise increases serum concentrations of metabolism products including pyruvate, lactate, glycerol, beta-hydroxybutyrate (BOHB), and amino acids (glutamine and alanine) [77]. It was shown that exercise increases the expression of monocarboxylate transporters (MCT 1, 2 and 4) in rat hippocampus and cortex. MCTs transport lactate and BOHB across the blood–brain barrier (BBB). These molecules act as signaling mediators through binding to hydroxycarboxylic acid receptor (HCARs) [78, 79] and improving memory, calcium signaling, neural activity, axonal myelination, and angiogenesis in the brain [80]. BOHB was indicated to decrease binding of histone deacetylase (HDAC 2 and 3) to BDNF promoters which increase hippocampal BDNF level and glutamate release [79].

Lactate receptor, HCAR1, mediates VEGF-A expression and angiogenesis by activating ERK1/2 and PI3K/Akt pathways [78]. Other mediators including irisin, kynurenine and kynurenic acid, cysteine protease cathepsin B (CTSB), IL-6, IL-15, chemokine CXC ligand 1 (CXCL-1) and the leukemia inhibitory factor (LIF), fibroblast growth factor 21 (FGF21), muscle Bmal1, nitric oxide (NO), ROS, and ATP are intra- and extra-skeletal muscle effectors [76].

Cathepsin B is a protease encoded by CTSB gene which is induced by exercise in muscle and other human tissues. It was indicated that CTSB crosses the BBB and might induce transcription of hippocampal DCX and BDNF [81]. In human and rhesus monkeys, treadmill exercise for 4 months increased the CTSB serum concentration which might be correlated with memory improvement [82].

Exercise-induced production of cytokines including IL-6, IL-8, IL-15 mRNA, murine chemokine CXC ligand 1, and leukemia inhibitory factor (LIF) is involved in many metabolic effects of exercise (e.g., insulin release, glucose uptake, and fatty acid mobilization and oxidation) [76, 83]. Elevations of peripheral and central levels of IL-6 cytokine superfamily members and other pro-inflammatory cytokines inhibit BDNF expression [84].

Irisin precursor protein (fibronectin type III domain containing 5 (FNDC5)) secretion by skeletal muscle is increased after exercise training. This myokine is also secreted from other tissues like the brain and acts as a thermoregulator of the nervous system, bone, and especially adipose tissue by elevating energy expenditure. Although in clinical investigations, the role of irisin in beneficial effects of exercise on hippocampus and memory-related brain function was not established, it was indicated that exercise-induced elevation of irisin might mediate differentiation of embryonic stem cells to neural cell and neurogenesis in mice (reviewed in [85]). Nevertheless, it was reported that subject response in terms of myokine (irisin) changes varies based on the exercise modality [86].

A defect in degradation of kynurenine (L-tryptophan metabolite) to kynurenic acid is associated with cognitive disorders such as depression. It was indicated that exercise increases kynurenine aminotransferase (KATs) expression in the skeletal muscle which leads to enhancement of kynurenine uptake from circulation and its conversion to kynurenic acid. Therefore, the protective effect of exercise against stress-induced disturbance in the brain could be related to the effect of KATs induced via PGC-1α- and PPARα/δ- dependent pathway, before the activity [87].

Circadian rhythms control genes or clock-controlled genes (CCG) are detected in almost all cells of mammalian body. Recent studies demonstrated that CCG are not only expressed in the brain but also in other tissues [88]. Therefore, a muscle brain signaling pathway may take part in sleep and circadian rhythm regulation [89]. Bmal1 protein is one of the main regulators of gene transcription related to control of circadian rhythms. Moreover, Bmal1 and other clock genes are candidates for determination of susceptibility to metabolic diseases [90]. Mutations in CCG including CLOCK, Rev-erb alpha and Rev-erb beta, Per1 and Per2, and ROR genes were showed to result in lower exercise-induced oxidative capacities, impaired endurance exercise, and defective muscle contraction and locomotion [91].

Fibroblast growth factor (FGF) superfamily is responsible for regulating several metabolic and developmental signaling pathways including energy balance, glucose and lipid metabolism, angiogenesis, neuroprotection, and behavior [92, 93]. FGF19 and FGF21 are members of this superfamily, and their genes are expressed in various tissues including the liver, muscle, brain, adipose, and pancreas [92]. FGF21 might be considered a myokine involved in cross talk between the brain and muscles [76, 93]. In muscle, it may act as a transcriptional co-regulator for PGC-1α, or activator of mTORC1 and AKT pathways [94, 95]. The effects of resistance and endurance training on FGF19 and FGF21 serum concentrations in healthy subjects were evaluated. After resistance exercise, the FGF19 level decreased, while endurance training increased plasma glucagon and thereby caused FGF21 elevation [96]. In addition, it was demonstrated that FGF21 increment after

resistance exercise was more pronounced than that observed following HIIT [86].

3.5 Perspectives

Although several experimental and human studies have documented the molecular mechanisms underlying beneficial and preventive effects of exercise, there are still several unanswered questions in this field. Most of the clinical evidence was obtained using muscle biopsy, and there are few findings about the impact of exercise on signaling pathways of other tissues. In addition, the available data on gene expression and signaling peptide production was achieved by computational studies using resting muscle for generating cDNA libraries; thus, more investigations in active muscle are needed. Moreover, according to recent investigations, skeletal muscle might be considered an endocrine metabolic tissue. However, the nature of inter- and intra-organ cross talk of muscle and other tissues needs to be investigated in more detail in future. Therefore, designing multicentered standard clinical trials with special consideration of individual variability and exercise modality and duration seems to be helpful for expansion of our knowledge in this field.

Acknowledgments *Competing financial interests.* The authors declare no competing interests.

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Exercise and Organ Cross Talk

4

Zhiqing Fan and Minjun Xu

Abstract

Chronic heart failure, diabetes, depression, and other chronic diseases are associated with high mortality rate and low cure rate. Exercise induces muscle contraction and secretes multiple myokines, which affects the signaling pathways in skeletal muscle tissues and regulate remote organ functions. Exercise is known to be effective in treating a variety of chronic diseases. Here we summarize how exercise influences skeletal muscle, heart, brain, gut, and liver, and prevents heart failure, cognitive dysfunction, obesity, fatty liver, and other diseases. Exercise training may achieve additional benefits as compared to the present medication for these chronic diseases through cross talk among skeletal muscle and other organs.

Keywords

Exercise · Skeletal muscle · Cross talk · Myokines

Z. Fan
Department of Cardiology, Daqing Qilfield General Hospital, Daqing, China

M. Xu (✉)
Cardiac Regeneration and Ageing Lab, Institute of Cardiovascular Sciences, School of Life Science, Shanghai University, Shanghai, China

4.1 Introduction

Skeletal muscle is one of the three major muscle types, accounting for 40% of a human's body weight [1]. Skeletal muscle is the largest organ in the human body important for physical activity. The communication between skeletal muscle and various organs is mainly reflected in the following aspects. On the one hand, other organs affect skeletal muscle function, which is caused by the pathological state of other organs. For example, heart failure, hepatitis, and intestinal flora disorder can all induce skeletal muscle metabolic disorders that lead to skeletal muscle dysfunctions [2–6]. On the other hand, skeletal muscle affects other organs mainly through the physical activity. It is known that musculoskeletal system can release a lot of signaling molecules and hormones upon exercise, such as growth factors, cytokines, and leptin [7–13]. These signaling molecules and hormones can not only affect the growth, metabolism, and motor function of skeletal muscle but also play important roles in the function of peripheral tissues and organs by endocrine pathway.

Skeletal muscle as an endocrine organ has been widely studied in inter-organ communication networks [14–16]. Exercise induces skeletal muscle to release signaling molecules, which activate cellular signaling pathways and affect cellular functions of target organs, thus achieving cross talk between other organs and skeletal

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_4

muscle. The stimulated release of metabolites from muscle cells caused by exercise can act as a medium for communication between organs. For example, enhanced expression of PGC1α in myocytes induces the intermediate product of β-aminoisobutyric acid (BAIBA) which modulates the metabolism cross talk between liver and fat [17]. Here we will make a detailed description of the communications among various organs and skeletal muscle upon exercise.

4.2 Cross Talk Between Skeletal Muscle and Heart Upon Exercise

Cardiomyopathy, myocardial infarction, coronary artery disease, and other cardiovascular diseases damage cardiac contractility variability, which leads to inadequate cardiac output and triggers the neurohumoral compensatory mechanism [18–20]. The increase of neurohormones can enhance the contraction of myocardium and peripheral blood vessels, thus temporarily preserving cardiac output. However, because of the increased blood pressure of peripheral blood vessels, cardiac afterload is also strengthened which is usually accompanied by pathological myocardial hypertrophy. When these compensatory responses develop to an advance stage, they will induce myocardial cell loss and pathological ventricular remodeling which could further progress to heart failure. It is known that physical activity is beneficial to patients with cardiovascular diseases.

4.2.1 Cardiac Dysfunction Affects Muscle Morphology via MicroRNA

MicroRNA (miRNA) is a single-stranded RNA with 19~25 nucleotides in length derived from the transcription of hairpin structure. It is a kind of small noncoding RNA that regulates the expression of target genes at posttranscriptional level [21, 22]. The function modes of miRNAs can be classified to three types: (1) cleavage of the mRNA strand into two pieces, (2) destabilization of the mRNA through shortening of its polyA tail, and (3) less efficient translation of the mRNA into proteins [23]. Some miRNAs accumulate in damaged myocardium are also increased in the circulation following chronic heart failure [24–28]. These myocardium-derived miRNAs can be encased in vesicles and delivered to skeletal muscle through a circulatory system and then silence their target genes and lead to metabolic and morphological disorders in skeletal muscle. The most representative of these myomiRs are miR-1, miR-133, miR-208, and miR-499 [29–34]. Among the myomiRs, expressions of miR-1 and miR-133a were downregulated by functional overload in muscle used bilateral synergist ablation model [41]. Downregulated miR-1 and miR-133a may help increase the expressions of muscle growth genes, such as IGF-1, HGF, c-Met, LIF, and SRF, to prevent morphological disorders of skeletal muscle. The more notable one is IGF-1 as a potential target of miR-1 which contributes to skeletal muscle hypertrophy [42, 43]. Additionally, decreased miR-1 level in heart was also be found through the exercise training, which may be contribute to cardioprotection by downregulate myocardial apoptosis. In the other hand, non-myomiRs, miR-21 is one of the greatly upregulated miRNAs during cardiac pathological hypertrophy [35]. In chronic heart failure patients with NYHA functional class IV and extensive fibrosis in the heart, miR-21 was notably increased in heart tissue and circulation, and found to be associated with cardiac remodeling [36–38]. As same with heart failure, Duchenne muscular dystrophy (DMD) which disrupts skeletal muscle homeostasis by substitution with fibrotic tissues also showed high expression of miR-21 concomitant with fibrosis [39].

4.2.2 Exercise Improves Cardiac Function

It is known that physical activity is beneficial to patients with cardiovascular diseases. The benefits of physical activity are reflected by enhanced

endothelial function, improved mitochondrial biogenesis, and increased activation of metabolic enzymes in both skeletal muscle and cardiac muscle [40–44]. MiRNAs are considered to be essential mediators for communication between skeletal muscle and myocardium during endurance exercise, which contribute to regulate hypertrophy, angiogenesis, neuron regeneration, and metabolism in skeletal muscle and myocardium [45–49]. Although the mechanism that how skeletal muscle releases miRNAs is still unclear, some miRNAs such as miR-1 (downregulated) [50], miR-27a (upregulated) [51], and miR-126 (upregulated) were consistently expressed in both skeletal muscle and myocardium after exercise [52].

Overexpression of miR-1 was proved to inhibit IGF-1 signaling pathway which leads to muscle atrophy [53]. In contrast, it has been shown that exercise can simultaneously reduce the expression of miR-1 in both skeletal muscle and myocardium, thus leading to physiological cardiac hypertrophy and preventing cardiovascular diseases. Swimming exercise could increase miR-27a and miR-27c which targets angiotensin converting enzyme (Ace) gene, while decrease miR-143 which targets Ace type 2 (Ace2) in the heart [54]. Swimming was also reported to induce miR-126 expression which regulates angiogenesis by targeting Spred-1 [55].

Exercise-induced miR-222 upregulation in the heart is essential for exercise-induced physiological cardiac hypertrophy. Interestingly, miR-222 was also proved to be effective to protect against myocardial I/R injury and heart failure. It was demonstrated that miR-222 was increased during both wheel running and swimming exercise training in mice model. In human, miR-222 was increased in the circulating blood in 28 exercise-trained patients with heart failure. Overexpression of miR-222 was sufficient to improve cardiomyocyte proliferation and hypertrophy [56, 57]. Similar to miR-222, miR-17-3p was also found to be increased in swimming exercise murine model and exercised patients with chronic heart failure [58], which conveys protective effect against myocardial I/R injury and heart failure (Fig. 4.1).

In addition to the above, research on FNDC5 and exosomes has increased. Exosomes can transmit signals to proximal or distal tissues and organs through their biologically active substances such as mi RNAs, peptides and proteins, which affect cell function. It has been shown that coculture of athlete's exosomes and cardiomyocytes can reduce apoptosis. Similarly, injecting isolated rat plasma exosomes into the MI-injured rat heart effectively reduced the infarct area [59]. Fibronectin Type III Domain-Containing Protein 5 (FNDC5) is a transmembrane protein which is highly expressed in skeletal muscle and myocardium. As a downstream molecule of PGC-1α, the expression of FNDC in myocardium and skeletal muscle is increased after exercise training [60]. It has been shown that high concentration of FNDC5 can increase myocardial cell metabolism and promote cardiomyocyte growth [61]. Thereby, to further clarify the cross talk mechanism via exercise between skeletal muscle and myocardium can effectively prevent and treat cardiovascular diseases [62].

4.3 Cross Talk Between Skeletal Muscle and Brain Upon Exercise

The brain weighs about 1.36 kg and mainly consists of blood. Although brain is only 2% of the body weight, it accounts for 25% of the whole body oxygen consumption and 15% of the cardiac output volume within 2000 L of blood flow per day [63–65]. The brain is the largest and most complex structure of the central nervous system. It is an organ that regulates the functions of human body, and also stands for the basis of higher neural activities such as consciousness, spirit, language, learning, memory, and intelligence. Cognitive function is the ability of human brain to process, store and extract information. It is a kind of advanced psychological function such as memory, attention, and thinking. Cognitive function plays an irreplaceable role in our daily life and study. Cognitive psychology has shown that the brain can modify its structure and function according to environmental changes

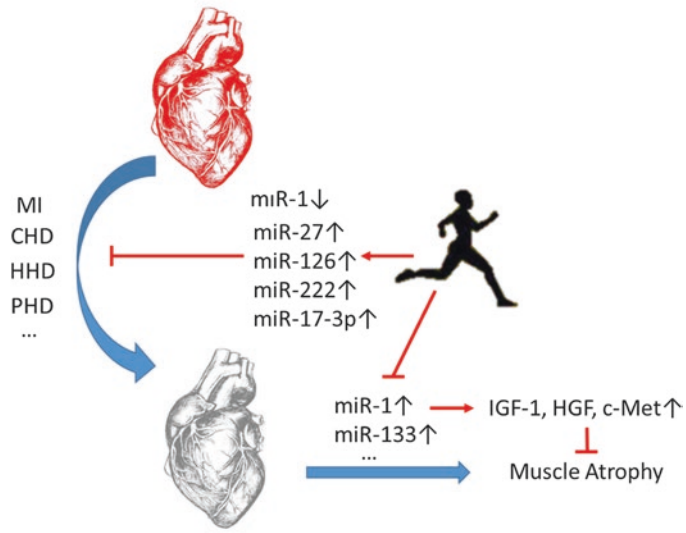

Fig. 4.1 Cross talk between skeletal muscle and heart. *MI* myocardial infarction, *CHD* coronary heart disease, *HHD* hypertensive heart disease, *PHD* pulmonary heart disease

and exercise experience, especially exercise training plays a crucial role in the evolution of the brain [66, 67]. For example, exercise can positively affect synaptic function and synaptic plasticity to promote cerebral cortex neural network and hippocampus function (an important structure in memory processing) [68–70]. Exercise also has a significant effect on brain metabolism [71]. Exercise not only promotes physical health but also delays cognitive aging and prevents mental illness. This paragraph summarizes the impact of exercise on the cognitive function of people at different ages.

4.3.1 Exercise Improves Age-Induced Cognitive Impairment

The function of our brain depends on the number of neurons, nerve fibers and synapses. The cognitive performance is closely related to the number of nerve fibers and synaptic connections, which can be reduced by diseases and aging process. The neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and neurotrophic factor (NGF), are required to provide nutrients to maintain the structure and function of nerve fibers and synaptic connections [72]. However with aging, the reduction of neuron number, contraction of nerves, sharp decrease of dendritic branches, and degeneration of glial cells may impede the transmission of electrical signals in the nervous system, leading to the shrinkage of gray matter in brain and cognitive impairment [73, 74].

Increasing studies have demonstrated that an active lifestyle could delay the aging of cognitive-control areas in brain, and exercise could significantly improve brain health in patients with Alzheimer's disease and schizophrenia [75, 76]. Colcombe et al. used high-resolution magnetic resonance imaging (MRI) to scan the brains of 55 healthy people aged from 55 to 79 years old, and observed that the tissue density in the frontal lobe and temporal lobe decreased with age. Noteworthy, the loss of brain structure was found to be correlated with aerobic fitness. Therefore, 59 healthy people aged from 60–79 years old were divided into exercise training group and control group. In the exercise training group, aerobic exercise intervention was conducted for 6 months which significantly increased the volume of gray matter and white matter, indicating that aerobic fitness could effectively delay brain aging and promote brain health [77–79]. In terms of the mechanism how exercise may delay brain aging and enhance cognitive ability, it has been proved that physical activity can induce FNDC5 expression in skeletal muscle which then be

released into the circulation with Irisin variant. Spiegelman found that of exercise training for 30 days in mice increased the activity of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which is a metabolic regulatory molecule in skeletal muscle. PGC-1α could stimulate the upregulation of FNDC5 expression, FNDC5 enters the hippocampus through the blood-brain barrier, thereby promoting the expression of BDNF in the dentate nucleus of the hippocampus which is responsible for learning and memory. Interestingly, sedentary mice injected with FNDC5 produced by exercise mice were able to activate gene for brain health and improve the growth of new neurons involved in learning and memory. This new discovery links PGC-1α, FNDC5, and BDNF in the cross talk between skeletal muscle and brain upon exercise [80].

In addition to PGC-1α/FNDC5 signaling, other molecules have also been found to affect BDNF expression in cognitive impairment. In a cell model simulating the effect of exercise by adding AMPK agonist to rat L6 myoblasts, proteomics and mass spectrometry were performed to screen the factors secreted by myoblasts. The data showed that Cathepsin B (CTSB) was increased upon treatment, while other cytokines were not altered. Meanwhile, the level of CTSB was also increased in the gastrocnemius muscle and plasma of mice after a voluntary running wheel exercise, and the spatial memory ability, coordinated movement and anti-fatigue ability were improved in exercised mice compared with sedentary controls. However, these beneficial effects were absent in CTSB knockout mice. Moreover, intravenous injected CSTB can get into the brain through blood-brain barrier and upregulate DCX and BDNF expressions thus promoting the growth of hippocampal nerve [81].

4.3.2 Exercise Relieves and Prevents Depression

The benefit of exercise on brain health also includes preventing stress-induced depression. Depression is a worldwide common mental illness. The world health organization (WHO) estimates that more than 350 million people are affected by the disease [82]. The increased level of canine uridine in the circulation contributes to the development of depression which can be however reduced by exercise. During exercise, the level of PGC-1α was increased in skeletal muscle which then upregulated the expression of kynurenine aminotransferase (KAT) enzyme. KAT enzyme was able to rapidly convert canine uridine to canine uric acid, thus induced a protective mechanism by inhibiting increased canine uridine levels in the blood [83]. Similarly, muscle specific PGC-1α overexpression mice showed many characteristics of exercised mice. When they were exposed to a stressful environment such as noise, flashing lights, and irregular circadian rhythms for 5 weeks, they showed no depressive symptoms, while the normal mice showed depressive behaviors.

In addition to the protection of brain health by exercise mentioned above, there are many studies on the alleviation of neurological diseases such as Parkinson's disease [84]. In summary, exercise training can regulate skeletal muscle function and activate muscle-related signaling pathways, and also shows protective effect for the brain through cross talk between skeletal muscle and brain.

4.4 Cross Talk Between Gut and Other Organs Upon Exercise

The gut is one of the most important digestive organs in the human body. In normal state, the small intestine plays a critical role in the digestion and absorption, as well as the barrier function of preventing harmful bacteria and antigens from blood circulation. Intestinal function can be altered by changes of external environment and certain pathological conditions. The microflora colonized in guts also regulates the physiological functions of intestinal tract and even the whole body metabolic function [85]. In recent years, studies on the relationship between intestinal

flora and the overall function of the host have become more and more extensive [86–88].

4.4.1 Exercise Influences the Composition of Gut Microbiota

Increasing evidence indicates that exercise can influence the composition of gut microbiota. The relationship between exercise, diet and gut microbiota was studied in 40 trained professional football players compared with 46 healthy men with matched age. The average body mass index (BMI) of athletes was 29.1. The healthy controls were divided into two groups, 23 in normal BMI group (BMI $\leq$ 25) and 23 in high BMI group (BMI $\geq$ 28). Data showed that the athletes had more diverse intestinal flora than the high BMI control group. In addition, the bacteria species in the athletes' intestine were also higher: 40 species of intestinal microflora were higher than those in the normal BMI control group, and 48 species were higher than those in the high BMI control group. In particular, a class of bacteria called Akkermansiaceae was significantly higher in the athlete's gut than in the control group [89]. Akkermansiaceae was negatively associated with obesity and related metabolic disorders. In an animal model experiment, a total of 2510 bacterial taxa were significantly different between sedentary rats and exercised mice. The number of *Enterococcus faecium* in Lactobacillales order was increased by 24 times in exercise mice, while the number of c11-k211 in Erysipelotrichales order was decreased by 361 times [90]. All the above results indicate that exercise can cause changes in intestinal microecosystem which may form a cross talk with immune organs and affect physiological function.

4.4.2 The Network Among Exercise, Intestinal Flora, and Immune System

Intestinal flora disorder is associated with immune-related diseases such as obesity and diabetes. Intestinal flora may directly or indirectly affect the functions of dendritic cells and macrophages, and regulate T cell activity and B cell maturation. Intestinal flora also promotes intestinal mucosal immunity through cross talk with the immune system, which may be an important mechanism for the body to prevent pathogen invasion. The innate immune system can recognize and differentiate pathogens from harmless substances through pattern recognition receptor (PRR) and nucleotide-binding oligomerization domain (NOD)-like receptor (NLR). Gut microbiota were shown to regulate TLRs expression through MAMP pathway, leading to the activation of NFκB pathway and T cells [91]. Short chain fatty acids (SCFAs) are also important signaling molecules produced by intestinal flora. It has been found that protein coupled receptor Gpr41 and Gpr43 are widely expressed in the small intestine and colon, and their ligands are propionic acid and acetic acid. Gpr43 is also highly expressed in neutrophils and eosinophils, which can be activated by SCFAs, thus reducing inflammatory response [92]. SCFAs could also affect the migration of leukocytes and induce the apoptosis of lymphocytes, macrophages, and neutrophils. In addition, SCFAs (e.g., propionic acid and butyric acid) were associated with reduced stimulus-induced adhesion molecule expression and chemokine production and reduced monocyte/macrophage recruitment, reflecting the anti-inflammatory effect of microbial byproducts [93].

Obesity is also an immune-related disease which has a close relationship with exercise and gut microbiota. T-RFLP analysis study on 33 obese Japanese (BMI > 25) showed that the composition of intestinal flora was different between obese (*Blautia hydrogenotorophica, Coprococcus catus, Eubacterium ventriosum, Ruminococcus bromii, Ruminococcus obeum*) and nonobese (*Bacteroides faecichinchillae, Bacteroides thetaiotaomicron, Blautia wexlerae, Clostridium bolteae, Flavonifractor plautii*) people. In obese people, the number of Bacteroides was decreased, while that of Firmicutes was increased; thus, the proportion of Firmicutes to Bacteroidetes was increased [94]. Firmicutes cause weight gain

because they promote metabolism and are better at absorbing calories than bacilli. Interestingly, exercise could inhibit obesity induced by high-fat diet, and the microbial composition similar to lean mice was found in the intestinal tracts of such mice. It has been suggested that exercised mice have *Faecalibacterium prausnitzii* which may protect the digestive tract by producing butyrate and lowering the oxygen tension in the lumen via a flavin/thiol electron shuttle [95]. Additionally, exercise in juvenile period induced an increase of Bacteroidetes and a decrease of Firmicutes. Compared with exercise in adult period, exercise in juvenile period modified more genera and led to an increase of lean body mass. These data suggest that early life exercise can influence the gut microbiota composition and is beneficial to induce adaptive changes in host metabolism [96]. Also, early life exercise was beneficial for the development of brain function [97].

Different metabolites and signaling molecules such as SCFAs produced by intestinal microorganisms can activate the vagus afferent receptors of enteric nervous system [98]. These signals are transmitted from the nucleus solitarius to different projection regions and are critical for mood and behavior [97]. Therefore, exercise and intestinal microflora are important factors in promoting brain and metabolic development [99] (Fig. 4.2).

Collectively, in addition to genetic and environmental factors, exercise plays an critical role in the regulation of composition and diversity of intestinal flora. Intestinal flora builds a bridge between exercise and other organs, leading to a new direction for investigating systemic and local effect of exercise.

4.5 Metabolism Network Among Exercise, Liver, and Adipose

The liver is an important organ of metabolism in the human body, which regulates the storage of liver glycogen and glucose metabolism. Insulin plays an important role in regulating plasma glucose concentration and glucose metabolism. The effective use of glucose is critically dependent on insulin sensitivity. However, obesity, aging, and unhealthy lifestyles can cause insulin resistance (IR) and carbohydrate metabolic disorders [100]. Thus, keeping the normal physiological function of liver is an effective way to alleviate IR induced by obesity and non-alcoholic fatty liver disease (NAFLD) [101]. With the increasing incidence of metabolism disorders and the onset at younger age, the improvement of liver metabolic function by exercise has become a hot topic in sports medicine research.

4.5.1 Exercise Prevents Fatty Liver Disease by Promoting Lipid Metabolism

Obesity, NAFLD, Type 2 diabetic mellitus (T2DM), and other chronic diseases are usually associated with peripheral IR, which then leads to lipid deposition in liver and skeletal muscle [102]. IR also causes a reduction of glucose uptake and utilization. In turn, excessive glucose is deposited as the form of triglyceride (TG) in the liver. In order to reduce the toxic effect of TG, the liver releases more TG into the blood which further increases TG level in peripheral blood. In addition, in the case of IR, the lipid synthesis of adipose tissue is weakened, while the lipolysis is strengthened. Activated lipolysis releases a large amount of free fatty acid (FFA) into the blood. Excessive circulating FFA can reach the liver and resynthesize TG. Elevated peripheral blood lipids and excessive lipid deposition in the liver lead to enhanced oxidative stress and exacerbated IR. Such a vicious cycle not only affects the normal function of liver but also leads to further deterioration of the metabolism disease [100].

Long-term exercise was reported to be effective to improve IR and reduce liver CLK2 content and liver fat deposition in the obese mice fed with high-fat diet for 16 weeks [103]. High-intensity treadmill exercise (2∗24 min, 50–90% VO_{2max}) was sufficient to increase systemic insulin sensitivity and activate AKT phosphorylation in the liver of rats exposed to intermittent hypoxia [104]. Moreover, moderate exercise for 24 weeks

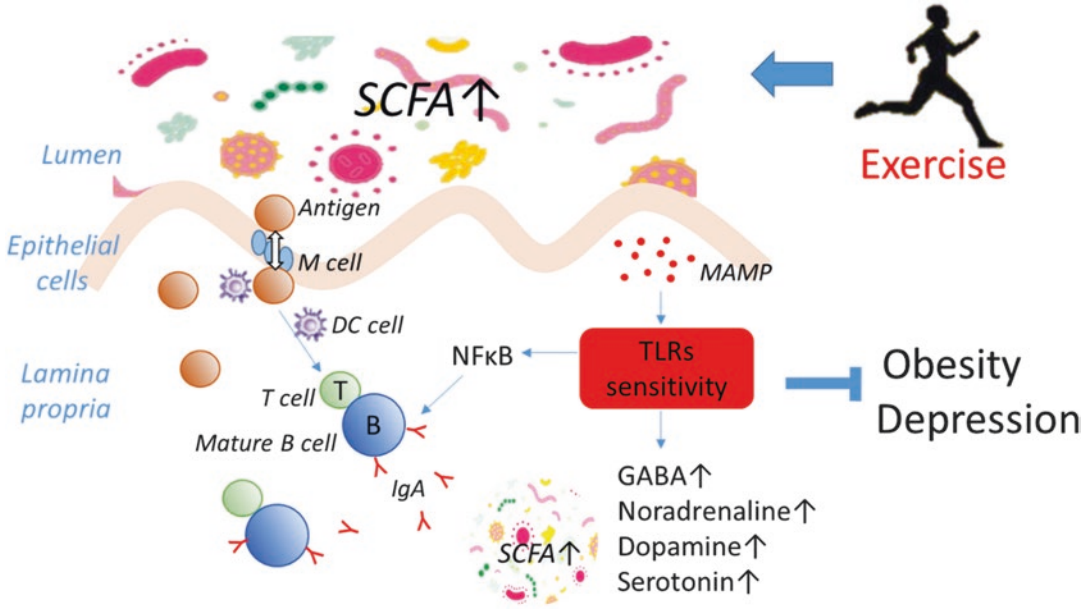

Fig. 4.2 The network of exercise, intestinal flora, and immune system. *SCFA* short chain fatty acid, *TLRs* pattern recognition receptor, *MAMP* microbe-associated molecular pattern, *GABA* gamma-aminobutyric acid

was proved to decrease weight gain in mice induced by a high-fat diet, accompanied by decreased IR, hepatic steatosis, and p62 protein level and increased glucose tolerance [105]. Other studies demonstrated that 10 weeks of exercise training could induce heat shock protein 72 (HSP72) and glucose tolerance in the gastrocnemius muscle and liver, and decrease TG and FFA levels in obese adult rats [102]. Exercise training can also reduce the accumulation of diacylglycerol and TC in the liver of high-fat diet mice, and decrease CD36 and fatty acid transporter 4 (FATP4) in liver thus inhibiting the entering of fatty acid to liver cells [106].

In T2DM mice model, aerobic exercise was shown to improve blood fat metabolism and decrease oxidative stress marker, IR and plasma glucose concentration, which was related to downregulation of Toll-like receptor 4 (TLR4) [106]. Endurance exercise training can significantly decrease TG and FFA levels in the liver of T2DM animals through upregulation and activation of AMPK1/2 signaling [107]. In addition, voluntary exercise can reduce the expression of suppressors-of-cytokine-signaling 3 (SOCS3) and promote glucose intake by phosphorylating AMPK, AKT and glycogen synthetic kinase 3β (GSK3β), thereby reducing TG content in the liver and preventing fatty liver caused by obesity [108]. Similarly, high-intensity acute exercise can reduce the blood glucose level and alleviate insulinemia in diabetic rats by activating AKT and ACC and decreasing the expression of leptin and leptin receptor levels in the liver and skeletal muscle [107]. In cellular immunology, macrophage migration inhibitory factor (MIF) is known to promote intracellular lipid oxidation; 4 weeks of exercise training was found to activate the phosphorylation of AMPK and ACC in the liver, thereby increasing the expression of MIF and preventing liver steatosis [109].

Collectively, exercise can induce the interaction of various signaling molecules in the liver which participate in a variety of cellular biological functions and metabolism (e.g., glucose and lipid metabolism, insulin resistance, and inflammatory process). The beneficial effects of exercise in metabolic disorders such as obesity, NAFLD, and type 2 diabetes are closely related to the metabolism network among exercise, liver, and adipose.

4.6 Perspectives

In recent years, the American College of Sports Medicine has put forward the concept that "Exercise is medicine" which is gradually gaining popularity. Accumulating evidence shows that exercise can effectively prevent and treat chronic diseases such as heart failure, cognitive dysfunction, obesity, fatty liver, and other diseases [110–113], so it is of great importance to explore the mechanisms by which exercise takes effect and improves health. In the twentieth century, researchers tried to find out whether there was a cross talk between skeletal muscle contraction and health promotion, namely, how skeletal muscle regulates changes in other organs (e.g., heart, lung, liver, bone, and adipose tissue) during exercise. In 1966, Erling Asmussen proposed that "During exercise, there is a control system that can regulate lung function, cardiac output, deep ventilation and body temperature" at a seminar held in Dallas. For many years, the factors that activate or regulate the control system have been called "work stimuli" or "work factors." In 2000, Pedersen's team (Copenhagen University) demonstrated that single legged model releases large amounts of IL-6 into the bloodstream. Therefore, "exercise factor" was used to describe the effect of muscle contraction on other organs. The substance released by skeletal muscle contractions were later named as myokines. Myokines play a specific endocrine effect on the distal organ; they also affect signal transduction pathways in skeletal muscles through autocrine or paracrine effect. Thus, skeletal muscle is the largest endocrine organ in the human body. A deep understanding of the link between skeletal muscles and other organs is an important way to explain the health benefits of exercise.

There are many types of exercise such as aerobic exercise, strength exercise, and stretching exercise, which can be selected according to different diseases. Aerobic exercise is known to be adapted to a variety of chronic diseases. Although some diseases are suitable for high-intensity training, moderate- and low-intensity exercises are more applicable [114]. It is very important to make appropriate exercise intensity, time, frequency and treatment measures according to the patients' physical conditions, contraindications and adverse reactions, in order to avoid the occurrence of hypoglycemia, osteoarthropathy, chest pain, hypotension, and other diseases which may be caused by inappropriate exercise prescription. Although the research on exercise prescription is becoming more and more systematic and detailed, it has not yet been widely popularized. Because of the patients' different social backgrounds, advanced age, physical condition, depression, fatigue, low resistance, and other reasons, the dropout rate is high and the compliance is low; thus, the exercise prescription lacks a better clinical treatment standard. In addition, some doctors are unable to provide effective individualized sports programs for patients due to insufficient knowledge of kinematics. Therefore, finding an effective, economic, and individualized exercise therapy program according to the principles of evidence-based medicine is the development direction of sports medicine to improve the quality of life of patients in the future.

Acknowledgments This work was supported by the grants from National Natural Science Foundation of China (81900360).

Competing financial interests: The authors declare no competing financial interests.

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Part III

Exercise and Metabolic Diseases

Exercise and Hyperlipidemia

5

Nana He and Honghua Ye

Abstract

Hyperlipidemia is one of the common pathological conditions of human, which occurs due to lipid metabolism disorder in the human body, resulting in serum lipid concentration beyond normal levels. Due to heredity, diet, nutrition, medicine, and other factors, the incidence of hyperlipidemia has been significantly enhanced and has become one of the most common pathological condition of the human. By introducing the background and pathogenesis of hyperlipidemia and the positive effects of exercise on a variety of related diseases, this chapter discusses the relationship between exercise and serum lipid concentration and the effects of different types of exercise on hyperlipidemia.

Keywords

Hyperlipidemia · Blood lipid concentration · Movement

5.1 Introduction

The rapid development of society has led to the improvement of people's material standard of living. However, public health problems have appeared along with the improvement of people's living standard [1]. The causes of this phenomenon is due to change in people's diet, combined with lack of physical activity, resulting in a decline in human health condition, and hyperlipidemia has become one of the common pathological conditions of human beings, especially for elder people [2]. However, due to the unhealthy lifestyle and diet structure of younger generation, dyslipidemia has also become the health problem of young population [3]. In the medical community, doctors generally use drug treatment for hyperlipidemia, but the high cost and side effects of drug treatment has driven researchers to search for other optimal treatment strategies [4]. How to prevent and treat dyslipidemia in a safe and effective way, which, in turn, would prevent and treat cardiovascular disease, has always been a hot topic of academic research [5]. At present, as a safe and effective method to prevent and treat dyslipidemia, exercise therapy is attracting more and more attention from

N. He
Department of Cardiology, Huamei Hospital, (Previously Named Ningbo No. 2 Hospital), University of Chinese Academy of Sciences, Ningbo, China

Department of Experimental Medical Science, HwaMei Hospital, University of Chinese Academy of Sciences, Ningbo, China

Key Laboratory of Diagnosis and Treatment of Digestive System Tumors of Zhejiang Province, Ningbo, China

H. Ye (✉)
Department of Cardiology, Huamei Hospital, (Previously Named Ningbo No. 2 Hospital), University of Chinese Academy of Sciences, Ningbo, China

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_5

domestic and foreign experts and scholars [6]. Based on the existent literature of hyperlipidemia and the positive effects of exercise on a variety of related diseases, this chapter will discuss the relationship between exercise and serum lipid concentration and the effect of different types of exercise on hyperlipidemia [7].

The circulating lipids in the blood exist in lipoprotein, which is composed of esterified and unesterified cholesterol, triglycerides, phospholipids, and proteins, which transport lipids to various tissues for energy utilization, lipid deposition, steroid hormone production, and bile acid formation [6, 8, 9]. Hyperlipidemia is due to abnormal fat metabolism that makes one or more plasma lipid higher than the normal systemic level [10]; blood lipids mainly refer to the serum cholesterol and triglycerides [11]; therefore, higher cholesterol levels, higher levels of triglycerides, or both, or low high-density lipoprotein cholesterol (HDL-C) are collectively referred to as hyperlipidemia [12].

People with hyperlipidemia have too many lipids (fats) in their blood—namely, cholesterol and triglycerides [13]. Cholesterol is a waxy substance produced by the body and found in saturated fats and animal products [14]. It has many uses in the body and is an important component of cells. Cholesterol can be divided into two classes: low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Lipoproteins carry cholesterol in the blood [15]. Low-density lipoprotein (LDL) is considered harmful because it can cause cholesterol to build up in the arteries and form plaques. High-density lipoprotein (HDL) is considered beneficial because it helps your body to get rid of cholesterol [16]. Triglycerides are another type of fat produced by the body, which can be intake from food. High levels of triglycerides are largely caused by unhealthy lifestyle, including poor diet, smoking, alcohol abuse, and lack of exercise, but sometimes genetics can also affect triglyceride levels [17].

High cholesterol can lead to buildup of platelets in the walls of blood vessels, which can clog arteries and lead to high blood pressure, stroke, or heart failure [18]. In addition, high triglycerides increase the risk of metabolic syndrome, which, in turn, increases the risk of heart diseases and other diseases, including diabetes [19]. The sources of blood lipids can be classified into exogenous and endogenous [20]. Exogenous lipids come from foods rich in cholesterol, while endogenous lipids are synthesized mainly in the liver and small intestine [21]. Under normal circumstances, when the lipid content in food increases, its intestinal absorption increases accordingly, and hence the blood lipid concentration increases and the lipid synthesis in liver is inhibited [22]. On the contrary, when the lipid intake is reduced, the lipid synthesis in the liver will be accelerated, to maintain the level of blood lipid [23]. Once liver function becomes abnormal as in patients with bowel disease, the body cannot adjust the lipid metabolism normally and blood fat concentration will stay high if high-fat food consumption is not controlled [24].

The clinical manifestations of hyperlipidemia are mainly xanthoma caused by lipid deposition in dermis and arteriosclerosis caused by lipid deposition in vascular endothelium [25]. Hyperlipidemia is the most dangerous factor that is associated with atherosclerosis [26]. Therefore, hyperlipidemia is a risk factor for stroke, coronary heart disease, myocardial infarction, and sudden cardiac death [27]. Secondly, hyperlipidemia is also an important risk factor for hypertension, abnormal glucose tolerance, and diabetes [28]. At the same time, hyperlipidemia can lead to fatty liver disease, cirrhosis of the liver, cholelithiasis, pancreatitis, fundus bleeding, blindness, peripheral vascular disease, claudication, and hyperuricemia [29].

5.2 Pathogenic Factors

Hyperlipidemia can be divided into primary and secondary subtypes [30]. Primary hyperlipidemia is caused by genetic defects and environmental factors or by unknown mechanisms [31]. Secondary hyperlipidemia refers to the metabolic disorders associated with diabetes, liver disease, thyroid, and kidney [32].

5.2.1 Eating Disorders and Genetic Defects Are the Main Pathological Basis of Congenital Hyperlipidemia

There are many genes related to lipid metabolism, including apolipoprotein ApoA, ApoB, ApoC, ApoE, and other genes [33]; low-density lipoprotein receptor LDL-R gene, lipoprotein esterase (LPL) gene; and ATP binding cassette transporter gene [34]. When a single gene or multiple genes are inherited, an individual may be susceptible to develop congenital hyperlipidemia [35]. ApoE plays an important role in blood lipid metabolism. It is involved in the synthesis, secretion, metabolism, and transport of lipoprotein [36]. Kastelein's studies have shown that familial hypercholesterolemia is caused by a mutation in the LDL-R gene. LPL is a key enzyme for lipid metabolism, which can hydrolyze the ester bonds of triacylglycerol to produce glycerol and free fatty acids [15, 37, 38]. ATP binding cassette transporter A1 (ABCA1) is an important protein located on the cell membrane to regulate the outflow of cholesterol, and it is the medium for intracellular cholesterol transport to extracellular transport [39]. The transferred cholesterol is reversely transported to the liver via high-density lipoprotein (HDL) to be metabolized into bile acid, and finally discharged in the form of feces [40]. Therefore, it is commonly believed that defects or mutations in the abovementioned single or multiple genes will lead to the occurrence of hyperlipidemia [41].

5.2.2 Metabolic Disorders Are the Key Pathogenic Factors of Secondary Hyperlipidemia

Metabolic diseases often accompany the occurrence of hyperlipidemia, such as diabetes, low thyroid gland function, liver disease, kidney disease, hypertension, and obesity [42]. In addition to regulating blood sugar, insulin is also an important factor in regulating fat metabolism [43], which will reduce lipolysis enzyme activity and HDL metabolism activity, result in triglyceride (TG) clearance problems. At early stage of diabetes, the plasma insulin level is very high, which leads to the excessive synthesis of fat in body, causing endogenous high blood TC and TG [41], and patients with hypothyroidism often show high TC [44]. In the late stage of primary biliary cirrhosis, LDL is elevated and HDL is decreased. The possible mechanism is that esterification of total cholesterol is inhibited [45, 46]. Nephrotic syndrome is a common nephropathy complicated with hyperlipidemia [47]. Studies have shown that chronic proteinuria can reduce the activity of the rate-limiting enzyme 7-hydroxylase during cholesterol catabolism and increase the activity of the rate-limiting enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) during cholesterol biosynthesis, thus causing hyperlipidemia [48]. Hyperlipidemia caused by metabolic disorders has been highly concerned by medical workers, but the inducing mechanism needs to be further studied to better guide clinical treatment [49].

5.3 Hyperlipidemia and Exercise

Recent studies on the prevalence of inactivity and cardiovascular disease have shown sobering results, suggesting that inactivity is a potential risk factor that largely increases cardiovascular disease susceptibility [50]. Recent research works have demonstrated that exercise is beneficial for human cardiovascular health. Additionally, exercise training is the treatment approach for prevention of cardiovascular diseases and diabetes [51]. Various agencies and associations have issued statements and guidelines detailing exercise prescriptions for preventing cardiovascular disease and maintaining good health [52]. Most guidelines, such as a report by the Department of Health and Human Services' Physical Activity Guidelines Advisory Committee, recommend at least 30 minutes of moderate-to-vigorous exercise per week [53, 54]. The longer the term of exercise training performed over 1 week, the more significant the observed benefit [54]. The additional cardiovascular health benefits of training are attractive

because of the multifaceted benefits of exercise and the diversity of mechanisms [55]. One important mechanism by which exercise is thought to be beneficial for coronary cardiovascular disease is its effect on lipoprotein metabolism [56]. Several previous studies have shown that exercise affects plasma lipoprotein [57]. Exercise is widely seen as a way to improve HDL cholesterol (HDL-C) and triglyceride (TG) lipoproteins, which are usually abnormal in people with diabetes and/or insulin resistance [58]. However, exercise-induced improvements in HDL function may be more than just modulate in HDL-C [59].

5.4 Relationship Between Exercise and Serum Lipid Concentration

Exercise training can improve blood lipid status, but the effect is limited [60]. Tran and Weltman conducted a meta-analysis of 95 studies between September 1955 and October 1983 that measured changes in serum lipid and lipoprotein levels after exercise training [61]. During exercise, training that causes weight changes may change serum lipid and lipoprotein levels [62]. Therefore, data from these studies were divided into three categories: constant body weight, weight gain, and weight loss [63, 64]. The results showed differences in cholesterol, triglycerides, LDL cholesterol (LDL-C), HDL cholesterol, and cholesterol/HDL cholesterol levels across the three weight categories [65]. When weight did not change, cholesterol and LDL-C levels decreased significantly (7.3 mg/dL and 3.3 mg/dL respectively); cholesterol and LDL-C levels also dropped significantly when weight was lost (13.2 mg/dL and 11.1 mg/dL, respectively). However, cholesterol and LDL-C levels increased by 2.9 mg/dL and 3.0 mg/dL respectively, in weight gain group. Weight loss is associated with exercise training [63]. In addition, Wood and his colleagues recruited 81 sedentary male subjects between the ages of 30 and 55 to study the effects of exercise on plasma lipoprotein concentrations over a one-year period. Forty-eight were assigned in the running group, while 33 were in the sedentary group (about 3:2). After a year, the running group turned to be healthier and had lost weight compared to the sedentary group [66]. Changes in lipoprotein concentration in the running group were associated with a reduced risk of coronary heart disease, but when complete data were collected for all 46 participants, the results were not significant. However, 25 men who exercised for at least 8 miles (12.9 km) per week on average had a 4.4 mg/dL increase in plasma high-density lipoprotein (HDL) cholesterol ($p = 0.045$), and a 33 mg/dL increase in HDL2 compared to the control group ($p = 0.059$). In addition, weekly exercise distance was significantly associated with changes in plasma HDL-cholesterol ($r = 0.48$), HDL2 ($r = 0.41$), and low-density lipoprotein cholesterol ($r = -0.31$). The study also suggested that exercise training may take long enough (9 months) to cause significant changes in lipid mass spectra [67].

5.5 The Mechanism by Which Exercise Mediates Changes in HDL

HDL cholesterol accounts for 20–30% of total serum cholesterol. HDL is mainly regulated by Apo AI and apolipoprotein a-ii, in addition to about 48 proteins that make up the HDL proteome, which together make up about 10% of lipoprotein particles [68]. Cholesterol transport delivery cholesterol from surrounding tissues to liver, in order to promotes cholesterol homeostasis [69, 70]. The formation of new HDL particles requires ATP binding cassette transport A1 (ABCA1) to transfer lipids from the periphery to lipid-deficient Apo AI, and many cells, such as macrophages, have ATP binding cassette transport protein GI (ABCG1), which can deliver cellular cholesterol to lipid-rich HDL particles [71]. In addition, free cholesterol released by macrophages (either by diffusion, interaction with ABCA1 and ABCG1, or via scavenger receptor B1 is esterified by LCAT in HDL granules into cholesterol esters, which are then transported via HDL to the liver and intestine [69].

The mechanism of increased RCT is best understood in humans, involving increased plasma HDL levels and increased LCAT activity. As early as 1993, the effect of exercise on HDL-c has been proved [72]. This research shows that 9–12 months of training reduced CETP concentration by 13.2% in women and by 14.2% in men, and increased HDL-c by 2.6 ± 6.2 mg/dL [73]. The indirect mechanism of exercise training affecting HDL function may be because of increasing of the bioavailability of nitric oxide (NO), thereby reducing the oxidative modification of HDL and enhancing its functions [74]. In addition, physical activity has been reported to increase the activity of the LPL; however, this is still controversial [75]. There is a direct correlation between plasma LPL activity and HDL because LPL helps HDL particles mature by loading cholesterol and protein [59]. The influence of different exercise patterns (intensity, endurance, aerobic, resistance training, etc.) on the hyperlipidemia was discussed and the mechanism was explored in physiological-pharmacological science youth BBS in Hunan province [76]. Long-term endurance exercise training can reduce blood lipids and has a protective effect on the blood vessel wall. Endurance training can increase the activity of L, P and L, thus promoting the decomposition of TG and TG-rich lipoprotein, and providing additional substrates for HDL synthesis, so as to reduce the concentration of LDL-C in blood and increase the plasma DHL-C. There have also been a few studies demonstrating that increased DHL-C in endurance training is partly due to decreased HDL catabolism. Similarly randomly assigned 111 sedentary, overweight men and women with mild to moderate dyslipidemia to either a control group (6 months) or a high-intensity, moderate-intensity, and low-intensity exercise group (8 months).High-intensity, high-intensity exercise, with the equivalent of running 20 miles (32.0 km) a week, reaches a peak oxygen consumption of 65–80%. Low-intensity, high-intensity exercise, equivalent to running 12 miles (19.2 km) a week, reaches 65–80% of peak oxygen consumption. Or low- to moderate-intensity exercise equates to walking 12 miles a week, reaching 40–55% of peak oxygen consumption. They encouraged subjects to maintain their baseline weight. Eighty-four subjects who met these guidelines were used as the basis for the main analysis. Lipoprotein was analyzed by nuclear magnetic resonance spectroscopy (NMR).The study compared the effects of three different amounts and intensities of exercise on lipoprotein levels in a prospective, randomized, controlled manner. The data showed that the amount of exercise had significant effect on lipoprotein and lipoprotein subcomponents. They also showed that relatively high levels of regular exercise—even without clinically significant weight loss—significantly improved overall lipoprotein shape. In particular, exercise with the equivalent of 17–18 miles (27.2–28.8 km) per week and moderate jogging intensity significantly reduced the concentration of small LDL and LDL particles and increased the average size of LDL particles without changing the plasma LDL cholesterol concentration. This exercise also increased the total HDL concentration, the concentration of large HDL particles and the average size of HDL particles, decreased the concentration of triglycerides and total VLDL triglycerides, and also decreased the concentration of IDL, large VLDL particles, and the average size of VLDL particles [77]. In some studies, exercise seemed to have a greater effect on plasma lipoprotein concentration than exercise intensity, consistent with data from Duncan et al. [78]. Other studies have shown that low-intensity exercise improved lipoprotein [79, 80]. To sum up, it can be basically determined that compared with the amount of exercise, exercise intensity has little effect on lipid.

In addition, acute exercise has been shown to improve postprandial plasma triglyceride (PPTG) elevation [81]. The direct effect of exercise intensity, however, is less clear. The aim of the study was to examine the effect of exercise intensity on PPTG and postprandial fat oxidation. One of the three experimental treatments was performed in healthy young men ($n = 6$). The experiment was divided into control group (CON) and moderate intensity exercise group (MIE) 0.50% VO_2 peak 60 min), and isoenergetic high-intensity exercise

group (HIE; alternate between 2 min (at 25%) and 2 min (at 90% VO_2 peak) for three sets. On the morning after exercise, a standardized diet (16 kcal/kg BM, 1.02 g fat/kg, 1.36 g CHO/kg, 0.31 g PRO/kg) was provided and plasma triglyceride (TG), glucose, and insulin concentrations were measured. Indirect calorimetry was used to determine fat oxidation under fasting conditions and 2, 4, and 6 h postprandial. Compared with the control group, both MIE and HIE showed significant reduction in PPTG [incremental AUC; 75.2 (15.5%), $P = 0.033$ and 54.9 (13.5%), $P = 0.001$], and HIE was also significantly lower than MIE ($P = 0.03$). And HIE [89.1 (9.8) % total] compared with CON [69.0 (16.1) % total, $P = 0.039$, $P = 0.018$)], in MIE, Postprandial fat oxidation was significantly increased [total energy consumption 83.3 (10.6%)], HIE was significantly greater than MIE ($P = 0.012$).

In terms of aerobic exercise, there is substantial evidence from clinical studies that aerobic exercise increases HDL-C [82]. It was first demonstrated in 1979 that HDL-C increased with exercise [83, 84]. Kelley and Kelly compiled 49 randomized controlled trials (RCTS) from 1955 to 2003, with 67 results from 2990 men (1741 athletes and 1249 controls) showing that aerobic exercise increased HDL-C by 2% [84, 85]. A meta-analysis of 25 randomized controlled trials by Kodama et al. found that 5.3 metabolic equivalent aerobic exercise (64.8% of maximum oxidization capacity) significantly increased HDL-C 2.53 mg/dL (the mean pre-exercise HDL range in the study was 49–67 mg/dL). Among the exercise variables, exercise time was the most effective element of HDL-C increase has been demonstrated, with no significant relationship with exercise frequency [86]. Multiple regression analyses showed that subjects with higher total cholesterol (>220 mg/dL) or less obesity (body mass index [BMI] <28) responded better to exercise training. Seventeen articles from 2007 to 2012 discussed HDL levels and impedance movement, but only one dealt with HDL function and impedance movement [59]. The researchers measured ABCA1 expression after exercise but did not directly measure function [87]. The aim of this study was to investigate the effect of impedance exercise on ABCA1 expression in lymphocytes and to correlate ABCA1 expression in 20 young women with plasma HDL-C. The exercises consist of nine major muscle group exercises, using free weights. Intensity was set at 40, 60, or 80% of the maximum value of each individual repeat. Observation immediately after exercise showed no significant change in HDL-C but increased expression of ABCA1 [88]. The effect of low intensity and moderate intensity exercise on the expression of ABCA1 was greater than that of high intensity exercise. There seems to be a contradiction in the ability of impedance exercise to increase HDL levels, but a meta-analysis of studies from 1955 to 2007 showed that impedance exercise had less effect on HDL than aerobic exercise [89].

5.6 Effects of Different Exercise Programs on Hyperlipidemia

5.6.1 Effects of Taijiquan on Hyperlipidemia

Taijiquan is one of the oldest martial arts of China. It has been widely studied for the prevention and improvement of hyperlipidemia. Taijiquan can promote the whole body blood circulation and regulate the blood fat of the human body [90]. Gong et al. studied the effect of 6 months of taijiquan movement on the elderly patients with hyperlipidemia; after the experiment, comparing the indicators before and after exercise of three exercise groups and the control group, the levels of blood total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL-C) were found to fall in the exercise groups. Among them, the LDL-C level of the medium- and high-intensity tai chi training group was significantly lower than that of the control group, and the difference in the change level of high-density lipoprotein (HDL-C) was relatively less obvious due to some undetected factors in the experiment. However, the overall results showed that long-term taijiquan exercise had a good effect on blood lipid index [91]. Some research works also analyzed the effect of taijiquan on

patients with hyperlipidemia, and pointed out that the taijiquan exercise for 24 weeks had significant improvement on the indicators of patients with hyperlipidemia, had a positive effect on the blood lipid metabolism of the elderly, and was conducive to the physical and mental health of the elderly [92]. It has been recommended, taking the study on the effect of taijiquan on hyperlipidemia as an example, moderate and reasonable exercise has a positive effect on improving dyslipidemia and reducing the risk of cardiovascular disease [91].

5.6.2 Effects of Brisk Walking on Hyperlipidemia

Brisk walking, a kind of light exercise, has become a popular way of exercise for the middle-aged and elderly people [81]. It is not prone to developing any sports injury, and the method is easy to master. It is not limited by the site and age. Therefore, walking is a safe and effective aerobic exercise [93]. Some research works studied the effect of exercise walking on blood lipid in the middle-aged and elderly women: after exercise the TC and TG levels were significantly lower, but still failed to fall into the normal range; it may be because of the 16 weeks of exercise time effects on the TC and TG is not enough. It is speculated that this pace influence on blood lipid results more optimistic words need longer time [94]. Therefore, patients with hyperlipidemia should reasonably set the time, intensity, and amount of brisk exercise according to individual conditions, and persevere, in order to achieve their own satisfactory results [95].

5.6.3 Effects of Exercise on Hyperlipidemia in Different Populations

Some researchers conducted a study to observe the effect of body building and running exercise on blood lipid of middle-aged patients with dyslipidemia (under the lactate threshold intensity). The researchers selected 45 middle-aged patients (male and female) with dyslipidemia, and randomly divided them into three groups: low intensity group, medium intensity group, and control group. The middle-aged and elderly patients with dyslipidemia in the low-intensity group and the moderate-intensity group participated in the exercise for 8 weeks and 60 days respectively [96]. Experiment results showed that after 8 weeks of moderate-intensity exercise, TG, LDL-c/HDL-c decreased significantly compared with control group, which was more than the decreased value of low-intensity group ($P < 0.05$). Blood lipid indexes of low-intensity group and moderate-intensity group both improved, under the lactate threshold intensity of regular jogging for a long period, the impact of the movement of blood lipids in patients with dyslipidemia could have the ideal therapeutic effect [97].

There is another research that studied the effects of physical exercise on the blood lipid content of a special population: middle-aged obese women [98]. The investigators considered 24 overweight middle-aged women as subjects and allowed them exercise for 40 days according to the exercise prescription. Serum triglycerides, body weight, and cholesterol levels were measured before and after exercise in 24 obese middle-aged women. The results showed that the body weight, serum triglyceride, and cholesterol levels of 24 subjects were all significantly reduced after exercise. This indicated that the exercise prescription could not only reduce body weight but also significantly reduce blood lipids, which is of great significance for the prevention of hyperlipidemia and hyperlipidemia-induced cardiovascular and cerebrovascular diseases [99].

In addition, foreign literature has also shown that strenuous exercise can reduce the postprandial triacylglycerol concentration in boys and girls. However, it was not clear whether gender contributes to differences in exercise outcomes [100]. Thackray AE et al. conducted a 2-day experiment on 15 boys of 11.8 ± 0.4 years old and 16 girls of 12.1 ± 0.7 years old with 1 day off [101]. Participants completed 10 × 1 min of high-intensity interval running and 1 minute recovery of 100% maximum aerobic speed (HIIR). On the second day, participants ate a standard breakfast

and lunch for 6.5 h, during which they took seven capillary blood samples. From the geometric mean ratio (95%CI as the ratio), the fasting boys were 32% lower than the girls (−44 to 18%, ES = 1.31, $P < 0.001$), and 12% lower than the control after HIIR (−18 to 5%, ES = 0.42, $P = 0.003$). There was no significant difference in the reduction between the sexes (8% (ES = 0.36) and 15% (ES = 0.47); $P = 0.29$). The ratio of total area to time curve was 27% lower for boys than girls (−40 ~ −10%, ES = 1.02, $P = 0.005$), and 10% lower for boys after HIIR (−16 ~ −5%, ES = 0.36, $P = 0.001$). The reduction was also similar between the sexes (11% (ES = 0.43) vs. 10% (ES = 0.31); $P = 0.87$). HIIR showed a small reduction in postprandial between genders [102].

The researchers also suggested that the increase in HDL cholesterol associated with exercise was associated with weight change, especially among women with higher levels of recreational running [103]. In another study, 1837 female recreational runners conducted running every week compared with medical data provided by female doctors. It found that women who exercised longer than the current recommendations had a significant increase in their HDL cholesterol levels and that higher HDL cholesterol levels could provide these women with additional health benefits [23].

5.7 Perspective

With the development of society and the improvement of people's living standards, the change of diet structure will further cause the change of disease epidemics. As one of the diseases with the highest mortality rate in the world, hyperlipidemia is enough to attract people's attention.

Hyperlipidemia is a typical form of abnormal lipid metabolism, which can be prevented by adjusting diet structure and strengthening aerobic exercise. Exercise, as an important means of treating hyperlipidemia, can reduce the harmful components of blood lipids and improve the beneficial components of blood lipids. Therefore, adherence to long-term aerobic exercise for the prevention and treatment of hyperlipidemia is very important.

Acknowledgments This work was supported by Ningbo Medical Science and Technology project (2016Z01), Ningbo Health Branding Subject Fund (PPXK2018-01), and Ningbo Huamei Research Fund (2017HMKY04).

Competing financial interests: The authors declare no competing financial interests.

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Exercise and Type 2 Diabetes

6

Sasan Amanat, Simin Ghahri, Aria Dianatinasab, Mohammad Fararouei, and Mostafa Dianatinasab

Abstract

The epidemic of diabetes mellitus has already become a serious global health threat. In the past three decades, the number of people with diabetes mellitus has quadrupled globally, and diabetes mellitus is known as the ninth major cause of death in the world nowadays. The increasing prevalence of type 2 diabetes mellitus is in coincidence with the augmentation of obesity in most developed countries as well as in developing countries. A sedentary lifestyle is well-known as one of the major reasons for the rising epidemic of type 2 diabetes mellitus besides the other reasons such as adopting energy-dense diets relative to the actual need for energy and population aging. Exercise as a regular physical activity at a medium to vigorous intensity is found to be an efficient influencer that would switch back most of the known type 2 diabetes mellitus factors toward healthier positions. Exercise is proven to have clinical benefits, such as improved insulin sensitivity, reductions in glycosylated hemoglobin (A1C) and increased peak oxygen consumption (VO_2peak) which are definitely preventive toward diabetes. Exercise training can favorably affect glycemic parameters, the lipid profile, blood pressure, and high-sensitivity C-reactive protein. Exercise improves blood glucose control in type 2 diabetes, reduces cardiovascular risk factors, and regulates body weight by reducing body fat percentage and enhancing lean mass. In this chapter, the effect of regular exercise on the prevention of diabetes and short-term glucose and energy metabolism will be discussed. In addition, the effect of exercise on most common complications of type 2 diabetes including cardiovascular diseases, dyslipidemia, nephropathy, neuropathy, and retinopathy will be reviewed.

S. Amanat
Department of Nutrition, School of Health, Larestan University of Medical Sciences, Larestan, Iran

S. Ghahri
Department of Sport Physiology, Shahrood University of Technology, Shahrood, Iran

A. Dianatinasab
Department of Biochemistry, Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran

M. Fararouei
Faculty of Public Health, Department of Epidemiology, Shiraz University of Medical Sciences, Shiraz, Iran
e-mail: fararouei@sums.ac.ir

M. Dianatinasab (✉)
Department of Epidemiology, Center for Health Related Social and Behavioral Sciences Research, Shahroud University of Medical Sciences, Shahroud, Iran
e-mail: dianatinasab@sums.ac.ir

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_6

Keywords

Exercise · Type 2 diabetes mellitus · Insulin resistance · Physical activity

6.1 Background

Diabetes is classified into four types according to the American Diabetes Association: type 1 diabetes, an autoimmune disease induced after pancreatic β-cell damage by immune system; type 2 diabetes mellitus (T2DM), an state of disruption in insulin signaling "insulin resistance" and simultaneously β-cell exhaustion; gestational diabetes mellitus which occurs usually after second trimester of gestation without previous diabetes symptoms; some rarer types of diabetes due endocrine disease drugs side effects [1, 2]. International Diabetes Federation estimates more than 9% of all adults worldwide now have diabetes mellitus, and this number is growing. Diabetes mellitus is a major risk factor of different disorders including renal failure, peripheral neuropathy, retinopathy, and especially cardiovascular diseases. The level of glycated hemoglobin A1c (HbA1c) seems to be a key predictor of diabetes-associated morbidity and mortality; So that reduction in serum HbA1c by 1% results in 14% lower of myocardial infarctions and more than 20% decrease in diabetes associated death risk [3].

It is well known that metabolic dysfunction in T2DM is accompanied with chronic inflammation [4]. Increase in secretion of inflammatory adipokines including leptin and resistin along with diabetogenic pro-inflammatory cytokines from adipocytes such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are the fundamental characteristic of T2DM. The interplay between inflammatory mediators and insulin resistance is a key to management diabetes. Strong evidences have demonstrated that intensive lifestyle changes dedicated on increasing physical activity can prevent the occurrence of diabetes more effective than pharmacological interventions [5]. Exercise is proven to induce beneficial changes in glycemic markers such as insulin resistance, HbA1C and fasting insulin which is definitely preventive toward T2DM. Along with these changes, exercise can favorably alter the lipid profile, blood pressure, and inflammatory markers [6]. Reduction in visceral and abdominal fat is found to be the major link between exercise and insulin resistance improvement. The results of aerobic, resistance, and combined exercise on obese men showed a change in cytokine/adipokine level as well as a decrease in insulin resistance [7]. This chapter tends to provide an update on the effect of different exercise programs on type 2 diabetes-related markers, mechanisms of action, and short-term and long-term outcomes.

6.2 Classification and Diagnosis of Diabetes

Diabetic patients usually fall into one of these two categories; type 1 diabetes (5–10% of total cases) occurs when the immune system arises against pancreas β-cells and insulin production increasingly declines to insufficient level. Type 2 diabetes with 90–95% of all diabetic cases is a chronic condition when body becomes resistant to insulin action and pancreatic β-cells gradually lose the ability to secrete adequate insulin [8]. Type 1 diabetes incidence is much more in youngsters than adults however, it occurs at any age. On the other hand, T2DM has known as a disease for adults with low prevalence among adolescents. Patients predispose to diabetes commonly experience lower level of hyperglycemia so-called prediabetes, an asymptomatic treatable state characterized by one of the following: (1) impaired fasting glucose (100–125 mg/dL), (2) 2-h plasma glucose 140–199 mg/dL, (3) HbA1C 5.7–6.4% mg/dL [5]. Plasma glucose or HbA1c more than that described for prediabetes is classified as diabetes. There is a probability that the diagnosis of diabetes type becomes unclear especially at the onset of the disease in adults [9]. Although prevalent signs such as polyuria and polydipsia are common among type 1 and type 2 diabetes, a decisive distinction is important. Certain diagnostic criteria for type 1 diabetes

include the presence of ketoacidosis and using βcell-specific autoantibodies.

Gestational diabetes mellitus is the occurrence of diabetes usually between 24 and 28 weeks of pregnancy in women without previous history of diabetes [8]. Gestational diabetes mellitus diagnosis includes the one-step 75-g oral glucose tolerance test or two-step approach with a 50-g no fasting screen followed by a 100-g oral glucose tolerance test for those who screen positive. Cutoff diagnosis for fasting, 1 and 2 h are plasma glucose equal or higher than 92 mg/dL, 180 mg/dL, and 153 mg/dL, respectively [1].

6.3 Treatment Goals

Glycemic goals for adults with T2DM are set under 7.5% for HbA1c and less than 130 mg/dL for fasting blood glucose according to American Diabetes Association (ADA) guidelines [10]. The therapeutic strategy should be comprehensive and along with pharmacotherapy comprise series of self-management education and smoke disuse counseling as well as prescribing dietary and exercise regimen [11]. Lifestyle management is described as an essential approach for diabetes care. The combination of physical activity with calorie restriction is proven to not only improve well-being status but also prevent weight gain in the long term and overall morbidity [12]. The American Diabetes Association's recommendation for prevention or postponement of type 2 diabetes is annual monitoring for patients with prediabetes to diagnose any progression toward diabetes. In addition, contributing to an intensive physically active lifestyle program to reach and maintain minimum 5% weight loss and increase moderate-intensity physical activity to at least 200–300 min/week. There are also recommendations for using new wearable technologies and mobile application to enhance education and or encourage patients to follow recommendations [13]. Furthermore, the assessment of clinical therapies, psychological, physical science, and sociology in elderly adults is necessary as part of treatment considerations [10]. Patient-centered care is critical to achieving optimal medical treatment results and psychological well-being. Medical treatment of diabetes necessitates the patient's full adherence to the treatment regimen [14]. A major effort suggested to fight against diabetes is through weight loss and health behavior changes [12]. Studies investigating perceived barriers and facilitators of diabetic patients performing the exercise suggest that supports from family members and an overall greater sense of well-being and fitness were the main factors associated with higher exercise adherence.

6.4 Types of Exercises and Physical Activity

Aerobic exercises are activities engaging larger muscles and mostly rely on energy generated by aerobic metabolism. The aerobic training may have mild to vigorous intensity and usually involve long duration. Running, jogging, cycling, and swimming are a sample of aerobic exercises. Resistance training includes activities aimed to enhance muscular power and endurance by using bodyweight, machines, or elastic bands [15]. Stretching exercises tend to increase flexibility such as yoga, upper and lower body stretch, and calf stretch. Standing on toe, tai chi, and heel to toe walk are among balance exercises that help especially elders prevent falling.

6.5 Effect of Exercise in the Prevention of Diabetes

ADA recommendations for the prevention of T2DM include physical activity more than 150 min/week and dietary intervention in order to attain 5–7% weight loss within 3–6 months. Similarly, the Diabetes Prevention Program (DPP) has recommended a series of behavioral and lifestyle modifications to achieve and maintain at least 7% of weight loss and 150 min of physical activity per week. The intensity of physical activity should be like brisk walking [16]. The 7% weight reduction is recommended to achieve in the first 6 months of intervention as 0.5–1 kg weight loss per week the exercise

modality is permitted to be personalized and is the least assessed change leading to lessen the risk of developing diabetes [16]. Widespread evidence resulted from diverse studies across countries and populations of all ages support the fact that exercise training has an effective role in the prevention of T2DM through promote insulin sensitivity and also changes body mass and composition. In this regard, a follow-up study on adult Swedish men and Chinese men and women with prediabetes showed a reduction in T2DM development through exercise intervention. Another study comparing the effectiveness of exercise and diet modification on T2DM revealed similar preventive results. This preventing effect was observed with the fact that no significant change in the body mass index was detected in either of groups [17]. Epidemiological studies demonstrated that various intensity of exercise throughout the week was associated with a decreased incidence of diabetes at long-term follow-up in both genders of different age groups [18]. Exercise training is well recognized to have an obvious diabetes preventive effect by ameliorating metabolism homeostatic, physical fitness, cardiovascular health in patients with T2DM mellitus and prediabetes. Moreover, to prevent or delay the most prevalent comorbidities after T2DM diagnosed in older adults such as neuropathy, nephropathy,, heart failure, depression, and cognitive impairment, targeted exercise prescriptions of different modalities including aerobic, resistance, or combined exercise programs have been proven to provide significant clinical benefits in all of the mentioned burdens [19]. In a study with a diabetes preventive approach, comparing the effect of 8 weeks of the aerobic exercise with the high-intensity resistance training on body composition and glucose homeostatic of obese sedentary adults without diabetes resulted in no significant difference within groups, except a significant increase in leg lean body mass observed within the high-intensity functional exercise group [20]. A study exploring the effect of leisure-time physical activity on prevention of T2DM who were prediabetic based on impaired glucose tolerance test. Results from 4 years of follow-up indicated that participants who increased physical activity with moderate to high intensity had 63–65% less chance of developing diabetes [21]. In 2015 a systematic review evaluating cost-effectiveness of dietary and physical activity promotion program to prevent diabetes was published. Of 28 reviewed studies, 22 reported the cost-effectiveness of the intervention program, and the cost was even lower for group intervention sessions [2]. Despite the benefits and effectiveness of the lifestyle intervention programs, the absence of such programs in communities and low insurance coverage is a serious challenge [22].

6.6 Short-Term Effect of Exercise on Diabetes

6.6.1 Energy and Glucose Metabolism

Physical activity is an energy-consuming action and induces much higher energy expenditure than resting state. A 77 kg man running with 8 km/h speed for half an hour burns an additional 324 kcal to usual energy expenditure. The energy source for muscles may change from glucose to fatty acids during activity based on the intensity of exercise [23]. However, the effect of exercise on energy metabolism is not limited to absolute energy consuming during exercise period. It is well-known that after a bout of exercise, energy expenditure stays elevated hours after activity. A study on 10 young male participant showed that 45 min of high intensity aerobic exercise induce higher energy expenditure for 14 h post exercise. The amount of burnt energy in this period was about 40 percent of total energy consumption during exercise [24]. The post-exercise increase in energy consumption can be stretch out to 22 h by replacing aerobic with high intensity resistance training [25]. Another study on overweight young adults demonstrated that a resistance training based on American College of Sports Medicine (ACSM) guidelines including one or three set of 10 different exercise induced a higher resting energy expenditure (about 5%) for 72 h. Surprisingly the result showed that one set of

exercise (15 min) was as effective as three sets (35 min) of the same exercise program [26]. This post-exercise energy expenditure is known as recovery energy expenditure and as previously mentioned is affected by type of exercise and the fact that which muscle groups have been trained [27]. Recently a skeletal muscle originate protein has discovered that induced after physical activity. The production of this protein so called Irisin is controlled by peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) transcriptional coactivator, which in turn upregulated by exercise. Irisin is proposed as a link between physical activity and health benefits of therefrom [28]. Increase in circulating irisin level is involved in browning of white adipose tissues and escalation of the thermogenesis and energy expenditure [29]. Despite the fact that irisin is secreted from skeletal muscle cells, there is still a debate on the effect of different exercise regimens on irisin production based on recent clinical trials [30]. Increased oxidative stress following short-term and long-term physical training found to inhibit inflammatory processes and improve insulin sensitivity by decreasing the vaspin serum concentration [31].

6.6.2 Glucose Metabolism and Insulin Resistance

Skeletal muscles have two well-controlled mechanisms to uptake glucose from the bloodstream and both of these mechanisms are dependent on glucose transporter type 4 (GLUT4). In the resting state, translocation of GLUT4 to muscle membrane where it imports glucose into the cell fully relies on presence of insulin. Insulin signaling consists of rapid phosphorylation of the insulin receptor, insulin receptor substrate-1/2 on tyrosine residues, and the activation of phosphatidylinositol 3-kinase; however, exercise has no effect on any of these actions. Insulin resistance disrupts this pathway and reduces the capability of insulin target cells to uptake glucose efficiently. However, when a muscle cell is in a contracting during exercise, second pathway is activated. Though the exact underlying mechanism of exercise stimulating effect on GLUT4 translocation is not fully understood, it is known that the pathway is independent of insulin. Shortly various changes in energy levels in consequence of muscle contraction such as increased AMP/ATP, increases in intracellular Ca^{2+} level, increased reactive oxygen species, and Protein Kinase-C which cause activation of various signaling cascades, some of which are likely acting as activator of GLUT4 translocation [32]. Despite different key regulators (contraction vs insulin signaling) some molecular signaling is common between two pathways [33]. Interesting results of the first animal studies in this area showed that knock out insulin receptors in skeletal muscle of mice had no deficit in glucose uptake stimulated by exercise [34]. In addition to distinct mechanism of glucose uptake by muscle cells, the increase in blood flow due to exercise in muscle tissue increase glucose availability contributes to higher glucose consumption. Improvement of glucose metabolism may be extent to insulin action by the exercise. Cassidy et al. demonstrated high-intensity intermittent training improves peripheral insulin sensitivity in 72 h after the last workout bout and attributed this action to accelerate glycogen breakdown and synthesis [35]. Way et al. conducted a study to explore the effect of systemic training on insulin sensitivity in T2DM patients and if the short inactivity period changes the insulin sensitivity after exercise. They observed that exercise group had significantly higher insulin sensitivity than control group that lasts for 72 h after last training session during inactive period [36].

Several studies demonstrated acceleration of insulin sensitivity induced by the increase in insulin-sensitive glucose transporter on the cell membrane and oxidative enzymes in skeletal muscle. Obese diabetic patients benefit from increased physical activity by the increase in muscle oxidative capacity, increase in muscle mass, decreased blood glucose level, and decreased deposition of total fat [12]. Observations have shown that aerobic exercise even at a low intensity, which lasts 60 min, would enhance insulin action for at least 24 h in obese, insulin-resistant adults. It affects by increasing

oxidative capacity, lipid, and glucose metabolism, and insulin sensitivity [8].

A suggested strategy in order to avoid postprandial hyperglycemia in diabetic patients is to benefit the glucose-lowering effect of exercise by performing the session approximately 1 h after a meal to compensate with peak postprandial rise in glucose [19]. Recorded evidence has shown that systematic training programs statistically and clinically affected the glycemic level in a favorable way, and this change has nothing to do with weight loss [37]. A great decrease in blood glucose after exercise intervention was observed; doing exercise causes a decrease in peripheral insulin resistance which leads to increase in peripheral glucose uptake, while liver glucose production remains the same [7].

Exercise may induce hypoglycemia more likely in patients with type 1 diabetes and unlikelier in T2DM patients using insulin or insulin secretagogue medications. It is suggested to perform a short-term (10 s) high-intensity sprint or bouts before, after or between a modest-intensity exercise session in addition to insulin and dietary carbohydrate change to protect against exercise induced hypoglycemia. Nocturnal hypoglycemic events may also occur typically within 6–15 h post-exercise, although risk can extend out to 48 h which can be avoided by insulin and carbohydrate dose and uptake timing adjustment and permanent glucose monitoring [8].

6.7 The Long-Term Effect of Exercise on Diabetes

Type 2 diabetic patients are 14.6 years earlier exposed to the risk of coronary heart disease, peripheral vascular disease and stroke. Diabetes mellitus also causes impaired renal function, induces albuminuria, and decreased estimated glomerular filtration rate. In addition, patients with T2DM are susceptible to other complications like retinopathy, gastrointestinal motility dysfunction, and even cognitive function and mental health disorders [5]. In addition to all of former complications, diabetes is strongly linked with oxidative stress and inflammation. Inflammation and insulin resistance are known to amplify each other. This chronic state of inflammation is involved in incidence of different diabetes-associated complication including the risk of cardiovascular and renal damage [38]. Insulin resistance is found to be related to skeletal muscle mitochondrial dysfunction. It is observed that mitochondrial content and activity enhancement alongside insulin sensitivity is achieved by endurance exercise training. Moreover, skeletal muscle GLUT4 is observed to be increased with endurance exercise training this effect is a cause of the muscle glucose uptake increased [32]. When Van Germet et al. compared the effect of 6–7% weight loss via exercise or hypocaloric diet on inflammatory marker in inactive, and overweight/obese postmenopausal women. They reported that despite significant decrease in circulating levels of the inflammatory marker, high sensitive c-reactive protein and leptin in both groups; Exercise were found to have more beneficial effect on high sensitive C-reactive protein due to altering body fat and fitness [39]. Evaluations on groups of sedentary T2DM adults after performing 10–20-min training three times per week for 6 weeks of high-intensity functional training, showed a significant increasing in beta-cell function, while decreasing fat storage, preserving lean body mass, improvements of cardiovascular health, lipid metabolism, and LDL cholesterol plus increased insulin sensitivity [20]. Interventions of exercise alone in patients with T2DM have proved to be effective in terms of prevention consisted of improvements in the management of blood glucose levels, body weight, lipids, blood pressure, cardiovascular disease, mortality, and overall quality of life [32].

6.7.1 Blood Glucose Control

Besides the acute and independent effect of physical activity on blood glucose, chronic exercise ameliorates insulin resistance and glucose control [40]. Resistance exercise may enhance glucose uptake during inactive stats by hypertrophy of skeletal muscle mass, a responsive tissue to insulin signaling. After comparing 12 weeks of

aerobic, resistance, and combined exercise in T2DM patients, a glucose level of all three exercise group was decreased however these changes were significantly greater in patients performed combined exercise [7]. A meta-analysis study comparing several trials results showed that all intensities resistance exercise significantly reduced HbA1c [3]. Additionally, aerobic, resistance, and combined protocols of trainings favorably changed A1C [6].

6.7.2 Bodyweight Management

The prevalence of overweight or obesity is high in patients with T2DM. This excessive weight comes with a burden. Improvements in body composition by the time in order to the elimination of weight burden on joints in overweight patients and decreasing eventual joint pain by exercise may have resulted in better exercise adherence [19]. The metabolic improvements caused by exercise training in type 2 diabetes patients are mostly attributed to decrease of visceral adiposity rather than weight loss in general [19]. In a study evaluating the impact of physical activity on diabetes risk factors an inverse association between physical activity and BMI and prevalence of overweight was found [41]. Exercise reduces body fat percentage which was justified the consequential decrease homeostasis model assessment of insulin resistance and a significant increase in serum omentin-1 [7]. Omentin-1 is an adipocytokine produce mainly from omental and epicardial adipose tissue. Although the effect of omentin-1 on pathogenesis of insulin resistance and diabetes has not been proven, studies have revealed that lower serum omentin-1 is related to increased incidence of diabetes [42].

Physical inactivity is reported to definitely incite accumulation of visceral fat, inflammation and metabolic disorders [43]. Physical activity, as a strategy used to reduce body weight, is effective in correcting the alterations in insulin sensitivity, appetite, serum omentin-1 concentration induced by overweight and obesity. In addition, weight reducing the effect of exercise lowers serum concentrations of vaspin which may lead to inhibition of inflammatory processes and insulin resistance [31]. Decreased liver and visceral fat which plays a key pathogenic role in type 2 diabetes patients was an achievement of Cassidy et al. study, evaluating the effect of vigorous intermittent exercise program on regional fat deposition in patients with T2DM. Therefore, they suggested that high-intensity intermittent exercise is an effective strategy to decrease liver fat in type 2 diabetes patients plus the modest improvements in glycemic control [35]. The magnitude of exercise training on the body fat mass varies according to the type, volume, and intensity of the protocol. Physical activity generally has been reported to cause adaptations in white adipose tissue, such as shrinking cell size, adipocytokine secretion, and modification of inflammation [20].

6.7.3 Hypertension

Previously, the effect of physical activity on blood pressure of diabetic patients was investigated. This cross-sectional study on 1766 person has demonstrated that diabetic active patients have significantly lower blood pressure than diabetic inactive patients [44]. Physical activity and diastolic blood pressure are found to have an inverse relationship whereas patients with highest active lifestyle had lowest prevalence of hypertension [41]. Clinical trial study on diabetic hypertensive patients showed that even single bout of aerobic exercise with maximal intensity results in 8 h of post-exercise lower blood pressure [45]. Patients with T2DM are more susceptible to exercise hypertension. Although exercise is proven to be beneficial to diminish and control hypertension, poorly controlled hypertensive T2DM patients are recommended to avoid high-intensity training, particularly resistance exercises [19].

6.7.4 Dyslipidemia

It is estimated that 30–60% of T2DM patients struggle with dyslipidemia [46]. Increase in serum triglyceride, VLDL, IDL and decrease in HDL cholesterol are the common changes in lipid profile among diabetic patients. Unlike type 1 diabetes, severe glucose control in T2DM does not lead to normal lipid profile [47, 48]. Along with routine therapies for dyslipidemia such as pharmacotherapy studies have evaluated the effect of exercise intervention. Physical activities have long been known as an effective strategy to modify dyslipidemia. Contributing the obese and overweight groups of adults in a study with 6 and 12 weeks of moderate exercise showed that regular exercise in overweight subjects decreases HDL-c, leptin, adiponectin and resistin levels and diastolic blood pressure. In the obese group, regular moderate exercise lowered the level of HDL-c, homocysteine, leptin, resistin, IL-6, and adiponectin [49]. In addition, Shakil-ur-Rehman et al. evaluated the effect of 25 weeks of supervised structured aerobic training on serum lipid profile. The results of this study suggest a favorable change in patients received exercise intervention in comparison with control groups [50]. In another clinical trial, even mild to moderate intensity of exercise as usually performed in yoga training was effective in improving dyslipidemia in diabetic patients [51].

6.7.5 CVD Risk

The evidence from a large cohort study firmly indicates that people with T2DM are at high risk of different cardiovascular diseases including peripheral arterial disease, heart failure, and ischemic stroke. A previous meta-analysis study investigated the effect of exercises of CVD risk factors indicated that aerobic exercise alone or in combination with resistance exercise leads to better glycemic control, systolic blood pressure, triglyceride, and waist circumference which are CVD risk factors. In addition, results showed that resistance exercise alone may not induce similar improvement on CVD risk factors as aerobic exercise did [52].

Cassidy et al. conducted a study to examine the effects of high-intensity intermittent exercise on cardiac function, fat deposition, and glycemic control in patient with T2DM. They found that an intermittent training program increased left ventricular wall mass; they explained that this physiological hypertrophy is a significant effect of exercise that is empowering the cardiac contractile capabilities and should not be confused with "pathological hypertrophy." Unlike physiological hypertrophy, pathological hypertrophy occurs with an increase collagen accumulation in cardiac tissue. T2DM patients have reduced cardiac contractile function. This study showed that exercise training could improve end-diastolic blood volume, systolic and diastolic function and reduce peak torsion. The researchers suggested that high-intensity intermittent training could be an effective strategy to reverse cardiac dysfunction [35]. Evidence-based results of some studies showed that aquatic exercise improved exercise capacity, cardiovascular system, metabolic profile, and muscle function high level of exercise training in patients with T2DM [53]. For diabetic patients with sedentary lifestyle history and additional cardiovascular risk factors, cardiac screening comprising a stress test to avoid the eventual risk of cardiac events during exercise is recommended [19]. Modulations of exercise, in any stage of treatment, are considered as a potential non-pharmaceutical therapy to improve cardiac structure and function [35]. Chronic inflammation is involved in CVD pathogenesis. Regular exercises are feasible treatment strategy toward reducing risk of CVD in patients with T2DM. One of the underlying mechanisms is regulation of inflammatory cytokines production. Exercise may directly reduce the inflammatory cytokines secretion, for example, reducing body fats or indirectly suppressing the inflammation by upregulating anti-inflammatory cytokines like IL-10 [43]. Muscle has been recognized as an endocrine tissue and is able to influence other systems such as the immune system. Generally, acute bout of exercises is proven to induce an immediate pro-inflammatory response and some

of the anti-inflammatory molecules at the same time. Prolonged and regular exercise might improve an anti-inflammatory activity and attenuates the acute response to exercise, which is probably involved in decrease the risk of inflammatory induce diseases such as atherosclerosis [54]. A recent study comparing aerobic and resistance exercise showed that both of these training programs are effective against cardiovascular autonomic abnormalities among diabetic patients. Though, no significant difference between aerobic and resistance exercise was reported [55].

6.7.6 Retinopathy

As one of the most common complications of diabetes, retinopathy pathogenesis depends on fasting blood glucose and the daily glycemic fluctuation. Patients with good glycemic control have lower risk to develop retinopathy [56]. Observational studies have demonstrated that the severity of retinopathy among diabetic patients is reversely correlated with physical activity. Therefore, patients with proliferative diabetic retinopathy are the less active of all evaluated groups. Interestingly the analysis of data showed that beneficial effect of physical activity is independent of HbA1c level [57, 58]. Similarly, the results of a 10-year prospective cohort of diabetic patients indicated that patients with higher physical activity are less likely to suffer from diabetic retinopathy [59]. Prescription of exercise and activity should be considered with caution, as high intensity of aerobic or resistance exercise may increase the risk of vitreous hemorrhage or retinal detachment [37].

6.7.7 Nephropathy

Aerobic exercise training is convincingly reported to decrease urine protein excretion likely due to improved glycemic control and reducing blood pressure. However, depending on the amount of blood pressure acute rise by exercise, there is a probability of an acute increase in urinary protein excretion. Resistance exercise training also seems to be of benefit in the glomerular filtration rate [37]. It is shown that combination of calorie restriction and exercise regimen in type 2 diabetic patients leads to mild weight loss of 6% and improvement of kidney function [32]. In addition, an animal study on obese diabetic rat models showed that 10 weeks of treadmill running caused a significantly less glomerular mesangial expansion and tubule-interstitial fibrosis in comparison with sedentary control group. Furthermore, exercised rats had significantly lower plasma advanced glycation end products such as Nε-carboxymethyllysine [60]. Regarding the increased risk for cardiovascular disease by microalbuminuria and proteinuria, it is recommended to perform an exercise electrocardiogram stress test in individuals with these disorders plus sedentary lifestyle history whenever aimed to begin exercise at a higher level intensity than the everyday living activities [37].

6.7.8 Neuropathy

Diabetes peripheral neuropathy is commonly associated with multiple issues such as pain, infection, sensory loss and risk of falling. A study following a 1-h session per week of a supervised Tai Chi practice intervention for 12 weeks found significant improvement in all mentioned symptoms of neuropathy including sensory function, balance, and plantar sensory perception in addition to glucose controlling effect and musculoskeletal and cardiovascular fitness. The study suggests that Tai Chi exercise improve diabetes peripheral neuropathy patients control their posture, physical fitness and preventing falls. Another study found that moderate-intensity treadmill running was a key in reversing the progression of diabetic peripheral neuropathy [61]. A clinical trial on patients with T2DM without neuropathy symptoms carried out to investigate the effect of aerobic and resistance exercise.

Peripheral neuropathy reduces sensation in the hands and feet of patients with T2DM, consequently, their awareness of eventual sores that may happen during impact-full activities even walking or running will be affected. In this

regard, proper footwear, routine foot supervision, and low-impact exercises such as cycling, swimming, and resistance training are necessary for patients with peripheral neuropathy, peripheral vascular disease and are advised [19]. Recently a systematic review evaluated 12 randomized clinical trials on the effect of aerobic exercise on nerve function of patients with T2DM. Despite heterogeneity of exercise protocols, 11 studies have reported the beneficial effect of aerobic training on nerve function [62].

6.8 Efficacy of Different Exercise Regimen on Type 2 Diabetes

6.8.1 Aerobic

The effect of aerobic exercise on a different aspect of T2DM has been assessed in several studies. These aspects will be discussed in following. Studies on the effect of aerobic exercise on glycemic control have shown that regular training induces favorable alteration in fasting blood glucose, glycated hemoglobin A1C, and insulin sensitivity [6, 63–65]. In addition, aerobic exercise could interfere with complications emerged with diabetes such as dyslipidemia, hypertension, nephropathy, and CVD. Moreover, studies have revealed that regular adherence to exercise enhances the quality of life in diabetic patients [66].

Aerobic exercise is shown to acutely increase muscle glucose uptake up to fivefold by insulin-independent mechanisms. If exercise prolonged, muscle glycogen repletion post-exercise demand, holds glucose uptake elevated for about 2 h by insulin-independent and up to 48 h by insulin-dependent mechanisms. The short duration of near-maximal intensity aerobic exercise (20 min) may cause about 24 h of post-exercise insulin action improvements [8]. Aerobic training is a very consistently reported physical activity to improve glycemic control, insulin resistance and dyslipidemia in patients with type 2 diabetes [3]. The results of several studies comparing the effect of different kinds of exercise on quality of life indicated improved physical activity, glucometabolic control, patients' feeling of physical and mental well-being, leptin and adiponectin levels, HbA1c, body fat percentage. The aerobic exercise can safely and effectively improve the quality of life of in patients with T2DM [61]. De Castro et al. investigated the effect of 12 weeks of resistance, aerobic, and combined exercise on diabetes-induced rats. They found reduction abdominal fat storage and increase serum adiponectin and omentin. In addition, exercised rats performed much better in controlling blood glucose as well as decrease in IL-6 and CRP serum concentration [67]. Aerobic exercise when compared with the resistance and combined training protocols was more effective in reducing abdominal fat deposits, preventing hyperglycemia, decrease in serum IL-6 and CRP and increasing circulating adiponectin and omentin in the visceral adipose tissue [20].

6.8.2 Resistance

Evidence from several clinical trials raised a debate on effectiveness of resistance exercise on handling glycemic abnormalities. Few studies such as McGinley et al.'s [68] meta-analysis has reported that despite all benefits from strength exercises, no significant improvement in HbA1c gained after using resistance bands. However, noteworthy research studies claimed different outcomes. Recent studies emphasizing the importance and necessity of systematic resistance exercise in efficient controlling of insulin action and management of blood glucose and other cardiovascular risk factors [3]. Both aerobic and resistance training is proven to create fitness in skeletal muscle, adipose tissue, and liver, and regulated insulin sensitivity which is dependent on weight loss. 150 min per week of resistance working out with machines or free weights showed decrease in A1C by 0.57%. However, aerobic exercise showed a significantly greater reduction (difference of 0.18%) of A1C compared with resistance exercise [8]. In the case of older patients, even low-intensity resistance exercise for 16 weeks results in gaining muscular size and strength and significantly better glucose con-

trol [69]. A published research surveying progressive resistance training in adult participants with T2DM demonstrated that exercised participants had a significant improvement in mental health status along with attenuated body. Considering the fact that there were also studies that found no significant change, the effect of strength exercise on the quality of life in patients with T2DM was considered to be uncertain [61].

It was observed that participants who performed either resistance exercise alone or combined resistance and aerobic exercise consisted of longer time adherence than those randomized to only aerobic exercise. Resistance exercise participants also reported more sense of enjoyment and more support from their trainers. This might explain their greater long-term exercise adherence. Participants who remained adherent to exercise over time documented to have the same barriers to exercise such as work commitments, weather and illness/injury, but they benefited more facilitators including perceived health benefits, family support and use of strategies to maintain activity level, when were compared with those whose exercise adherence diminished over time [14].

6.8.3 Combined

Combined training is found to be the most effective for the aim of glycemic control when compared to either aerobic or resistance training alone [8]. Results from several studies documented improvements in anthropometric and biochemical parameters including increased muscle mass, better glycemic control, decreased in total intra-myocytic fat. In addition, patients receiving combined exercise had higher fatty acid oxidation capacity, physical function and mental health [61]. Most of the studies demonstrated that achieving both aerobic and resistance exercise by diabetic patients results in the strongest effect on increasing insulin sensitivity compared with when doing only aerobic exercise [7]. Interesting evidence demonstrated that resistance exercises, being less efficient in reducing serum glucose than aerobic workout when is performed prior to aerobic exercise at the same session. Results in greater stability in glucose levels, and less hypoglycemic experiences, both during the exercise session and after its completion, were reported in combined exercises [70].

6.9 Physical Activity Recommendation for Patients with Type 2 Diabetes

Since the challenges related to controlling blood glucose depend on diabetes type, activity type, and presence of diabetes-related morbidities, exercise recommendations should be designed to achieve the precise necessities of each person [8]. According to the American Diabetes Association recommendation for youngsters with type 1 or type 2 diabetes should have moderate- or high-intensity aerobic exercise for 60 min or more per day. It is recommended to resistance exercise for at least 3 days per week to strengthen muscles and bones. Type 1 and type 2 diabetic adults should follow moderate- to high-intensity aerobic exercise for 150 min or more per week in at least 3 sessions per week and a 2-day rest for recovery. Performing high-intensity or interval training depending on individual fitness level may need shorter duration: at least 75 min/week and 2–3 sessions/week of strength training on nonconsecutive days is also recommended. Additionally in order to increase flexibility, muscular strength, and balance, flexibility and balance training such as yoga and tai chi are recommended 2–3 times/week for older adults with diabetes [11]. For patients with T2DM and or prediabetes in order to prevent or manage the progression of the disease morbidity a minimum of 210 min/week of moderate-intensity exercise or 125 min/week of high-intensity exercise recommended. Exercise intensity should be selected depending on disease level, health condition, and primary individual fitness evaluation [19]. Given that performing aerobic exercises, such as jogging, brisk walking, cycling, and swimming, engages large and multiple groups of muscles, relatively prolonged periods of performing time

are required. In relation to morbidity and common health complications of type 2 diabetes patients such as being obese or overweight with physical disability, vision difficulty, or cardiovascular burdens, it is almost infeasible to achieve the adequate volume and intensity of the aerobic exercise to meet the expected results. On the other hand, resistance exercise especially high-intensity progressive resistance workout can be performed in a residential setting. Hence resistance exercises are more achievable and a safe choice for inactive older diabetic patients to achieve the goal without additional difficulties. Strength exercise should be carried out at 75–85% (1 RM) using muscular strength to move a weight or to work against a resistive load in a more adjustable way.

6.9.1 Type/Intensity/Duration

Moderate to high intensity aerobic exercise has been shown to reduce the risk of cardiovascular disease, thereby reducing the mortality of type 1 and type 2 diabetes. In type 1 diabetes, aerobic exercise improves the quality of life of patients by increasing cardiorespiratory fitness, reducing insulin resistance, and improving blood lipid levels and endothelial function. In patients with type 2 diabetes, exercise training result in lower A1C, triglycerides, blood pressure and insulin resistance. In order to promote skeletal muscle oxidative capacity, insulin sensitivity and glycemic control in type 2 diabetic adults, high intensity interval training (HIIT) can be performed. In addition, diabetes is known to be a factor that causes low muscle strength and accelerates muscle strength and functional decline, so it is necessary to participate in resistance exercise to improve muscle mass, body composition, fitness, bone mineral density, metabolic constants, and so on. On the other hand, resistance exercise can reduce blood glucose in patients with type 1 diabetes. Therefore, in combination with resistance and aerobic exercise in one exercise, it is recommended to perform resistance exercise first to lower blood glucose. Due to the formation of advanced glycation end products, these terminal glycation end products accumulate and accelerate during normal aging, so it is common to have limited joint mobility in elderly patients with T2DM. Therefore, flexibility training or balance training can increase the range of motion around the joints to reduce the risk of falling. In the case of peripheral neuropathy, yoga and tai chi are recommended to improve symptoms and quality of life. High-intensity physical exercise may bring some health risks to diabetic patients, including acute complications such as heart disease and hyperglycemia. For those who wish to increase their exercise intensity, it is recommended to exercise under medical supervision. However, if you want to do low- or medium-intensity physical exercise, you do not need medical monitoring before exercise. Most international guidelines recommend 3–7 days per week, at least 150 min per week for moderate to strong exercise, or more than 75 min per week for aerobic exercise. It is recommended to perform moderate to resistance exercise 2–3 days per week. Resistance exercise while performing flexibility and balance exercises such as yoga and Tai Chi was recommended. For each type of exercise, time and individual abilities should also be considered, and intensity and time should be appropriately increased and supervised by an exercise physiologist with knowledge of diabetes or a certified fitness professional. Proper exercise can lead to increased body heat and elevated core temperatures, resulting in increased blood flow and increased sweating. This can lead to poor glycemic control, neuropathy, dehydration, and heat-related diseases. Due to changes in joint structures related to glycemic excursions, and in order to prevent exercise-related overuse injuries and excessive aggravation to joint surfaces and structures, exercise training progression for individuals with diabetes should apply appropriately and personalized programs, particularly when taking statin medications for lipid control. Additionally, patients with peripheral neuropathy contributing exercise should take proper foot care and be supervised to prevent, and detect eventual problems early to reduce the risk of ulceration and amputation. Patients with a sign of progressive retinopathy should avoid vigorous aerobic or resistance exer-

cises, such as jumping, jarring, headstand, and breath-holding activities [8].

Taking together, diabetic and prediabetes individuals are strongly advised to contribute a regular exercise in a personalized mode and intensity at least for 150 min per week. To avoid any adverse effects, patients need to consult with and be supervised regularly by expert physiologists to prescribe an appropriate individualized exercise program and follow-up. It is obviously necessary to have social and family support to keep adherence to medical care alongside physical activity to meet the expected management and control of the disease.

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Exercise and Type 1 Diabetes

7

Xiya Lu and Cuimei Zhao

Abstract

Diabetes mellitus (DM) is the most common endocrine and metabolic disease caused by absolute or insufficient insulin secretion. Under the context of an aging population worldwide, the number of diabetic patients is increasing year by year. Most patients with diabetes have multiple complications that severely threaten their survival and living quality. DM is mainly divided into type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T1DM is caused by absolute lack of insulin secretion, so the current treatment for T1DM patients is exogenous insulin replacement therapy. At present, exercise therapy has been widely recognized in the prevention and treatment of diabetes, and regular aerobic exercise has become an important part of T1DM treatment. At the same time, exercise therapy is also used in conjunction with other treatments in the prevention and treatment of diabetic complications. However, for patients with T1DM, exercise still has the risk of hypoglycemia or hyperglycemia. T1DM Patients and specialist physician need to fully understand the effects of exercise on metabolism and implement individualized exercise programs. This chapter reviews the related content of exercise and T1DM.

Keywords

Exercise · Diabetes mellitus · Type 1 diabetes mellitus

7.1 Background

Diabetes mellitus (DM) is a chronic metabolic disease caused by a variety of pathogenic factors leading to a series of metabolic disorders (glucose, protein, fat, water, electrolytes, etc.) and chronic deficiency and/or dysfunction of blood glucose level and insulin secretion. With the global social and economic development, people's living standards gradually improved with the population aging, and some chronic diseases are becoming more and more common. Among them, the number of diabetic patients is increasing rapidly. According to relevant data, there were about 108 million diabetic patients in the world in 1980, reaching 422 million by 2014; developing countries such as China have become one of the countries with the largest number of diabetic patients. It is predicted that the number

X. Lu
Division of Gastroenterology and Hepatology, Digestive Disease Institute, Shanghai Tongji Hospital, Tongji University School of Medicine, Shanghai, China

C. Zhao (✉)
Department of Cardiology, Shanghai Tongji Hospital, Tongji University School of Medicine, Shanghai, China

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_7

of diabetic patients worldwide will reach 143 million by 2035 [1]. According to the World Health Organization (WHO), the number of people with diabetes in developing countries will increase by 69% in 2010–2030, and that in developed countries will increase by 20% [2]. According to the latest report of the International Diabetes Federation (IDF) in 2018, about 451 million adults (greater than 18 years old) worldwide suffer from diabetes. Among them, about 5 million people with diabetes die from diabetes and its complications. In addition, it is expected that the number of patients with diabetes may reach 693 million by 2045 [3]. Long-term metabolic disorders caused by diabetes may lead to progressive structural and dysfunctional abnormalities in multiple tissues and organs of the body, including heart attack, stroke, kidney failure, amputation, blindness, and nerve injury [4–6]. Except for the complications caused by chronic metabolic disorders, acute metabolic disorders may occur when the condition of diabetes is severe. If the patient is misdiagnosed or even poorly controlled, the disease progresses and the mortality rate is high. According to statistics from the American Diabetes Association (ADA), the incidence of complications in patients with diabetes for more than 3 years is higher than 46%, and the probability of complications for more than 5 years is higher than 61% [7]. According to WHO, there are more than 100 complications of diabetes with an incidence of about 98% [8]. Clinically, nearly 80% of diabetic patients die from diabetic cardio-cerebral vascular diseases [9, 10]; 20–40% of diabetic patients develop diabetic nephropathy [11–14]; diabetic retinopathy is the most common causes of blindness in adults in developed countries [15–17]; 2–4% of diabetic patients have foot ulcers [18]. Diabetes and its complications seriously affect patients' quality of life and increase mortality. Meanwhile, the medical expenses of diabetes and its complications, as well as work and wage losses, bring enormous economic pressure on diabetic patients [19–21]. Therefore, diabetes has become one of the world's three major diseases in addition to cancer and cardiovascular and cerebrovascular diseases, and has attracted the attention of researchers worldwide.

Currently, the World Health Organization (WHO, 1999) has adopted the Diabetes Typing Method proposed by the American Diabetes Association (ADA, 1997) [22]. According to the ADA diabetes classification, diabetes is divided into the following four types:

1. Type 1 diabetes (T1DM): T1DM is an abnormal glucose metabolism caused by absolute deficiency of insulin due to destruction of pancreas islet β cells. Among them, most patients are caused by autoimmune factors, called autoimmune type 1 diabetes (T1ADM). According to the existence of islet autoantibodies, T1DM can be divided into autoimmune type 1 diabetes (T1ADM) and idiopathic type 1 diabetes (T1BDM). And T1ADM can be further divided into classic type 1 diabetes and latent autoimmune diabetes in adults (LADA) [23]. Information about T1DM will be described in detail later.
2. Type 2 diabetes mellitus (T2DM): T2DM is caused by insulin resistance (decreased insulin sensitivity of peripheral tissues) or accompanied by insufficient insulin secretion, and is closely related to various factors such as genetic and environmental factors, obesity, and oxidative stress. Insulin resistance refers to a decrease in the sensitivity of target organs (liver, muscle, adipose tissue) to insulin. T2DM represents the most common type of diabetes at present, and is mostly developed in the middle-aged and elderly people, and often coexists with obesity. It can be independent of insulin therapy in the early stage.
3. Gestational diabetes mellitus (GDM): Any degree of abnormal glucose metabolism in the first stage of pregnancy, that is, pregnant women have normal glucose metabolism before pregnancy, abnormal glucose metabolism during pregnancy, and most of them return to normal after delivery.
4. Special types of diabetes: including genetic defects of the β-cell (maturity-onset diabetes mellitus of the young (MODY), mitochondrial diabetes mellitus (MDM)), genetic defects in

insulin action, diseases of the exocrine pancreas, endocrinopathies, drug- or chemical-induced diabetes, infections, uncommon forms of immune-mediated diabetes, and other genetic syndromes associated with diabetes (Fig. 7.1).

According to the latest standard issued by the American Diabetes Association (ADA) in 2019, the diagnosis of diabetes can be based on: fasting blood glucose (FPG), 75 g oral glucose tolerance test (OGTT), 2 h blood glucose (2 h-PG) value, random blood glucose, and glycosylated hemoglobin (GHbA1) [23] (Table 7.1).

7.2 Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM), also known as insulin-dependent diabetes mellitus, is a kind of disease caused by T lymphocytes which specifically damage pancreas islet β cells and cause absolute insulin deficiency. T1DM requires endogenous insulin for lifelong treatment, most commonly in children and adolescents [24]. At present, the increasing global incidence of T1DM is expected to increase by 50% in 20 years and reach 55 million by 2030 [25–27]. Among them, the annual average growth rate of childhood T1DM incidence is about 3–4% [28]. The annual incidence of T1DM in developing countries is also steadily increasing [29–31]. In the 1980s to 1990s, the incidence of T1DM in China was about 0.51/100,000 per year, while the latest survey data showed that it is about 1.01/100,000 per year [32]. According to WHO statistics, T1DM is more common among Nava, Sardinian and Kuwaitis, but much less in Asians and Latinos [28]. With the significant increase of prevalence, T1DM has received great attention.

7.3 Etiology and Pathogenesis of T1DM

The etiology of T1DM is very complicated, but it is currently believed that most T1DM belong to autoimmune diseases associated with genetic factors and environmental factors [33]. According to clinical data, 10–20% of newly diagnosed T1DM children have a first-degree family history, in which the incidence of TIDM is about 3–7%, and it is much lower than 1% in general family [28]. In the Caucasian population, the risk of T1DM is about 6% with siblings, which is 15 times higher than the risk of T1DM in general

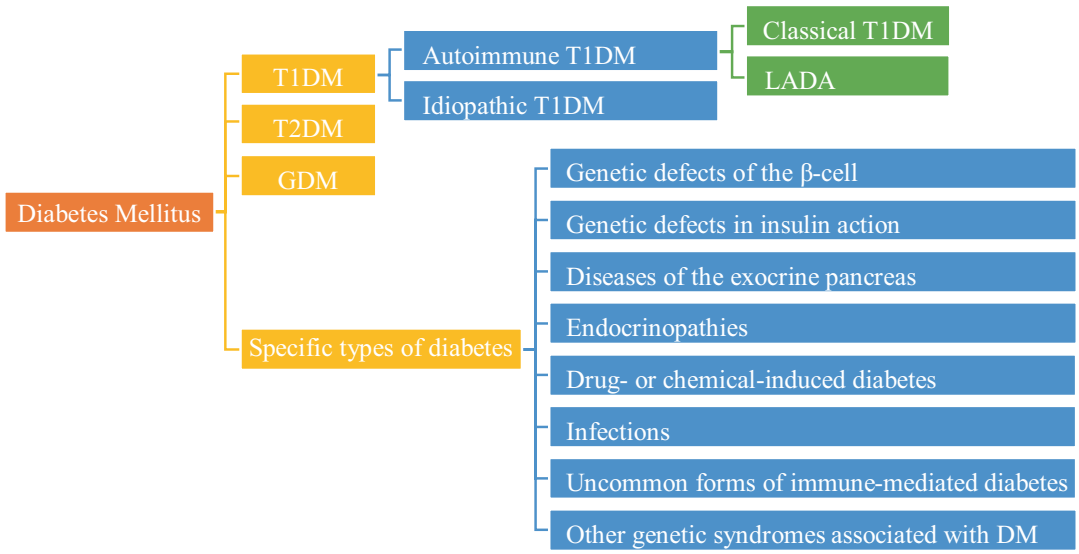

Fig. 7.1 Classification of diabetes mellitus

Table 7.1 Diagnosis of diabetes mellitus

		Blood glucose concentration	
Diabetes mellitus (DM)		FPG or	≥126 mg/dL (7.0 mmol/L)
		OGTT 2 h-PG or	≥200 mg/dL (11.1 mmol/L)
		Random blood glucose or	≥200 mg/dL (11.1 mmol/L)
		GHbA1	≥6.5% (48 mmol/mol)
Prediabetes	Impaired glucose tolerance(IGT)	FPG and	<126 mg/dL (7.0 mmol/L)
		OGTT 2 h-PG	140–199 mg/dL (7.8–11.0 mmol/L)
	Impaired fasting glucose(IFG)	FPG and	100–125 mg/dL (5.6–6.9 mmol/L)
		OGTT 2 h-PG	<140 mg/dL (7.8 mmol/L)
Gestational diabetes mellitus (GDM)		FPG or	≥92 mg/dL (5.1 mmol/L)
		OGTT 1 h-PG or	≥180 mg/dL (10.0 mmol/L)
		OGTT 2 h-PG or	≥153 mg/dL (8.5 mmol/L)

family; in addition, the coincidence rate of identical twins is 30–40%, but the coincidence rate of fraternal twins is only 6–8%, indicating that genetic factors play a significant role in the pathogenesis of T1DM [34].

The human leukocyte antigen (HLA) gene located on the 6p21 region of chromosome 6 is the major gene of T1DM. The HLA gene expresses HLA-DR3 and HLA-DR4 antigens which can be recognized by T cells and is closely related to the pathogenesis of T1DM. While HLA-DQ consists of a dimer of α chain and β chain, and its second exon is polymorphic [35]. It is generally believed that the heterozygote "DR3/DR4" is the highest risk gene for T1DM. More than 90% of T1DM patients have been found to carry DR3 or DR4, and approximately 30% of T1DM patients have two haploids simultaneously, of which 5% of children with this gene haplotype progress to T1DM [36]. However, HLA susceptibility genes have less influence on the pathophysiological processes after islet autoimmune activation and cannot directly induce T1DM [37]. Some non-HLA genes affect disease progression through autoimmune regulation after islet autoimmune activation [38]. To date, more than 50 non-HLA susceptibility genes or polymorphic sites of T1DM have been identified by genome-wide association studies (GWAS) [36]. Among them, the insulin gene (INS), protein tyrosine phosphatase non-receptor type 22 gene, cytotoxic T lymphocyte-associated protein type 4 gene (CTLA4), and interleukin 2 receptor gene (IL2RA) were mostly studied. At the same time, ubiquitin-proteasome-related gene variants such as PSMA3, PSMA6, and PSMC6 are also found to be associated with the risk of developing T1DM [39]. These non-HLA susceptibility genes are mostly affected by islet autoantibodies and HLA-DQ genotypes [40]. Currently, non-HLA allele single nucleotide polymorphisms and risk allele scores have been widely used in determining the prevalence of T1DM risk in children [41].

It is noteworthy that the coincidence rate of identical twins is less than 50%, indicating that in addition to genetic factors, the incidence of TIDM is also related to other factors, including environmental factors [34]. On the basis of carrying the T1DM risk gene, environmental factors can influence the expression of genes through epigenetic mechanisms and then induce T1DM. However, the specific mechanism has not yet been elucidated. These environmental factors that contribute to the pathogenesis of T1DM include infant feeding methods, vitamin D deficiency, intestinal microbial composition, and viral or parasitic infections [42–44]. The probability of developing T1DM in risk-generating formula-feeding infants is higher than that in breast-fed infants [45]. Thus, high-hydrolysis of bovine insulin during the processing of milk can avoid the islet autoimmune response and reduce the incidence of islet autoantibodies in the risk-bearing infants within 5 years [46]. For pregnant women and infants carrying T1DM risk genes, reasonable vitamin D supplementation can reduce the risk of T1DM in infants [47]. It was also reported that some patients with newly

diagnosed T1DM have specific IgM antibodies against Coxsackie virus, indicating that chronic viral infection may induce autoimmune reactions and promote T1DM development in genetically susceptible populations [47].

The pathogenesis of T1DM is closely related to autoimmune factors [48–50]. Some external factors acting on individuals with genetic susceptibility can activate T lymphocytes to mediate a series of autoimmune responses, leading to selective pancreas islet β cell destruction and insufficient insulin secretion in the body [51]. The whole process involves the regulation of a variety of immune cells of innate and adaptive immunity, including $CD4^+$ and $CD8^+$ T lymphocytes [52, 53], macrophages [54, 55], natural killer (NK) cells [56, 57], and dendritic cells [58]. In the pathogenesis of T1DM, Th1 cells mainly secrete IL-2, IFN-γ, TNF-α and other inflammatory factors, which mediate cellular immunity and cause local inflammation of islets; while Th2 cells mainly secrete IL-4, IL-5, IL-13 and other inflammatory factors, which induce B lymphocytes to proliferate and produce corresponding autoantibodies and participate in humoral immunity; in addition, antigen-presenting cells are processed and MHC-II molecules are copresented to activate cytotoxic T lymphocytes, resulting in destruction of pancreas islet β cells.

7.4 Clinical Manifestations of T1DM

The typical clinical symptoms of T1DM are "three more and one less," namely, polydipsia, polyuria, polyphagia, and weight loss. Some patients lack the typical performance of "three more and one less," but can also be manifested as fatigue, loss of appetite, muscle pain, changes in consciousness, and so on, but only some of them show obesity and diabetic ketoacidosis (DKA). DKA is the most common acute complication of diabetes. It is induced by the absolute deficiency of insulin, causing serious disorders of carbohydrate, fat and protein metabolism. Clinically, hyperglycemia, hyperketonemia, and metabolic acidosis are the main manifestations of DKA.

T1ADM, called autoimmune type 1 diabetes, is commonly develops in children and has more urgent onset, more obvious symptoms, and faster progress. If not treated in time, DKA may occur in T1ADM patients. The islet autoantibodies in the body fluid are mostly positive, including glutamate decarboxylase 65 (GAD65) antibody, protein tyrosine phosphatase-like protein (IA-2/ICA512) antibody, IA-2B/phogrin antibody, insulin antibody (IAA), and islet cell antibody (ICA). Compared with T1ADM, LADA has slow onset, inconspicuous clinical manifestations, less likely of DKA, and progressively decreased islet β cells function. Although patients with T2ADM also have acute onset and obvious pancreas islet β cell hypofunction or failure, islet autoantibodies are always negative. The damage of pancreas islet β cell function is transient so that insulin therapy is not required after the recovery of pancreas islet β cell function for T2ADM patients.

7.5 Treatment of T1DM

Due to the complications of T1DM, the current treatment for T1DM mainly focuses on symptomatic treatment which can be divided into four parts as follows:

7.5.1 Insulin Therapy

Because of the absolute insulin insufficiency, patients with T1DM need lifelong exogenous insulin replacement therapy to maintain their lives. Exogenous insulin replacement therapy should simulate the pattern of physiological insulin secretion as much as possible, including the supplementation of basal insulin and prandial insulin. The development and implementation of the program is based on the condition of disease, taking into account the economic situation, lifestyle and personal choice of T1DM patients and their family.

7.5.2 Medical Nutritional Therapy

The goal of medical nutrition therapy for patients with T1DM is to ensure the normal life and growth of patients, correct metabolic disorders, delay and reduce the occurrence and development of diabetic complications, and improve the quality of life.

1. Maintain dietary nutrition balance: to ensure a variety of nutrients required for T1DM patients;
2. Correct metabolic disorders: to control blood glucose, supply high-quality protein, prevent other essential nutrient deficiencies, and ensure that the child maintains optimal growth and development;
3. Maintain appropriate body weight: to adjust energy intake and consumption;
4. Select appropriate food varieties and eating patterns: to reduce blood glucose fluctuations, and prevent all kinds of acute and chronic diabetic complications;
5. Develop a healthy eating habit: to improve the living quality of T1DM patients and improve overall health.

7.5.3 Exercise Therapy

Information about exercise therapy will be detailed in Part 4.

7.5.4 Other Treatments

7.5.4.1 Pancreas and Islet Transplantation

T1ADM is a pancreas islet cell-specific autoimmune disease that requires lifelong dependence on exogenous insulin therapy. Pancreas transplantation and islet transplantation are currently the only treatment that can partially or completely restore physiological insulin secretion.

7.5.4.2 Stem Cell Therapy

At present, stem cell therapy for diabetes is still in the research and observation stage, awaiting clinical application. It is not currently available for clinical routine treatment.

7.5.4.3 Oral Hypoglycemic Agents

Oral medication is currently not recommended for the treatment of T1DM patients.

7.6 Exercise and T1DM

Exercise therapy refers to a training method that uses the power of device, the freehand or the patient's own strength, and through certain exercise modes (active or passive exercise, etc.) to enable the patient to obtain systemic or local motor function and sensory function recovery. According to the nature of muscle contraction or the presence or absence of external force, it can be divided into three categories: active exercise, assistive exercise and passive exercise. Exercise therapy has the characteristics of good effect, low treatment cost, easy patient acceptance, and relatively few adverse reactions.

Exercise is an important method for the treatment of diabetes patients together with drug therapy and diet therapy [59]. Aerobic exercise refers to a durable exercise that increases the inhalation, delivery, and utilization of oxygen in the body [60, 61]. Studies have shown that aerobic exercise plays an essential role in secondary prevention of diabetes [62]. However, based on the particularity of T1DM, some potential adverse events may still occur during exercise. Therefore, it is of vital importance to understand and master the regular and reasonable exercise therapy for patients with T1DM.

7.6.1 Effects of Exercise on Patients with T1DM

Aerobic exercise and diet control are the two cornerstones of diabetes treatment. Aerobic exercise can improve insulin sensitivity and blood glucose and lipid metabolism, thereby reducing insulin dosage and improving glycemic control [63–65]. Boniol et al. performed a literature research to evaluate the effect of per additional minutes of

physical activity per week on fasting blood glucose and HbA1c changes using mixed-effect random models [66]. It was found that exercise reduced the levels of fasting blood glucose and HbA1c in T1DM patients, and its beneficial effects were associated to the duration of weekly exercise rather than the type of exercise [67].

In addition to the beneficial effects on fasting blood glucose and HbA1c levels, exercise therapy can also play a positive role in the treatment of diabetic complications such as cardiovascular disease and peripheral neuropathy. The main mechanism is as follows:

1. Aerobic exercise can increase the number of cellular glucose transporters, improve the function and quantity of insulin receptors on skeletal muscle cells and fat cells, enhance the sensitivity of peripheral tissues to insulin, and regulate blood glucose metabolism [68–71];
2. Aerobic exercise can regulate energy balance, enhance the uptake and oxidation of fatty acids in muscle tissues, and improve cardiovascular function [72];
3. Aerobic exercise can reduce inflammation, increase the expression of nitric oxide synthase (NOS) in vascular endothelial cells, promote the release of nitric oxide, improve vascular endothelium and mitochondrial function, and increase myocardial cell activity [73, 74];
4. Aerobic exercise can promote lipoprotein activity, increase serum high-density lipoprotein content, improve blood lipid metabolism, reduce insulin resistance and platelet aggregation, reduce body weight, and lower blood pressure [75, 76];

7.6.1.1 Effects of Exercise on Diabetic Microangiopathy

Diabetic microangiopathy, including diabetic nephropathy and diabetic retinopathy, is one of the most common complications in patients with T1DM. Particularly, diabetic retinopathy is more common in children [77, 78]. There are many risk factors for T1DM complicated with microangiopathy, including T1DM duration, poor glycemic control, hypertension, and dyslipidemia [79–85]. It has been found that functional changes in microcirculation and subclinical vasculopathy in patients with T1DM preceded the occurrence of complications of microvascular disease [86]. A prospective cohort study showed that the incidence of diabetic nephropathy was 10.0 per 1000 person-years, of which T1DM patients with persistent micro/macroproteinuria had higher HbA1c levels and were more likely to have retinopathy and subclinical peripheral nerves [87]. In a prospective cohort study of 335 patients with T1DM, Kramer et al. found that diabetic retinopathy is associated with exercise-related heart rate changes [88]. In 2019, a cross-sectional multicenter study of 18,028 T1DM patients from Germany and Austria found an inverse association between exercise and HbA1c, diabetic ketoacidosis, dyslipidemia, hypertension, as well as between exercise and retinopathy or microalbuminuria [89]. Therefore, on the basis of conventional insulin therapy, exercise therapy for patients with T1DM can improve microvascular complications in patients with T1DM, thereby improving the quality of life of patients.

7.6.1.2 Effects of Exercise on Diabetes Complicated with Macrovascular Disease

In addition to microcirculatory lesions, large blood vessel lesions are also common complications of diabetes patients. The pathogenesis of diabetic macroangiopathy is closely related to age, disease course, hyperglycemia, insulin resistance, abnormal lipid metabolism, and abnormal blood coagulation [90, 91].

Atherosclerosis is the most common macrovascular disease in diabetic patients [92]. Diabetic patients with atherosclerosis are more likely to develop coronary heart disease, angina pectoris, acute myocardial infarction, ischemic stroke, or peripheral vascular disease. Adamska et al. collected data from 148 patients with T1DM and found that atherosclerotic dyslipidemia is associated with increased neovascularization, manifested by high CD34 expression and low-reactivity with single-point laser Doppler flowmetry (LDF) [86]. Lovshin et al. found that the presence of high coronary artery calcification in long-term

T1DM patients was associated with both large neurofibrillary neuropathy and retinopathy, but not renal hemodynamic function, revealing a relationship between atherosclerosis with microvascular complications [93].

Exercise therapy was proved to improve the circulation of diabetic patients to some extent. Atherosclerosis occurring in patients with T1DM is associated with endothelial dysfunction, and 18-week exercise training can effectively reverse endothelial dysfunction in children with T1DM and also delay the progression of T1DM disease [94]. It was also reported that exercise therapy based on conventional treatment can better control blood glucose and lipid levels, thereby delaying the occurrence of macrovascular disease [70].

7.6.1.3 Effects of Exercise on Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy (DPN) is a clinical or subclinical chronic sensory nerve and motor nerve damage caused by hyperglycemia and substance metabolism disorders [95, 96]. Diabetic foot is the most common DPN in patients with T1DM. Due to peripheral nerve injury, T1DM patients often present with progressive sensory dysfunction (pain and numbness), foot ulcers, gangrene, and even amputation [97, 98].

Recent studies have shown that proper exercise such as brisk walking, fitness running, and cycling can improve the symptoms of peripheral nerve injury and effectively reduce fasting blood glucose and glycated hemoglobin, thus improving the quality of life for DPN patients [99, 100]. Balducci et al. selected 78 patients with diabetes without peripheral neuropathy for a 4-year prospective randomized controlled trial in which the exercise group performed a 4 h fast-moving exercise every week; the control group without intervention remained the habit of sedentary life style [99]. The results of this study showed that the exercise group had faster nerve conduction velocity and lower neuropathy rate than the control group, indicating that exercise can prevent or delay the onset of DPN. Yoo et al. performed a 16-week exercise intervention on 14 patients with sedentary DPN in a step-by-step manner [100]. The exercise time was gradually increased from 30 to 50 min/d, and the exercise intensity gradually reached 70% from 50% oxygen reuptake reserve (VO2R). The results showed that exercise can alleviate pain and reduce the impact of pain on patients' daily lives and improve the living quality of DPN patients. In addition, studies have shown that high-intensity interval training (HIIT) is more effective in improving exercise capacity and skeletal muscle metabolism, and is easier to adhere to for diabetes patients [101, 102].

7.6.2 Risk of Exercise in Patients with T1DM

Although T1DM patients are encouraged to participate in various physical exercises, the potential risks of exercise cannot be ignored. Under physiological conditions, exercise increases insulin sensitivity and inhibits hepatic glucose production, thereby maintaining blood glucose levels [103–105]. Studies have shown that after a single moderate intensity exercise (maximum heart rate 60–75%) exercise, insulin sensitivity improvement can be observed for up to 17 h [106]. Due to the absolute lack of endogenous insulin secretion in patients with T1DM, T1DM patients only depend on subcutaneous injection of exogenous insulin, but the release of exogenous insulin is not physiologically regulated. When exercise leads to increased skeletal muscle energy consumption and increased insulin sensitivity, it further promotes blood glucose intake [107]. However, in the condition of exogenous insulin intervention, hypoglycemia may occur in patients with T1DM. Reduced storage of hepatic glycogen and muscle glycogen after exercise will accelerate blood glucose intake and resynthesize glycogen, which may lead to hypoglycemia at night. In addition, the ability to recover blood glucose levels in T1DM patients is very limited compared to nondiabetic patients. When hypoglycemia occurs in patients with T1DM, neuroendocrine (catecholamine and glucagon), autonomic (sympathetic activity), and metabolic (glycogen and lipolysis) regulations are slower

than those in the nondiabetic patients. Conversely, when T1DM patients are not injected with insulin or when they have low levels of insulin before exercise, the levels of glycogen output and hyperglycemic hormones such as glucagon were elevated. However, skeletal muscle cells do not have a corresponding increase in glucose uptake, and the progressive increase of blood glucose occurs. At the same time, exercise also promotes the decomposition of fat in the body, which increases the concentration of free fatty acids and ketones in the blood, and may cause diabetic ketoacidosis if it is severe.

On the other hand, excessive exercise may aggravate the chronic complications of diabetes. In T1DM patients with macrovascular disease especially coronary atherosclerosis, exercise may induce angina pectoris [108]. However, in patients with simple cardiovascular diseases, the risk of sudden severe heart disease during exercise training is small [109]. In patients with diabetic retinopathy, excessive strenuous exercise may promote proliferative retinopathy and increase the risk of retinal detachment and fundus hemorrhage [110, 111]. A study of T1DM patients with proteinuria found that strenuous exercise was associated with increased urinary protein excretion [112]. Moreover, excessive exercise can increase the risk of skin ulceration and infection in patients with partial DPN [113]. For patients with diabetes mellitus with autonomic neuropathy, clinical manifestations such as decreased cardiac output, decreased heart rate, orthostatic hypotension, abnormal sweating, and impaired gastrointestinal function may be further aggravated after exercise [114].

7.6.3 Precautions Against Exercise-Related Risks in Patients with T1DM

The fitness of T1DM patients is related to many factors, including age, duration of diabetes, dose and injection time of exogenous insulin, time and type of meal, physical status, and duration and intensity of exercise. Individualized exercise treatment regimens should be performed based on the specific response of T1DM patients to exercise [115, 116]. In addition, the control of blood glucose and insulin injection dose as well as appropriate dietary supplementation is necessary to prevent hypoglycemia or hyperglycemia caused by exercise in T1DM patients.

Low or moderate intensity aerobic exercise is more suitable for patients with T1DM [117, 118]. Due to the potential risk of hypoglycemia or retinal hemorrhage, T1DM patients cannot participate in high intensity professional sports such as diving, rock climbing, fighting, and weightlifting. To prevent hypoglycemia after exercise, exercise is preferably scheduled to be 1–3 h after insulin injection or after meals, and the insulin injection dose is recommended to be reduced by 10–40% before exercise. At the same time, blood glucose monitoring is an important means of preventing potential risks of exercise. The ideal blood glucose range for exercise is 6.7–10.0 mmol/L. Exercise therapy should not be used when blood glucose is <4.0 mmol/L or > 14.0 mmol/L. In order to avoid metabolic disorders, it is necessary to supplement sufficient insulin to maintain blood glucose stability and blood ketone negative.

Blood glucose is the most important source of energy for the body, which plays a potential role to prevent hypoglycemia during exercise. It is more effective to use an appropriate amount of carbohydrates than to control insulin dose. T1DM patients should routinely prepare carbohydrates as energy supplements before and after exercise, especially for easily absorbed carbohydrates. Most T1DM patients undergo 30 min of exercise which can generally prevent hypoglycemia. When exercise lasts longer than 30 min, especially when exercise intensity is high, additional carbohydrates can be added after exercise to prevent hypoglycemia after exercise. An amount of 20–60 g carbohydrates can be replenished every 30 min during moderate or higher intensity exercise [119].

In order to ensure the rationality of exercise prescriptions, it is necessary for specialist physicians to assess the physical condition and exercise level of T1DM patients before exercise prescription. According to the actual situation of

the patient, a reasonable exercise prescription should be established to improve the blood glucose and lipid levels, and also to make the exercise training more secure. In addition, according to the type and degree of complications of T1DM patients, a more personalized exercise prescription is formulated to solve the patient's complications more specifically.

7.7 Summary and Prospects

T1DM is caused by the destruction of pancreas islet β cells, which leads to insulin secretion dysfunction and abnormal blood glucose regulation. It is believed that T1DM is closely related to the immune mechanism, but the specific pathogenesis has not yet been fully elucidated. In addition to metabolic disorders, T1DM patients have different diabetes complications, which seriously affect their quality of life. At present, the major treatment of T1DM is still dominated by exogenous insulin replacement therapy. In recent years, researchers have paid more and more attention to the relationship between exercise and T1DM, which provides a new idea for the treatment of T1DM. Exercise, in particularly regular aerobic exercise, has been included in one of the important interventions of diabetes treatment. Exercise has been proved to improve blood glucose and lipid metabolism, reduce and alleviate the occurrence of diabetes-related complications, and improve the living quality of T1DM patients. However, there are still many potential risks of exercise. Therefore, T1DM patients and specialist physician should strictly follow the principles of exercise therapy and develop individualized exercise treatment programs according to the situation of T1DM patients. Meanwhile, effective measures should be taken into account in advance to prevent hypoglycemia or hyperglycemia caused by exercise. Moreover, the supervision, maintenance, and regulation of exercise therapy should be further explored and promoted in the treatment of T1DM patients in the future.

Acknowledgments This work was supported by the grants from Shanghai Health and Family Planning Commission (20154Y0026 to Cuimei Zhao), and National Natural Science Foundation of China (81600228 to Cuimei Zhao).

Competing financial interests: The authors declare no competing financial interests.

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Exercise and Polycystic Ovary Syndrome

8

Amie Woodward, Markos Klonizakis, and David Broom

Abstract

Polycystic ovary syndrome (PCOS) is a complex endocrinopathy affecting both the metabolism and reproductive system of women of reproductive age. Prevalence ranges from 6.1–19.9% depending on the criteria used to give a diagnosis. PCOS accounts for approximately 80% of women with anovulatory infertility, and causes disruption at various stages of the reproductive axis. Evidence suggests lifestyle modification should be the first line of therapy for women with PCOS. Several studies have examined the impact of exercise interventions on reproductive function, with results indicating improvements in menstrual and/or ovulation frequency following exercise. Enhanced insulin sensitivity underpins the mechanisms of how exercise restores reproductive function. Women with PCOS typically have a cluster of metabolic abnormalities that are risk factors for CVD. There is irrefutable evidence that exercise mitigates CVD risk factors in women with PCOS. The mechanism by which exercise improves many CVD risk factors is again associated with improved insulin sensitivity and decreased hyperinsulinemia. In addition to cardiometabolic and reproductive complications, PCOS has been associated with an increased prevalence of mental health disorders. Exercise improves psychological well-being in women with PCOS, dependent on certain physiological factors. An optimal dose–response relationship to exercise in PCOS may not be feasible because of the highly individualised characteristics of the disorder. Guidelines for PCOS suggest at least 150 min of physical activity per week. Evidence confirms that this should form the basis of any clinician or healthcare professional prescription.

Keywords

Polycystic ovary syndrome · Exercise · Physical activity · Reproductive health · Cardiovascular disease

8.1 Background

8.1.1 Diagnosis and Prevalence

Polycystic ovary syndrome (PCOS) is a complex endocrinopathy affecting both the metabolism and reproductive system in women of reproductive age [1]. Currently, three sets of diagnostic criteria exist; (1) the National Institutes of Health (NIH) criteria from 1990, (2) the American Society of Reproductive Medicine sponsored

A. Woodward · M. Klonizakis · D. Broom (✉)
Faculty of Health and Wellbeing, Centre for Sport and Exercise Science, Sheffield Hallam University, Sheffield, UK
e-mail: d.r.broom@shu.ac.uk

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_8

European Society of Human Reproduction and Embryology (ASRM/ESHRE) criteria revised in 2003, and (3) the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society criteria from 2009 [2]. Each of the criteria is predicated on the presentation of the main characteristics of PCOS; polycystic ovaries (PCO), clinical or biochemical hyperandrogenism (excessive levels of androgens), and chronic oligo-anovulation (infrequent or absent ovulation) [2].

The NIH criteria indicates that chronic anovulation and clinical or biochemical hyperandrogenism must both be present [3]. The ASRM/ESHRE criteria are known as the Rotterdam criteria, named after the place where the consensus meeting was held. The criteria states that of the main characteristics (PCO, clinical or biochemical hyperandrogenism, and chronic oligo-anovulation), any two of the three could be present [4]. Both of the aforementioned criteria stipulate that other disorders that could be responsible for these symptoms must be excluded first, such as congenital adrenal hyperplasia, Cushing's syndrome, which is a condition caused by excessive adrenal production of cortisol, androgen secreting tumours and hyperprolactinemia, where an individual has excessive serum levels of prolactin [2]. The more recent AE-PCOS criteria are based on three conditions: hyperandrogenism (clinical or biochemical), ovarian dysfunction (encompassing both PCO and oligo-anovulation) and the exclusion of other androgen excess related disorders [5].

The prevalence of PCOS therefore depends on which criteria are used. Reports of prevalence range from 6.1 to 19.9% [6]. Table 8.1 indicates reported prevalence from studies using different diagnostic criteria in Australia [7], Turkey [6] and Iran [8].

It is clear from the data in Table 8.1 that the Rotterdam criteria is the least restrictive, because the NIH and AE-PCOS criteria both consider hyperandrogenism as a central facet in the pathogenesis of PCOS indicating this should be present along with PCO or oligo-anovulation [9]. The Rotterdam criteria allows for additional phenotypes of PCOS, such as those with PCO and menstrual irregularity without hyperandrogenism.

Table 8.1 Prevalence of PCOS (%) based on individual criteria[a]

	Diagnostic Criteria		
	NIH[b]	AES[c]	Rotterdam[d]
March et al. [7]	8.7	12.0	17.8
Yildiz et al. [6]	6.1	15.3	19.9
Mehrabian et al. [8]	7.0	7.9	15.2

[a]Adapted from Burks and Wild [2]
[a]National Institutes of Health international conference 1990
[b]Androgen Excess Society diagnostic criteria 2009
[c]Task force sponsored by the European Society of Human Reproductive and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), 2003

Nevertheless, it can be considered as an emerging epidemic that needs to be attenuated due to numerous debilitating symptoms and co-morbidities.

8.1.2 Associated Symptoms and Co-morbidities

Though not acknowledged in the diagnostic criteria, women with PCOS often have higher amounts of visceral fat (around the organs in the peritoneal cavity) [10], up to 80% prevalence of insulin resistance [11] and up to 70% prevalence of dyslipidaemia [12]. PCOS is associated with reproductive and cardiometabolic complications and increased risk of cardiovascular diseases (CVD); 40% of women with PCOS are affected by infertility [13], while there is a two to four-fold higher incidence of metabolic syndrome in the PCOS population in comparison to weight-matched healthy women [14]. This is primarily true for those phenotypes presenting with hyperandrogenism; this phenotype has been associated with a metabolic profile that encompasses higher incidences of insulin resistance and a worse lipid profile than those women with a normoandrogenic profile, despite comparable distributions of body weight [15].

It is hypothesised that insulin resistance underpins this worse metabolic profile rather than androgen excess itself. Insulin acts as a co-gonadotropin, stimulating the ovary to produce

testosterone, whilst simultaneously inhibiting the production of sex hormone binding globulin (SHBG) which leads to a higher concentration of bio-available testosterone [16]. Additionally hyperinsulinemia can lead to hepatic overproduction of very low density lipoproteins (VLDL), and elevation in triglycerides (TG) through decreased lipoprotein lipase-mediated lipolysis, leading to increased circulating chylomicrons and VLDL [17]. Skeletal muscle insulin resistance may also promote dyslipidaemia by redirecting dietary carbohydrate sources away from skeletal muscle glycogen synthesis into hepatic de novo lipogenesis, and subsequently increased circulating triglycerides assembled from glucose substrates and a reduction in high-density lipoprotein (HDL) concentrations [18].

8.1.3 Treatment

It is difficult to isolate a single disruptive factor for treatment, since PCOS is often presumed to be the result of an endocrine system feedback loop [19]. In addition, the individual presentation of PCOS symptoms, resulting in various phenotypes, plays a role in the treatment chosen. Because of the complex pathophysiology of PCOS, treatment ranges from pharmacological to alternative therapies such as acupuncture [20]. Pharmacological options include biguanides to improve insulin sensitivity, the oral contraceptive pill to restore menstrual regularity, clomiphene to induce ovulation and statins to lower blood cholesterol [21].

Lifestyle modification should be the first line of therapy for women with PCOS [22]. Interventions that target insulin sensitivity and, for women with obesity and PCOS, promote weight loss are a critical in the management of the condition [23]. Recent research indicates that exercise of a moderate intensity (~50–70% VO_{2max}), for approximately 12 weeks, produces improvement in cardiometabolic risk factors, including blood pressure, TG, insulin resistance and inflammation, and reproductive outcomes such as increased ovulation rates and greater responsiveness to IVF [10, 24]. The remainder of this chapter will outline and describe current research examining the effects of exercise on cardiometabolic, reproductive and mental health outcomes in women with PCOS.

8.2 Exercise and PCOS

8.2.1 Reproductive Function

PCOS accounts for approximately 80% of women with anovulatory infertility [25]. PCOS causes disruption at various stages of the reproductive axis, including the hypothalamus–pituitary axis, leading to inappropriate regulation of ovarian steroidogenesis and folliculogenesis [26]. The key neuroendocrine abnormalities involved in PCOS are increased gonadotropin-releasing hormone (GnRH) pulsatile activity, leading to disproportionate levels of luteinizing hormone (LH) in comparison to follicle-stimulating hormone (FSH) [26], known as the LH:FSH ratio. In turn, overproduction of LH stimulates ovarian theca cell hyperactivity, culminating in increased ovarian steroidogenesis. The lack of FSH stimulation of granulosa cell development and aromatase production means that the androgens are not converted to oestrogen, and disruption of follicle maturation and ovulation occurs [27, 28].

8.2.1.1 Effects of Exercise on Reproductive Function in Women with PCOS

Several studies have explored the impact of exercise interventions on reproductive function, with results indicating improvements in menstrual and/or ovulation frequency following exercise in comparison to diet or control groups [29–31]. These improvements included a change from non-ovulatory to ovulatory cycles, restoration of cycle regularity and improvement in inter-cycle variation [24] indicating that exercise may be more beneficial to reproductive function than caloric restriction alone. Evidence suggests that the pregnancy rate among women with PCOS undertaking an exercise intervention is 35% [31], with pregnancy being a common reason for

drop-out amongst participants with PCOS in exercise trials [32]. It has been noted that lifestyle modification for overweight or obese infertile women with PCOS is a cost-effective solution for those women wishing to conceive, either as a primary intervention or in conjunction with fertility treatment [33].

It has been suggested that the type and frequency of exercise is not important in improving reproductive function in PCOS [24], but contradictory findings suggests otherwise. A recent feasibility trial examining the effects of progressive resistance training (PRT) on women with PCOS found PRT to be effective at improving cardiometabolic outcomes, but found no such effect on reproductive outcomes [34]. The optimal type or intensity of exercise needed in order to elicit a response from the reproductive system remains to be elucidated. However, there are an insufficient number of studies that examine the impact of resistance training in PCOS [32].

Weight loss does not appear necessary to achieve improvements in reproductive function. However, a weight loss of as little as 5% may improve spontaneous ovulation rates, reduce associated metabolic complications and increase chances of conception [35]. In addition, optimisation of body mass index (BMI) into the "healthy" range for women with obesity or overweight may attenuate the risk of pregnancy-related complications in women with PCOS, including gestational diabetes, hypertensive disorders and premature delivery [36].

Therefore, for the two-thirds of women with PCOS with overweight or obesity, an exercise intervention intended to maximise weight loss may offer additional benefits. This can also be important for those overweight women with PCOS, intending to undertake fertility treatment. Excess body mass can blunt the response to treatment, and higher doses of ovulation-inducing medications may be needed [25]. Subsequently, exercise with concurrent weight loss may be optimal and cost-effective in these cases. If weight loss is to be targeted through exercise interventions, greater weight loss is achievable with an intervention of a duration of at least 6 months [24].

8.2.1.2 Mechanism of Action

In keeping with the presumption of PCOS occurring as a result of an endocrine feedback loop, it is not immediately clear whether neuroendocrine abnormalities are a cause or consequence of PCOS [26]. In normal menstrual physiology, both oestradiol (depending on the stage of folliculogenesis) and testosterone provide negative feedback to the hypothalamus to inhibit the frequency and amplitude of the GnRH pulse [37]. In PCOS, it appears that persistent elevated androgen levels may decrease the sensitivity of the GnRH pulse activator to inhibition by ovarian steroids, preventing the normal negative feedback suppression of LH [37, 38].

The hyperandrogenemic milieu, exacerbated by hyperinsulinemia, may over-stimulate the growth and recruitment of antral follicles, which in turn may lead to threefold higher concentrations of anti-Müllerian hormone (AMH), produced by granulosa cells, in women with PCOS compared to healthy women [39]. AMH reduces follicular sensitivity to FSH and serves a purpose to prevent the depletion of all primordial follicles at once [40]. However, elevated concentrations may disrupt folliculogenesis by inhibiting aromatase and preventing the selection of a dominant follicle, resulting in follicular arrest at the small antral stage [39].

Enhanced insulin sensitivity underpins the mechanisms of how exercise restores reproductive function [24]. Reducing hyperinsulinemia decreases ovarian steroidogenesis and increases SHBG, and the resulting return to a normoandrogenic environment may restore sensitivity of the GnRH pulse activator to steroid inhibition of LH. Subsequently, decreased levels of LH and androgens may halt the excessive recruitment of antral follicles, allowing a dominant follicle to mature, eventually leading to ovulation.

Weight loss in PCOS, either with or without exercise, can lead to reductions in visceral fat as indicated by improvements to waist-to-hip (WHR) ratio, a measure which is strongly correlated with insulin resistance [24]. Indeed, studies reporting a reduction in WHR have also reported reductions of fasting insulin [24]. Subsequently, the resultant reduction in circulating androgens

may explain the additional benefits of weight loss in overweight or obese women with PCOS.

8.2.2 Cardiometabolic Outcomes

Women with PCOS typically have a cluster of metabolic abnormalities that are risk factors for CVD. These include obesity, metabolic syndrome, impaired glucose tolerance, hypertension, impaired endothelial and myocardial function, and dyslipidaemia [14, 41, 42]. Evidence suggests that sub-clinical atherosclerosis, indicated by carotid intima–media thickness (cIMT), is higher in women with PCOS compared to weight-matched controls [41, 43]. Additionally, PCOS is associated with increased low-grade inflammation, with higher circulating concentrations of many inflammation markers that mediate CVD, such as C-reactive protein, increased white cell count, neutrophil–lymphocyte ratio, tumour-necrosis factor-alpha (TNF-a) and interleukin-6 (IL-6) [44–49]. It follows that women with PCOS have a 50% increased risk of CVD events compared to weight-matched counterparts [14] and that the rate of diabetes is 2.6 times higher than that of the general female population [50].

There has been a lot of discussion on whether the increased association with CVD risk factors is due to PCOS itself, or whether it is due to the associated obesity. Indeed, the increased rate of diabetes in women with PCOS positively correlated with BMI [50]. However, while obesity may certainly be an exacerbating factor [19], it is estimated that at least half of women with PCOS are not overweight or obese [50]. As evidenced by those risk factors that are increased in comparison to weight-matched healthy women, there are clearly additional mechanisms underlying the increased CVD risk in PCOS. Nevertheless, a common feature in both overweight and lean women with PCOS is central adiposity [16]; the tendency for fat to accumulate around the abdominal area, including both visceral fat and the subcutaneous fat present underneath the skin. A woman with a BMI within the "healthy" range could still exhibit abdominal obesity due to excessive visceral fat. This type of body composition may contribute to insulin resistance because visceral fat secretes IL-6, an adipokine that inhibits insulin-mediated glycogenesis and stimulates hepatic (liver) gluconeogenesis [51].

8.2.2.1 Effects of Exercise on Cardiovascular Disease Risk Factors in Women with PCOS

There is irrefutable evidence that exercise mitigates CVD risk factors in healthy populations [52], populations with dyslipidaemia [53], populations with metabolic syndrome [54, 55], and in women with PCOS [56]. One of the most prominent studies is the case-control INTERHEART study, which found moderate to vigorous intensity exercise to be one of nine lifestyle modifications that are protective against myocardial infarction (heart attack) [57]. However, some studies have produced inconsistent results with respect to the effectiveness of exercise only, without any additional dietary or pharmacological interventions, in improving biomarkers of CVD risk: This is particularly true regarding cholesterol and lipoprotein concentrations [10], and inflammation [58].

Longer exercise interventions (e.g. >20 weeks; [54, 55, 59]) are associated with improved lipid profile, and the reversal of metabolic syndrome in healthy populations. This might account for some of the discrepancy in PCOS research, with exercise interventions typically ranging from eight to 24 weeks in duration. PCOS studies with longer intervention durations have found improvements in VLDL and HDL [60], whereas shorter interventions have found no change in LDL and HDL, despite improvements in cardiorespiratory fitness [10]. In order to promote changes to blood lipids in a shorter duration, the addition of a dietary component may make this achievable [30].

Exercise interventions for 12 weeks, 3 sessions per week, can promote weight loss and reductions in BMI in women with PCOS [10]. These changes are typically associated with a reduction in WHR or waist circumference, indicating a decrease in abdominal obesity. Waist circumference and WHR may be a better indicator of health than BMI alone because of its association with other CVD risk factors, such as impaired

glucose metabolism [57, 61]. While changes to BMI and waist circumference seem to be more effectively reduced with combined exercise and dietary interventions in comparison to dietary intervention alone, weight loss is still achievable in shorter exercise-only interventions [24]. However, the amount of weight lost seems to be proportionately related to duration of the intervention [10]. Longer duration (20 weeks+) may be the key to promote greater weight loss, irrespective of type and frequency of exercise [30].

In the INTERHEART study, hypertension is well recognised as a CVD risk factor, stated as one of the main modifiable risk factors responsible for most incidents of myocardial infarction [57]. Hypertension is one of the key characteristics of metabolic syndrome, and there is an inverse relationship between blood pressure and insulin sensitivity [54]. Evidence supports the role of exercise as treatment for hypertension, with exercise training decreasing blood pressure in around 75% of hypertensive adults, with a more pronounced affect in women [62].

In women with PCOS, the results are less clear; some studies find no statistically significant improvements in systolic blood pressure (SBP) or diastolic blood pressure (DBP) in exercise interventions from 12 to 24 weeks [63, 64], while others have found small, but clinically meaningful, improvements in SBP with exercise or exercise in combination with dietary intervention [30, 65]. These conflicting results may be due to the wide range of phenotypes possible under the PCOS diagnostic criteria; indeed, prevalence of hypertension in PCOS is reported to be between 5.5 and 12% [66, 67] and as such many PCOS participants may be normotensive.

Finally, there is much evidence to support the role of exercise as treatment for one of the most common metabolic aberrations of PCOS: insulin resistance. PCOS research supports the role of exercise in improving insulin sensitivity immediately after an acute bout of exercise [68], but also in the long-term with exercise interventions from 3 months [63, 65] to 20+ weeks [30, 31]. Insulin resistance has been linked to abdominal obesity, hypertension, the development of type II diabetes (T2D) [69], dyslipidaemia and inflammation [70], meaning it is a key indicator of CVD risk in women with PCOS, where the prevalence of insulin resistance is up to 80% [11], independent of weight. Improvements in insulin sensitivity and/or hyperinsulinemia in PCOS have been associated with lowered androgen concentrations [71] and improvements in many of the other CVD risk factors mentioned previously [24, 72], providing support for the role of insulin resistance as a key, underpinning mechanism in the pathophysiology of PCOS.

8.2.2.2 Mechanisms of Action

The mechanism by which exercise improves many CVD risk factors is again associated with improved insulin sensitivity and decreased hyperinsulinemia. In PCOS, the cause of insulin resistance is hypothesised to be caused by a post-receptor defect in insulin signalling, where phosphorylation of insulin-receptor substrate 1 (IRS-1) serine residues is increased while the phosphorylation of the tyrosine residues is decreased [71]. This exaggerated serine phosphorylation may cause a decrease in insulin-stimulated IRS-1 activation and subsequently a decrease in translocation of glucose transporter 4 (GLUT4), the insulin sensitive glucose transport protein, leading to decreased cellular glucose uptake [71, 73].

The pro-inflammatory cytokine TNF-a is elevated in PCOS independent of obesity, and TNF-a is a known mediator of insulin resistance by inducing the exaggerated serine phosphorylation of IRS-1 [73]. TNF-a is produced by visceral adipose tissue [74], and this increased distribution of intra-abdominal fat has been shown to be more prevalent in women with PCOS compared to weight-matched controls [75]. In addition, intra-abdominal fat releases more free-fatty acids (FFA) into circulation than subcutaneous fat [71], and the increased availability of FFA may lead to storage of lipids in non-adipose tissue such as muscle cells, leading to lipotoxicity and inflammation [68, 70, 71]. The accumulation of these intra-myocellular lipid metabolites (such as diacylglycerols and ceramides) have been postulated to activate intra-cellular serine kinases which may be key to the insulin-signalling pathway

defect that results in insulin resistance [68, 71] Women with PCOS have been shown to have increased FFA availability [68].

Obesity in PCOS also exacerbates insulin resistance and inflammation due to hypoxia-related adipocyte death, resulting from adipose tissue expansion. This leads to mononuclear-cell (MNC) infiltration which become macrophages, subsequently releasing TNF-a and IL-6, contributing to insulin resistance [70, 73]. However, even in the absence of obesity, MNC sensitivity to glucose is increased in PCOS, and glucose ingestion promotes an inflammatory response [73].

Exercise improves glucose and insulin metabolisms by restoring glucose homeostasis through increased skeletal muscle glucose disposal [76]. This is achieved via increases in (1) skeletal muscle capillarisation, (2) expression of glucose transporter proteins and (3) mitochondrial function [77]. Indeed, exercise-mediated glucose disposal does not rely on insulin receptor or IRS-1 phosphorylation as in normal insulin signalling, but does so through distinct proximal signalling mechanisms [76]. Chronic exercise increases mitochondrial content and activity, and this is associated with improved skeletal muscle insulin sensitivity and whole body metabolic health [77]. A possible mechanism for this is the increased mitochondrial lipid oxidation of intra-myocellular lipid metabolites, which interfere with insulin signalling [68]. The subsequent improvement in insulin sensitivity may therefore reduce inflammation and the release of cytokines that promote insulin resistance. In addition, as previously outlined, weight loss (in particular a reduction in abdominal obesity) is often associated with exercise in PCOS [24], and this reduction of the metabolically active visceral adipocytes may also lead to reduced secretions of TNF-a and IL-6.

The resulting improvement in insulin metabolism may lead to improved lipid profile through decreased mobilisation of FFA through lipolysis, and the increased uptake and storage of glucose and triglycerides [70]. Blood pressure may also be reduced by improving insulin sensitivity. In the insulin-resistant state, compensatory hyperinsulinemia results in vasoconstriction and increased sodium reabsorption which lead to hypertension [54, 70]. Thus, exercise bestows a multitude of positive effects that reduce many of the CVD risk factors associated with PCOS.

8.2.3 Mental Health and Psychological Well-Being

In addition to a multitude of cardiometabolic and reproductive complications, PCOS has been associated with an increased prevalence of mental health disorders [78–83]. PCOS symptomology includes a number of features that are associated with poor body image and decreased quality of life, such as obesity, acne, excess body hair growth, scalp hair thinning, infertility and menstrual irregularity [79].

Research has long identified a link between women with PCOS and increased incidences of depression and anxiety [78]; a recent report suggests that the odds ratio (OR) for women with PCOS compared to controls for depression and anxiety is 1.26 and 2.76, respectively [79]. In China, a study of 120 patients with PCOS and 100 controls reported the prevalence of anxiety and depression to be 13.3 and 27.5% in PCOS compared to 2 and 3% in controls [80]. Similarly, a study in India of 110 PCOS patients and 40 controls identified the prevalence of major depressive disorder and generalised anxiety disorder (GAD) to be 23.64% and 15.45% in PCOS, compared to 7.5 and 0% in controls [82]. The increased prevalence of mental health disorders is not limited to depression and anxiety. Reports also indicate an increased prevalence of bipolar disorder [84], personality disorders [83] and binge eating disorders [85].

8.2.3.1 Effects of Exercise on Mental Health in Women with PCOS

The benefits of exercise on psychological well-being, including improvements in mood, reduced depressive symptoms, and improved body-image and quality of life are documented in overweight women [86, 87] and adults in general [88, 89]. However, this is less well-documented in women with PCOS. While various studies have assessed

the impact of an exercise intervention on health-related quality of life (HRQoL) in PCOS, these have mostly been combined "lifestyle" interventions with exercise undertaken as an adjunct to different diets [90, 91] or drug therapy [92].

Other studies have compared exercise alone with other treatment groups, rather than a standard-care or control group [93]. These include the comparison of exercise with both an acupuncture group and a control group [94], and the comparison of a traditional exercise programme with yoga among adolescents [95]. Despite not being able to isolate the effects of exercise independently, most interventions including exercise improved HRQoL, anxiety or self-esteem [90, 91, 94, 95], suggesting that exercise has a place in a lifestyle intervention aimed at improving mental well-being in women with PCOS [93].

Moreover, cross-sectional and observational studies lend support to the idea that physically active women with PCOS are likely to have less severe depression, or no depression, compared to inactive women with PCOS [96, 97]. The psychological benefits of exercise are not necessarily related to weight loss since an observational study of women with PCOS found that those completing a self-directed brisk walking programme improved their body image significantly in comparison to those women who did not complete the walking intervention, despite no changes to BMI [98].

8.2.3.2 Mechanisms of Action

The mechanisms by which exercise improves psychological well-being in women with PCOS are dependent on certain physiological factors. For example, various studies suggest increased mental distress related to body image in women with overweight or obesity [81, 98]. Exercise interventions (combined with diet) that result in weight-loss lead to improved self-esteem and HRQoL [90, 91]. As outlined previously in the chapter, exercise and associated weight-loss may also improve fertility which is another factor that improves HRQoL. Improvements in BMI may also reduce sleep disturbances which affect day-to-day functioning [81]. For example, obstructive sleep apnoea (OSA) is closely related to obesity and insulin resistance, and weight loss is a key treatment of this condition, which may increase sleep duration [99]. Indeed, research reports that women with PCOS may be 30 times more likely to experience sleep disordered breathing than controls [100].

Another physiological factor may be the cycle of inflammation and impaired insulin metabolism present in PCOS that has been described previously. Clinical and experimental evidence links activation of the brain cytokine system to depression [101] and may be a factor in the increased prevalence of depression in PCOS. Subsequently, interventions that reduce obesity-related inflammation or normalise insulin metabolism to the effect of reducing pro-inflammatory cytokines, may reduce rates of depression. In addition, severity of hyperandrogenism experienced by the individual may be related to higher levels of mental stress in PCOS because of the clinical presentation, that is, cystic acne, hirsutism and thinning scalp hair which may lead to negative self-image and poor self-esteem [78, 81]. Exercise can restore insulin sensitivity and thus reduce hyperinsulinemia [24], which causes ovarian steroidogenesis and reduces hepatic output of SHBG, leading to hyperandrogenemia. The subsequent reduction in androgens may therefore improve the related clinical symptoms and improve body image.

Finally, research indicates that women with PCOS may have enhanced hypothalamus–pituitary–adrenal (HPA) axis activity in response to stress, characterised by markedly increased psychological distress, which may provide a link between PCOS and the increased prevalence of mental health disorders [102]. Habitual physical activity may modulate the sympathetic nervous system's response to stress and therefore reduce the negative impact of stress on health [103, 104].

8.3 Translating Evidence into Practice: Exercise Programming

The summary of current research outlined in this chapter provides compelling evidence that exercise can be used to alleviate or mitigate many of the cardiovascular, metabolic, reproductive and psychological aberrations that are associated with PCOS. While a single, unifying theory of the cause of this disorder is yet to be found, the main theories for the aetiology of PCOS include primary disordered gonadotropin secretion, primary ovarian and adrenal hyperandrogenism, and primary insulin resistance [28]. Whichever the true cause may be, exercise has been shown to play a role in normalising symptoms associated with each suggested aetiology.

An optimal dose–response relationship to exercise in PCOS may not be feasible because of the highly individualised characteristics of the disorder. Indeed, the AE-PCOS Society suggests that individualised exercise programmes may improve compliance, and suggest group or home exercise [105].

Specifically, Australian guidelines for PCOS suggest at least 150 min of physical activity per week [106]. This is in line with current UK physical activity guidelines for adults aged 19–64 years, and this should form the basis of any clinician or healthcare professional prescription. Most research examining the effects of exercise on PCOS symptoms is aerobic such as walking, jogging, running and/or cycling [24, 56, 107]. For example, many of the benefits associated with exercise can be obtained by brisk walking, defined as faster than normal walking but at a pace that could be sustained for at least 20 min, and this is also the mode suggested by the AE-PCOS Society [98, 105].

Metabolic improvements are possible in as little as 12-weeks [10]. However, if weight-loss and/or improvement to lipid profile is also recommended, women with PCOS should undertake exercise programmes of longer duration (20+ weeks), and/or consider the inclusion of a dietary component to achieve the best results, regardless of type or frequency of the exercise [30, 54, 55, 64].

Higher-intensity exercise (90–100% VO_{2max}) is less well-documented. However, positive improvements to insulin metabolism have been shown with high-intensity interval training sessions in PCOS [10, 108]. In addition, PRT is a mode of exercise that complementary to its effectiveness in treating insulin resistance, may also decrease the loss of fat-free mass (FFM) and increase lean body mass, whilst simultaneously reducing waist circumference [34, 109]. This may be a particularly important consideration for older women at risk of sarcopenia [110].

Regardless, an effective exercise programme that is engaging and that women with PCOS will adhere to is one that is client-centred, offering a choice of modes that may suit a variety of women of different physical abilities and preferences. In addition, the presence and support of other people may be a contributing factor to the compliance of an exercise programme, and group or supervised exercise sessions should be considered in addition to solitary exercise [93].

8.4 Practical Considerations for Exercise Prescription in PCOS

It is important to consider the practical applications of exercise prescription for women with PCOS. Below are some key points to keep in mind to maximise adherence to an exercise intervention:

1. Consider that the client may have issues or anxieties surrounding body-image and self-esteem. As such, individual exercise sessions or small groups within private facilities may be more effective than large, publicly accessible gym spaces.
2. Clients should be informed of the benefits of exercise and physical activity even in the absence of weight loss, such as improved cardiovascular and metabolic health and increases in mental health and well-being.

3. Enjoyment should be a key tenet of an exercise intervention; try to ask the client about previous exercise modes they have enjoyed and implement these.
4. Undertake individual fitness testing and assessment before commencement of the programme and use the results to set bespoke training thresholds for the client. This will avoid discomfort from over-exertion which may increase injury risk and impact adherence.
5. In addition, if the client is not or has not been a habitual exerciser, begin training at low aerobic thresholds, i.e. 55–60%HR_{max} and increase the thresholds as the individual adapts to the demands of exercise.
6. For very untrained individuals, intermittent activity with regular breaks may be more achievable at first.
7. If increased risk for CVD is present, such as hypertension and T2D, close monitoring of heart rate and rate of perceived exertion (RPE) is recommended.

8.5 Key Points

- PCOS is a complex endocrinopathy affecting up to 20% of reproductive-aged women. It is associated with cardiometabolic and reproductive complications. Symptoms may be exacerbated by obesity.
- Insulin resistance is a key underpinning feature and exercise programmes that attenuate insulin resistance or hyperinsulinemia may be integral to improving associated symptoms.
- Research shows that exercise can improve reproductive function, cardiovascular and metabolic health, and mental well-being.
- Weight loss is not necessary for health improvements, and clinicians and healthcare professional should use the minimum physical activity guidelines as a basis to prescribe exercise.
- Future research may be beneficial in indicating the efficacy of different exercise intensities, such as high-intensity exercise and progressive resistance training.

Acknowledgement *Competing financial interests*: The authors declare no competing financial interests.

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Exercise and Insulin Resistance

9

Stephney Whillier

Abstract

In insulin resistance, alterations occur in the signalling pathways that modulate glucose uptake into cells, especially skeletal muscle cells, resulting in impaired glucose homeostasis. Glucose uptake into cells is controlled by a number of pathways, some of which are insulin-dependent. During exercise glucose uptake can occur independently of insulin regulation, and hence research into the effects of exercise on insulin resistance must be clearly defined to reflect whether glucose uptake has been enhanced as a result of the utilisation of these insulin-independent pathways, or whether exercise directly affects insulin resistance in cells. Research into the benefits of exercise for insulin resistance is also problematic in the need to clarify whether it is the exercise itself, or the visceral fat/weight loss that has resulted from the exercise, that has led to improved insulin sensitivity. The research presents a promising picture for the benefits of exercise in insulin resistance.

Keywords

Insulin resistance · Insulin sensitivity · Type II diabetes mellitus · Exercise · Insulin-independent pathways

S. Whillier (✉)
Faculty of Science and Engineering, Macquarie University, Sydney, NSW, Australia
e-mail: stephney.whillier@mq.edu.au

9.1 Introduction

Insulin resistance can be defined as an abnormally high level of insulin required to maintain normal metabolic homeostasis, which is to say lowering postprandial plasma glucose concentrations by stimulating glucose uptake in muscle and adipose tissue, and inhibiting hepatic glucose production. Insulin resistance is due to reduced peripheral sensitivity to insulin, especially in skeletal muscle [1–3]. In insulin resistance, alterations occur in the signalling pathways that modulate glucose uptake into cells, resulting in impaired whole-body glucose uptake [4, 5]. The result is a requirement for increased insulin concentrations to maintain blood glucose levels. Metabolic flexibility, or the ability to shift between carbohydrate or fat as a source of fuel in response to circumstances, is reduced when insulin resistance is present [6]. The condition can progress to impaired glycaemic control, and risk of type 2 diabetes mellitus and pancreatic failure [5].

Insulin resistance is usually associated with dyslipidaemia and a group of conditions referred to as the metabolic syndrome. Although there is controversy over the defining criteria for this condition, in essence, it is associated with a high risk of developing cardiovascular disease, stroke and type 2 diabetes mellitus [2, 7]. It is estimated that 25% of prediabetic individuals in the USA will go on to type 2 diabetes mellitus in 3–5 years [8].

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_9

The prevalence of insulin resistance is 15–20% in developed countries, and it is estimated that about 8% of the global population is affected by diabetes mellitus [5]. A genetic predisposition, physical inactivity, and overeating energy-dense diets contribute to insulin resistance [2, 4]. Insulin sensitivity declines with inactivity [2, 9]. It has been known for almost 30 years that physical activity can prevent the development of type 2 diabetes mellitus, and this has been documented in long-term prospective studies that have followed large cohorts over long periods of time [10]. Overweight/obesity, particularly excess intra-abdominal fat, is a risk factor that accounts for 80–85% of the likelihood of developing type 2 diabetes [2, 8]. But there are individuals with insulin resistance who are not obese, and obese who have normal insulin function [8], indicating that the aetiology of this condition is not simple.

9.2 The Normal Physiological Mechanism of Glucose Entry into Cells at Rest

Skeletal muscle is a major target tissue for glucose uptake in the insulin stimulated state, accounting for 80–90% of total uptake [2, 11]. The uptake of glucose is complex, and is controlled by a number of pathways, some of which are insulin-dependent, and some which are activated by exercise.

Most (90%) of insulin-stimulated glucose uptake occurs in skeletal muscle. Insulin binds to its tyrosine kinase receptor on the cell membrane, causing tyrosine phosphorylation of insulin receptor substrates 1–4 (IRS1, IRS2, IRS3 and IRS4). The tyrosine-phosphorylated IRS protein binds to phosphoinositide 3-kinase (PI3K), activating it, enabling the phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2). This becomes the docking site for various kinases that are important in glucose uptake, including phosphoinositide-dependent kinase 1 and 2 (PDK1 and PDK2) and AKT (also known as protein kinase B or PKB). The targets of AKT are the GTPases AS160 (also known as TBC1D4) and the RAL–GAP complex [3, 11–14]. The TBC1D4 is phosphorylated, which deactivates it. This increases GLUT4 translocation. This is because TBC1D4 in its active form promotes hydrolysis of GTP to GDP on Rab proteins, and this prevents GLUT4 translocation. But when it is deactivated, the GTP reaction with Rab protein increases GLUT4 translocation and increases insulin sensitivity [5]. The binding of GTP with Rab proteins increase vesicle activity, and translocation of GLUT4 to the cell membranes. Rab4 in particular causes insulin-stimulated GLUT4 translocation [13, 14].

In adipocytes, insulin also stimulates Adaptor Protein with a Pleckstrin Homology and Src Homology Domain (APS) independently of PI3K, which causes the tyrosine phosphorylation of proto-oncogene cCBL, resulting in a cascade that activates TC10, a GTPase, and this can also regulate GLUT4 vesicle exocytosis and inclusion into the cell membrane. It is uncertain whether this operates in muscle cells [12].

9.3 The Normal Physiological Mechanism of Glucose Entry into Cells During Exercise

It has been known for a long time that physically active individuals are less likely to develop insulin resistance. In the years from 2002 to 2004, healthy adults aged between 30 and 60 years were recruited into the European Relationship between Insulin Sensitivity and Cardiovascular risk (RISC) study. This was a cross-sectional study of 346 men and 455 women, recruited in 18 clinical centres in 13 European countries. The study looked at the relationship between insulin sensitivity and total activity, and it found that accumulated daily physical activity was a major determinant of insulin sensitivity [15].

A single bout of exercise causes increased glucose uptake into skeletal muscle by at least 40%, during the exercise and for hours afterwards, the effect dissipating within about 48–72 h [8, 16, 17]. This has been attributed to an initial stimulation of an insulin-independent pathway followed by a transient activation of an insulin-dependent pathway after exercise [5, 16, 18, 19].

There appears to be no increase in IRS-1 tyrosine phosphorylation, increased PI3K activity or AKT activation resulting in activation of TBC1D4/AS160 normally associated with a response to insulin in this acute period [20], but this pathway appears to be activated downstream in the post-exercise period. All of this is transient and wears off after the acute bout of exercise.

The glucose uptake during exercise that occurs via an insulin-independent mechanism, is stimulated by the muscle contraction, which results in increased need for glucose and oxygen and is mediated via increased AMP and other metabolites such as NO [21, 22]. The increase in AMP stimulates the insulin-independent pathway of AMP-activated protein kinase (AMPK), and the effect is time and intensity dependent [23–25]. AMPK causes the phosphorylation of TBC1D1 and hence its inactivation. TBC1D1 inactivation inhibits its inhibitory effect, and thus GTP can now react with Rab proteins on GLUT4 vesicles, creating their translocation to the cell membrane for glucose transport. Post exercise, the TBC1D4 rather than TBC1D1 is inhibited and transient increased insulin sensitivity persists as a delayed response of this pathway [5, 18, 19]. It has been shown that exercise itself decreases IRS-2-associated PI 3-kinase activity, but then this insulin-stimulated pathway activity starts to increase at 30 min post-exercise [21]. An increase in the phosphorylation of AKT and increases in AS160 have been recorded after exercise, which indicates activation of this section of the insulin-sensitive pathway after the exercise [26–28]. Thus exercise does not cause phosphorylation of the insulin receptor or PI3-kinase activity initially [13, 29, 30], but insulin- dependent mechanisms do occur as a downstream event after exercise has occurred and the convergence of exercise and insulin signalling is at TBC1D1 and AS160 [3, 31, 32].

Changes in Ca^{2+} concentrations can also activate glucose uptake, mediated via calcium/calmodulin-dependent protein kinase. Calcium is released by the sarcoplasmic reticulum during exercise and this increase in calcium is also thought to stimulate glucose entry into the cells [13, 33]. The increased number of Ca^{2+}/calmodulin complexes induces the signalling pathway downstream via activation of protein kinases, and leads to increased GLUT4 expression. Higher intensity and longer duration exercise appear to have the greatest effect [4, 34]. The activation is rapid and is sustained through the exercise [34]. Hence exercise can also activate this pathway which is independent of the AMPK pathway [35].

If exercise is repeated regularly in non-insulin resistant people, it produces long-term improvements and an active person has reduced basal and glucose-stimulated insulin levels, due to reduced secretion by the β-cells of the pancreas and improved mitochondrial function. In addition, training, whether it is endurance or resistance exercise, results in increased muscle, GLUT4 concentrations, improved insulin-stimulated IRS-1-associated PI3-kinase activity and better free fatty acid oxidation [18, 27, 36]. Bird and Hawley in their review report that regular aerobic exercise has been shown in a meta-analysis of the research to increase insulin sensitivity 25–50% [5], although there is some research suggesting this effect is localised to skeletal muscle [37].

9.4 The Hypothesised Mechanism of Insulin Resistance

The mechanism of development of insulin resistance is unclear. In 1963, Philip Randle, Peter Garland, Nick Hales and Eric Newsholme described a “glucose–fatty acid cycle”. Using isolated heart and skeletal muscle tissue, they showed that there was competition between glucose and free fatty acids for oxidation in muscle and adipose cells. The utilisation of the one fuel source was shown to inhibit the use of the other [8, 33]. This old but recently revived observation may explain dysregulated fuel metabolism. It was originally called the “fatty acid syndrome”, and could explain how glucose uptake and utilisation in cells could be downregulated if free fatty acids are in high concentrations in the cell, and are entering into the Krebs/citric acid cycle at the level of acetyl-CoA. To prevent further fuel

entering the mitochondrial cycle at this point, the uptake and utilisation of glucose through the glycolytic pathway to pyruvate, and thereafter into the same Krebs cycle, is reduced. Increased acetyl-CoA activates pyruvate dehydrogenase kinase, which phosphorylates pyruvate dehydrogenase to a less active form. Increased citrate levels inhibit phosphofructokinase, and both of these enzyme down-regulatory effects would reduce the flux through glycolysis, and have consequences for glucose uptake into the cell [2]. Thus, increased free fatty acid concentrations have been implicated in the development of insulin resistance [38]. High levels of plasma free fatty acids are found in the overweight or obese, especially if the weight is around the abdominal viscera [2, 8].

It has been known for some time that obesity, and especially visceral adiposity, is associated with insulin resistance [1, 7, 8]. Obesity appears to be associated with an impaired capacity for lipid oxidation and abnormal lipid metabolism. It has been found that obese individuals do not effectively suppress lipid oxidation during insulin-stimulated conditions. If the adiposity is intra-abdominal, this metabolically more active fat exhibits a high rate of lipolysis, increasing plasma free fatty acid concentrations which circulate to peripheral cells [2]. Hence catabolism of visceral and other fat depots and release of circulating free fatty acids can lead to an accumulation of fatty acids in cells, and this may be leading to the "fatty acid Syndrome" [8].

The decreased uptake of glucose could explain the insulin resistance that develops in metabolic disease [33]. In an earlier study (1999), Krssak et al. used linear regression analysis to show that intramyocellular lipid concentration, as assessed by NMR spectroscopy, is inversely related to insulin sensitivity, and is a good indicator of whole body insulin sensitivity in non-diabetic, non-obese humans [39].

The accumulation of fatty acids as a causative factor is complicated by the knowledge that lipid accumulation in cells is even higher in endurance trained athletes who do not have insulin resistance. However enhanced lipid oxidation also results from training [8]. A study on the effects of moderate increases in physical activity in obese older adults showed that reduced fat mass and improved insulin sensitivity was accompanied by increased intramyocellular lipid content, but also in reduced diacylglycerol and ceramide in these cells, by-products of incomplete oxidative ability [40]. There is some indication that mitochondrial function itself may be compromised in insulin resistance, a susceptibility that may partially be genetically determined [8]. Thus the fatty acids accumulate and are incompletely utilised. A further illuminating explanation is that the partial oxidation of fatty acids, and accumulation of incompletely oxidised lipid intermediates and other reactive oxygen species constitutes oxidative stress for the cell, and decreasing further entry of fuel into the aerobic respiration pathway prevents any further increase in this stress [8]. Hue and Taegtmeyer have described a process of free fatty acid binding to peroxisome proliferator-activated receptors (PPAR) which regulate many pathways, including lipid metabolism. In particular, overexpression of PPARα in muscle favours fatty acid uptake and oxidation, and induces triglyceride accumulation, glucose intolerance and insulin resistance [33].

The exact point of alteration in the pathway is not clear, but inhibition of GLUT4 translocation has been observed [33]. Accumulation of fatty acids in cells has been linked to impaired TCB1D4 deactivation [41], and hence reduced translocation of GLUT4 channels to the cell surface for glucose uptake, and this may be the mechanism. Another hypothesis is that it is the accumulation of the sphingolipid precursor ceramide, associated with increased free fatty acids in the mitochondria, that may be impairing insulin sensitivity [38, 42]. It is thought that these inhibit AKT/PKB phosphorylation and activation, and in this way impair GLUT4 translocation to the membrane [5]. Other studies have shown that in obese, obese insulin-resistant and in type 2 diabetes mellitus, insulin fails to induce sufficient IRS-1 tyrosine phosphorylation [4, 5] and that insulin stimulation of the PI3-kinase pathway, involving the phosphorylation of the insulin receptor and IRS-1 has been compromised [43], a

possibility supported by research on insulin resistant transgenic mice models [3].

9.5 The Possible Benefits of Exercise for People with Insulin Resistance

In exercise the activation of AMPK can overrule the mechanisms involved in the glucose–fatty acid cycle, and so the high fatty acids in the cell do not inhibit glucose uptake during the exercise itself [33]. Exercise stimulation of the MAP kinase pathway appears to be normal in obese and diabetic subjects [43]. During an active bout of exercise in insulin resistant people, glucose uptake reverts to near-normal, due to the transient insulin-independent activation of the glucose uptake pathway [4, 20, 44]. The effect appears to be at its greatest 3–4 h after the exercise [4], may be evident up to 72 h post-exercise, and is lost within 5 days after the last bout of exercise [5, 45]. It has been shown in both healthy and insulin resistant individuals that a 45–60 min aerobic cycle at 60–70% VO_2max increases the GLUT 4 transporters in the muscle cell membrane by about 70% above resting level, again due to the stimulation of the independent pathway by muscle contractions [2].

Improved insulin sensitivity in subjects with insulin resistance is reported to result from repeated exercise. Recent studies have shown consistently that moderate aerobic exercise for 30 min or more, at least 3 times a week for at least 8 weeks improves insulin sensitivity in a range of populations, from men and women with diabetes, glucose intolerance, obesity, sedentary moderately overweight, metabolic syndrome and type 2 diabetes mellitus [5]. It is also the case that loss of body fat during exercise has been correlated with improved insulin sensitivity. Cuff et al. found that combined resistance and aerobic training enhanced insulin sensitivity in postmenopausal women with type 2 diabetes, but related that change to weight loss, and especially loss of abdominal subcutaneous and visceral adiposity and to increased muscle density [46]. As will be explained more fully in Sect. 6, the loss of adiposity in exercise makes for a confounder in determining what is actually causing the improved insulin sensitivity.

9.6 The Hypothesised Mechanism of Increased Insulin Sensitivity Due To Repeated Exercise

It has been shown in numerous studies that exercise can not only prevent the development of insulin resistance and the progression to type 2 diabetes mellitus; it can actually increase insulin sensitivity [5, 47–49].

An important question is whether this effect is the result of the exercise directly or the weight loss, or more specifically, fat loss (change in body composition), that accompanies the exercise. Herein lies a dilemma in assessing the results of studies. For example, Bharath et al. conducted a randomised controlled trial of combined resistance and aerobic exercise training over 12 weeks in obese adolescent girls. The intervention effectively reduced the percentage of body fat, body weight and waist circumference. It also improved blood insulin and glucose levels, and insulin resistance, relative to baseline and the controls [50]. But the question is, were the improvements in insulin sensitivity directly due to the exercise, or due to the weight and abdominal adiposity reduction, or both? The pragmatic answer is that it does not really matter which is doing it, exercise often has all of these effects, and so exercise is beneficial. But elucidation of this important distinction has implications in understanding the mechanism by which the change in insulin resistance is occurring as well as determines which interventions are going to be of benefit. For example, if someone does not take up exercise but loses weight on a diet, will that be beneficial for insulin resistance? Similarly, if someone does exercise without changing body composition significantly, will that still increase insulin sensitivity?

A large cross-sectional study consisting of 2321 non-diabetic Pima Indian men and women from Arizona and 2716 non-diabetic men and

women from Mauritius, correlated insulin sensitivity (estimated from mean insulin concentration) with physical activity, derived from participants answering a questionnaire. In both populations they found that activity was significantly associated with mean insulin concentration, after they controlled for age, BMI and waist-to-thigh or waist-to-hip ratios [51]. This does suggest that the association is independent of weight and body composition. However, it would benefit our understanding to know whether an exercise intervention over a period of time, rather than a cross-sectional observation, benefits insulin resistance when other variables such as changes in fat composition are controlled. A review conducted by Berman et al. on the relationship between physical activity and insulin sensitivity in children and adolescents came to the conclusion that from the 42 studies included in their review, 78% showed physical activity "may improve or maintain healthy (insulin sensitivity) in children and adolescents independent of adiposity status or changes in adiposity". However, this was a mix of both interventions and cross-sectional cohort studies [47].

Just as confusing are the results of a 4-year follow-up on a lifestyle intervention (advice on weight loss and moderate daily activity), in which insulin sensitivity was measured in a subgroup of people who had participated in the Finnish Diabetes Prevention Study. The researchers found a strong correlation between the 4-year changes in insulin sensitivity and weight. Insulin sensitivity improved by 64% in the highest tertile of weight loss but decreased by 24% in those who gained weight and were in the lowest tertile. They concluded that the insulin sensitivity improved in consequence of weight reduction, and improvements in insulin secretion remained constant for years in those who kept the weight off [49]. However, it is important to know whether or not exercise was correlated with the weight loss, and so again it is difficult to know whether weight loss alone is sufficient to reduce insulin resistance.

Further, it is becoming clear that measuring body weight or BMI is not sensitive enough a measure, when research indicates that changes in body composition, both lean mass and fat mass, are likely effecting insulin sensitivity. Many studies only measure body weight or BMI, and especially fail to measure truncal fat [1, 52–55]. Kim & Park reviewed the literature on the association between exercise, insulin resistance and weight loss in children and adolescents. They found 6 randomised controlled trials on the benefits of aerobic exercise in reducing insulin resistance, and another 6 on resistance or combined training, both without weight loss. However, although body weight or BMI may not have changed, it is important to know if body composition, and especially, if body fat content had changed, and this was indicated in only some of the papers in this review [53]. To elucidate the importance of this further, Mendelson et al. investigated the effect of exercise over 12 weeks in obese adolescents, and found that although insulin concentrations and insulin resistance decreased, there was no weight loss. However total fat mass had decreased and lean mass had increased, resulting in an unchanged BMI. Not only that, the change in insulin concentrations and resistance was greater in those participants who lost visceral fat, and in this group changes in visceral fat mass was inversely associated with increases in fat oxidation [56].

Some studies come to the conclusion that it is the fat loss in exercise that **is** a key factor [5, 8, 57–59]. One study on 18 individuals who were either sedentary, or who had metabolic syndrome, investigated the effects of 8 weeks of increasing intensity stationary cycle training on insulin sensitivity. They found that there was no change in weight, lean body mass or fat mass, and there was also no change in insulin resistance, even though activated muscle AMP-dependent kinase, and muscle mitochondrial marker ATP synthase all increased [60]. Conversely, another trial evaluated the effects of body weight reduction with and without exercise on insulin resistance in 48 obese subjects. They were randomised to either a diet-only group or a diet and exercise group, and the study was continued until 5% of the initial body weight was lost. Both groups showed similar significant decreases in visceral adipose fat and insulin resistance. The authors concluded

that exercise did not add to the effect of weight loss on the outcome variables [61]. Similarly, O'Leary et al. associated a reversal of insulin resistance in a group of elderly participants in an aerobic exercise intervention primarily to visceral fat loss as it proved to be the primary correlate with improved glucose control [59].

Segal et al. specifically maintained body composition and weight in 10 lean, 10 obese, and 6 diet-controlled type 2 diabetic men who underwent aerobic training for 4 h a week at 70% VO_2max. They found no change in insulin resistance in the obese and diabetic men, in spite of the exercise [62]. Ross et al. randomly assigned 52 obese men to 4 groups (diet-induced weight loss, exercise-induced weight loss, exercise without weight loss, and control) for 3 months. The total fat reduction was 1.3 kg greater in the exercise-induced weight loss group than in the diet-induced weight loss group. They found that when weight loss induced by diet restriction or exercise was matched, reductions in abdominal obesity, visceral fat, and insulin resistance were similar, and insulin sensitivity improved by approximately the same 60% in both of the weight loss groups [63]. The trial does suggest that weight loss whether due to diet or exercise results in significant and similar reductions in insulin resistance.

However, Ross went on to conduct a randomised controlled trial using a similar protocol in a cohort of moderately obese women, once again to determine the independent effect of diet- or exercise-induced weight loss on obesity and insulin resistance, and whether exercise without weight loss had an effect on abdominal obesity and insulin resistance. Body weight was static in the control and exercise without weight loss group, whilst that in the diet and exercise weight loss was the same, at 6.5% of initial body weight. Total fat and abdominal fat decreased in both weight loss groups, but was greater in the exercise weight loss group. Surprisingly though, they found that insulin sensitivity did not change in the diet alone group, whilst in the exercise weight loss group there was a substantial 32% reduction in insulin resistance [64]. This seems to conflict with other research on the effects of weight loss. For example, Giugliano et al. found improved insulin resistance 6 months after significant liposuction (2.7 ± 0.7 kg), without any exercise regimen [65] and it has been shown repeatedly that glucose homeostasis improves and that insulin secretion and plasma insulin concentrations decrease significantly after weight loss alone [3, 6]. Not only that, but Kim et al. found that a very low calorie diet intervention in obese non-diabetic subjects significantly increased IRS-1 tyrosine phosphorylation, compared with the pre-treatment level [66]. DiMenna suggests that the differences may lie in whether there has been a reduction in fatty acid mobilisation [8], and uptake in cells. Dietary weight loss involves the mobilisation and catabolism of fatty acids for energy, which could result in large intracellular concentrations of fats. The effect, if understood within the context of the glucose–fatty acid cycle hypothesis, would be accumulation and impaired or incomplete utilisation of these fatty acids in cells leading to a downregulation in glucose uptake. Thus, the results of a weight-loss intervention might be effected by the amount of free fatty acid mobilisation occurring at the time measurements were taken.

But changes in insulin sensitivity have been recorded in studies in which an exercise intervention has been conducted without any change in body composition. Duncan et al. found that a walking intervention for 6 months in 18 previously sedentary but healthy individuals resulted in no changes in BMI, waist circumference or VO_2max, but did increase insulin sensitivity. An editorial by Ross (2003) points out that this study fails to show individual variation, as the standard deviation for the change in insulin sensitivity was substantial [16]. Poehlman et al. conducted a 6-month intervention of either resistance or aerobic training in young non-obese women. They reported unchanged total body fat, visceral or subcutaneous abdominal fat. Insulin sensitivity, corrected for fat free mass, improved with aerobic training but not resistance-training. Aerobic training increased glucose disposal independent of changes in fat free mass, and they suggest an intrinsic alteration in the muscle glucose metabolism pathway had occurred [67].

It is clear that further research is necessary to bring clarity to this issue. From a practical point of view, it seems likely that the composite of exercise and change in body composition is most beneficial in reducing insulin resistance.

9.6.1 Does the Type of Exercise Matter?

There are many aspects to consider in exercise protocols: the intensity, frequency, duration per session, actual type of exercise (e.g. aerobic vs resistance), whether it is done habitually and how long it was followed. Research looks at different aspects of exercise, and the results are not consistent across the research.

9.6.1.1 Intensity

Ross et al. conducted a large 24-week habitual exercise trial on a group of 300 participants with abdominal obesity, randomly assigned to four groups: control; low-amount, low-intensity exercise at 50% of maximum oxygen consumption; high-amount, low-intensity exercise (HALI) at 50% of V O_2max; or high-amount, high-intensity exercise at 75% of VO_2max. A 2-h glucose tolerance test was performed 36 and 48 h after the last exercise session at baseline and at 16 and 24 weeks. All groups lost similar amounts of waist circumference compared to the controls. After adjustment for covariates, reductions in 2-h glucose levels were significant in the high-amount high-activity group compared to the controls, but not different in the other groups [68]. This would tend to favour high intensity high duration habitual exercise.

High intensity exercise seems to have a greater effect on the activation of the AMPK signalling pathway. Acute cycling at 80% of the VO_2max resulted in greater activation, compared to less intense endurance exercise, for the same energy expenditure [4]. Low intensity walking for 30mins, 3–4 days a week for 6 months did improve markers of glycaemic control, but a further 6 months of jogging 3–4 days a week for 6 months resulted in substantially better results [5]. Intense exercise (70% of HR_{max}) for 45 min has been shown to activate TBC1D1 and 2, and the AKT substrate of AS160, indicating positive effects for the insulin independent and dependent pathways [4].

High intensity interval training has become the more suggested type of exercise in the literature: it involves periods of high-intensity (e.g. sprint interval training) interspersed with periods of low-intensity or rest. This would maximise muscle stimulation and minimise fat usage. This type of exercise has been shown to improve glycaemic control, decrease insulin resistance, improve pancreatic β cell function, plus reduce abdominal fat, in study participants with type 2 diabetes and participants at risk for insulin resistance [69, 70], although one study found no change in insulin sensitivity when weight was held constant [6].

Although some reviews advocate higher intensity over lower intensity exercise, this is not a consistent finding [5]. Kraus et al. had a different finding in a clinical trial similar to the Ross et al. trial. The study was of a Targeted Risk Reduction Intervention through Defined Exercise (STRRIDE) of 260 overweight or obese participants assigned to 8 months in either: a control; low-amount, moderate-intensity (40–55% VO2max); low-amount, vigorous-intensity (60–75% VO2max), or high-amount, vigorous-intensity exercise. All groups showed beneficial outcomes for body weight and composition and whole-body insulin sensitivity compared to the control, but the moderate-intensity exercise was reported to be 3-times more efficient at improving insulin sensitivity compared to the high-intensity exercise, once other factors such as weight loss and changes in body composition were controlled. Further work done by this group to elucidate a possible mechanism at play favouring moderate-intensity exercise found that Krebs cycle intermediates were higher in this group compared to the high intensity group. This could indicate improved metabolism of fatty acids in the cell, and in terms of the Randle hypothesis, this could account for improved insulin sensitivity in this group [71].

Similarly, McGarrah et al. cite well-controlled randomised trials that control for total energy

expenditure, that show moderate-intensity aerobic exercise improves insulin-sensitivity more than the high intensity exercise. They suggest improved metabolism of skeletal cell fatty acid stores directly improve insulin sensitivity [31], and this again would fit well with the Randle hypothesis: if fatty acid oxidation improves, the inhibitory effect of these molecules on glucose uptake is decreased.

9.6.1.2 Mode of Exercise

Aside from intensity, there is also the question of the type of exercise. Resistance and aerobic training have both shown benefits [38, 72, 73]. A meta-analysis of 17 studies investigating the benefits of either aerobic, resistance or combined exercise in overweight or obese children or adults done over at least 6 weeks found that either and both together did reduce fasting insulin levels and insulin resistance, although aerobic exercise seemed to have the best outcomes [74]. Similar evidence was presented in a meta-analysis of aerobic, resistance or combined exercise intervention studies conducted from 1965 to 2012, which showed all modalities were beneficial, and a dose–response relationship was seen between volume and intensity of exercise and improvements in insulin sensitivity [75].

A review on studies of aerobic versus resistance exercise detailed a randomised crossover study that examined the acute outcomes of these two modes of exercise. Three different interventions were conducted, each lasting 3 days: a single bout of aerobic exercise, a single bout of resistance exercise and a control period. Glucose was monitored for 24 h after each intervention. Three different groups were monitored, all consisting of 15 middle-aged overweight to obese males: impaired glucose tolerance, type 2 diabetes on oral glucose-lowering agents and type 2 diabetes on insulin. What they found was that aerobic and resistance training equally reduced 24 h glucose post exercise by 7–12% [76].

Resistance training at 2–3 sessions a week for 8–26 weeks has been shown to increase GLUT4 concentrations and translocations by 30–70% and enhance insulin sensitivity by 10–48% [5]. Benefits of resistance exercise that have been reported are increased insulin sensitivity and increased GLUT4 translocation in skeletal muscle [77].

9.6.1.3 Acute Versus Habitual Exercise

Some research has shown no effect of acute exercise on insulin sensitivity, especially if it is short and light [4]. Habitual exercise of over 10 weeks shows positive effects, and appears to be independent of the type of exercise [4].

Habitual exercise seems beneficial in reducing insulin resistance, causing more tyrosine phosphorylation of the insulin receptor IRS-1 plus increased PI3-K activity in the muscle in both untrained healthy and insulin-resistant participants. Both habitual aerobic and resistance exercise induced AMPK activation and changes in gene expression for GLUT4 translocation [4]. Habitual exercise has been shown to increase muscle capillarisation, and this is also correlated with increased insulin sensitivity in older adults with impaired glucose tolerance following 6 months of aerobic exercise with weight loss [5].

Bird and Hawley in their review do indicate additional benefits from higher volumes of habitual exercise (>1900 kcal/week) in adults with insulin resistance, but point out that much of the actual benefit is attained at a volume of about 475–950 kcal of expenditure a week, which equates to ~5 × 30 min of moderate intensity a week, and this is the oft-prescribed habitual exercise [5].

In summary, DiMenna et al. give a well-reasoned argument for the type of exercise taken up in a management program [8]. If the major problem is a mitochondrial defect, then exercise of high intensity will maximise improvements as this will maximise the use of glycolytic pathways, rather than aerobic respiratory pathways that utilise mitochondria. However, if the ideal management is to reduce the fat accumulation, then low-intensity exercise that maximises lipid oxidation is favoured. If though the goal should be to reduce weight, then training regimes should maximise a sustainable pace that can be maintained over longer periods of time.

As we have insufficient overwhelming evidence to support one over the other, the possible

management might be a habitual program of all of these types of exercise done on different training days [8].

9.7 The Downside to Exercise Interventions in the Management of Insulin Resistance

Building an evidenced case for the benefits of exercise in insulin resistance does not take into consideration a few important realities facing individuals with this condition. There are a number of physiological limitations that occur as a result of impaired intake of glucose into cells and the compensatory rise in insulin that occurs to overcome the problem. Insulin is a hormone that favours the storage of fuel sources [9], rather than expenditure, and so accessing energy stores to do exercise is difficult for individuals with this condition, resulting in easy fatigue. Insulin sensitivity has been shown to correlate positively with VO_2 max. There is an indication, which fits well with the glucose–fatty acid cycle hypothesis, that mitochondrial function is compromised in insulin resistance [8, 78]. As mitochondria are the aerobic respirators of the cell, impaired function will also result in easy fatigue and reduced exercise capacity. Vascular changes associated with developing metabolic syndrome could well impact oxygen delivery to cells, further compromising aerobic respiration [78]. This can make exercise difficult, and could affect the outcome of a management plan for individuals with insulin resistance.

9.8 A Few Final Words

A lifestyle of regular exercise has been shown to be associated with better glycaemic control in a numerous studies (see Bird and Hawley [5], for more details), and has been shown to reduce the odds ratio for metabolic syndrome by 50% [79], and lower the prevalence of metabolic syndrome in people who exercised moderately for 30–60 min, 5 days a week [80]. In research on participants who have insulin resistance, studies that use exercise interventions usually report a reduction in insulin resistance, and in some cases, a complete reversal of the condition [5, 59]. In regard to improving the prognosis of those with the condition, the evidence seems to be promising. In the large Impaired Glucose Tolerance and Diabetes Study, published in 1997, 577 people with impaired glucose tolerance from 33 clinics were randomly assigned to 4 groups: control, diet only, exercise only and diet and exercise combined. After 6 years of follow-up, the incidence of type 2 diabetes in the control group was 68%. In the diet only group it was 44%, 41% in the exercise only group and 46% in the diet plus exercise group [81]. Similar large randomised control studies have yielded positive results. The Finnish Diabetes Prevention Study and the US Diabetes Prevention Program both showed that lifestyle interventions that included dietary control and moderate intensity exercise followed over at least a year resulted in significantly lower progression of impaired glucose tolerance to type 2 diabetes mellitus [82, 83]. The suggested dose response is for every 500 kcal/week of increased exercise, the risk of type 2 diabetes is reduced by 9% [5].

Finally, it is clear that while generalisations can be drawn on the benefits of exercise in reducing insulin resistance, there is much equivocal information on the subject in the research. This can be due to a number of things, not least of which would be the heterogeneity in the protocols used to study the subject. Results would greatly depend on the participants chosen, the exercise protocol used, the outcome measures used to determine changes in insulin resistance, the statistical analysis and the interpretation of findings. In addition, it cannot be overlooked that there is some individual heterogeneity in the underlying insulin-resistant phenotypes and this would impact the physiological response to exercise [84]. However, the findings do indicate that exercise is beneficial for healthful glycaemic control, either in the prevention of insulin resistance or the management of the condition.

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Part IV

Exercise and Cardiovascular Diseases

Exercise and Hypertension

10

Şeref Alpsoy

Abstract

Hypertension is a fatal yet preventable risk factor for cardiovascular disease and is responsible for majority of cardiovascular mortality. Hypertension is closely associated with inactive lifestyle. Physical activity and/or exercise are shown to delay development of hypertension. Both aerobic and resistance exercise have been proven to reduce blood pressure (BP) effectively. Since brisk walking is an easy, inexpensive, simple, and effective way of exercise, this type of an aerobic workout can be recommended to society. All professional organizations and government bodies recommend moderate-intensity aerobic exercise for at least 30 min on at least 3 days of the week or resistance exercise on 2–3 days of the week. Exercise sessions can either be continuous for 30 min or be composed of at least 10 min of short exercise duration to a daily total of 30 min. After an exercise session, BP decreases, and this decline continues for up to 24 h; which is called post-exercise hypotension. Overall 5 mmHg decrease in BP with regular exercise may be ensured. With a decrease of 5 mmHg in systolic BP, mortality due to coronary heart disease decreases by 9%, mortality due to stroke decreases by 14% and all-cause mortality decreases by 7%. Regular exercise should therefore be recommended for all individuals including normotensives, prehypertensives, and hypertensives.

Keywords

Exercise · Hypertension · Blood pressure

10.1 Introduction

Hypertension is one of the most fatal but preventable causes of cardiovascular disease (CVD) worldwide [1]. The overall prevalence of hypertension in adults is about 30–45%. Blood pressure (BP) increases gradually with age, owing to the hardening of the blood vessels and increased vascular resistance. The prevalence of hypertension in individuals over the age of 60 years exceeds 60% [2, 3]. As the frequency of hypertension increases directly in proportion to age, the risk of developing hypertension in people over 50 years of age or older is 90% [4]. There is a positive correlation between the prevalence of hypertension and stroke-related mortality [5]. The increase in BP due to age leads to an increase in incidence and prevalence of hypertension [6]. In addition, aging leads to an inactive lifestyle and increased body weight, further increasing the prevalence of hypertension worldwide [7].

Ş. Alpsoy (✉)
Faculty of Medicine, Department of Cardiology, Namık Kemal University, Tekirdag, Turkey
e-mail: salpsoy@nku.edu.tr

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_10

Optimal BP is below 120/80 mmHg. The results of the Framingham Heart Study showed that there was a twofold increase in the relative risk of cardiovascular disease in "prehypertensive" patients when compared to those with normal BP. In Seventh Joint National Committee (JNC 7), prehypertension is described as having a BP level of 130–139/85–89 mmHg [8]. Cardiovascular disease risk starts to rise as the BP rises above 115/75 mmHg, in which, with every 20 mmHg increase in systolic BP (SBP) or 10 mmHg increase in diastolic BP (DBP) doubles the risk of stroke, ischemic heart disease, or other vascular-induced death [9]. Hypertension develops in 30–40% of prehypertensive individuals within 2–4 years [10]. The most important factor in the progression of prehypertension to hypertension is shown to be the lack of physical activity [11]. Prehypertension is a risk factor for the development of hypertension. Provided that appropriate measures are taken, the development of hypertension can be delayed. Hypertension can be delayed with lifestyle changes which include exercise [12]. Regular exercise is one of the most important activities in preventing hypertension and improving long-term survival [13].

The amount of oxygen consumed during rest is equal to 3.5 mL O_2 per kilogram of body weight and is defined as 1 metabolic equivalent (MET). This is a simple, practical, and easy-to-understand concept to express the amount of energy spent in physical activity. In those who are not well conditioned in aerobic activities the level of MET corresponds to the 40% of maximal MET. In patients in good fitness this level corresponds to the 85% of maximal MET. In healthy individuals, a density of 60–70% of the maximum MET with anaerobic threshold is recommended during continuous aerobic exercise [14].

Activities such as sleep, watching television, playing video games, or computer use, which do not increase energy expenditure above the resting level, are defined as sedentary behaviors. The energy consumption of these kinds of activities is ≤1.5 MET [15].

Body movements are defined as physical activity when they result in an expenditure of energy above the resting levels of skeletal muscles. Activities such as routine daily housework, gardening, shopping, or professional activities are examples of physical activities.

The subgroups of physical activity which are planned, structured and repetitive, done to improve and maintain health, are called exercise. Physical fitness is the ability of an individual to perform a physical activity without extreme fatigue [16]. Exercise can be classified in different ways such as aerobic, anaerobic, dynamic, static, durability, or resistance exercises. Aerobic exercise is the type of exercise in which oxygen is utilized by working muscles. In aerobic exercise, heart rate and respiratory rate increase steadily to maintain exercise. Anaerobic exercise is a state of asphyxiation as it is in sprinting or lifting weights.

Dynamic aerobic or endurance exercise is the type of aerobic exercise that increases heart rate and energy consumption by dynamic repetitive contractions of major muscle groups. Exercises, such as jogging, rowing, swimming, or cycling, strengthen the heart and lungs and increase the oxygen consumption of the body. Aerobic exercise is the modality of exercise which is used in most of the studies evaluating the effect of exercise on hypertensive subjects.

In aerobic endurance exercises such as cycling and jogging, increase in SBP depend on the intensity of exercise and often it may increase up to 200 mmHg. DBP, on the other hand, usually falls due to vasodilation in muscles or may slightly increase by 10–20 mmHg depending on the amount of resistance to blood flow due to strong contractions. After exercise, BP returns to normal quickly. Sometimes a rapid but temporary drop in BP occurs. This is in response to the vasodilation of vessels in muscles that stopped exercising. BP normalized by baroreceptors that balance circulating vasodilators within 10 min.

Resistance exercise: It is the activity in which effort is spent against a specific resistive force and which is especially designed to increase muscle strength and endurance. According to the type of muscle contraction, resistance exercise can be divided into two main subgroups: "dynamic" and "static or isometric" resistance exercise. Dynamic resistance exercise includes

concentric and/or eccentric contractions when the length and tension of the muscles change. Isometric exercise is a continuous contraction of muscles with minimal change in the length of the muscle group held against a fixed force. In isometric exercises such as weight lifting, sympathetic vasoconstriction in tissues that do not participate in resistance training exercises and mechanical compression of exercising muscles cause a more profound increase in systolic and diastolic BP levels. Sudden decrease in BP after exercise may also be more profound [17].

There are both static and dynamic components of each type of exercise. The increased dynamic component is defined as the estimated percentage of maximum oxygen consumption (VO2max) achieved and results in an increase in heart rate. The increased static component is related to the maximum predicted rate of voluntary contraction reached and results in an increase in BP. Static contractions in exercise stimulates mechanical and metabolic afferents in skeletal muscles, which leads to changes in BP through exercise pressor reflex. As muscle mass increases intensity of contractions increases, and consequently BP increases. During dynamic exercise there is an increase in blood flow to meet metabolic needs. As a result, dynamic exercise primarily causes volume overload on the left ventricle, while static exercise causes pressure overload [18]. During the dynamic exercise, heart rate and left ventricular contractility increase with increased sympathetic activity and withdrawn parasympathetic activity. This results in vasoconstriction in venous bed and increased venous return and stroke volume. In this way, adequate perfusion of the muscles is provided. In exercising tissues, vasodilation is performed in arterioles due to the effects of adenosine, potassium, nitric oxide, while vasoconstriction ensues in non-exercising tissues. SBP increases due to increased cardiac output and vasoconstriction in non-exercising tissues. However, this increase in systolic BP is balanced with vasodilatation in exercising tissues which results in minimal increase in diastolic BP. As the exercise continues at the same intensity, BP begins to descend from peak values in order to preserve cardiac filling and for heat dissipation [17]. Blood pressure decreases after acute resistance exercise or submaximal dynamic exercise. In the fifth minute of exercise average arterial BP rises to its highest level and then begins to decrease [19].

Exercise intensity is typically expressed by the maximum percentage of oxygen a person uses during exercise. For example, in moderate aerobic exercise, approximately 45–64% of the maximal oxygen use is achieved or 55–74% of the maximal heart rate is ensured, while in heavy aerobic exercise, about 70–85% of the maximal oxygen is used and 95% of the maximal heart rate is reached. Maximal oxygen use in high-intensity exercise is 70–100% [20].

It is known that physical inactivity is a risk factor for many diseases such as hypertension, diabetes, CVD, and in people who are inactive, the diseases progress faster [21]. Being physically inactive is a major risk factor for heart disease, and people who are less active and less fit have a greater risk for hypertension [22]. It has been reported that hypertensive patients are physically less active than normotensive individuals [23]. Exercise is recommended in hypertensive adults by all professional committees and institutions. It is shown, in various studies, that physical activity causes BP reduction independent of weight loss in both normotensive and hypertensive individuals [24, 25]. In Coronary Artery Risk Development in Young Adults (CARDIA) study, during 20 years of follow-up, development of hypertension was shown to be lower in physically active individuals [26]. In various studies, an inverse relationship was found between physical activity or level of cardiovascular fitness and BP [26–29]. In addition, cardiorespiratory fitness was shown to be protective against progression prehypertension to hypertension [30]. In sedentary individuals, cardiovascular risk factors such as hypertension, total cholesterol, height, excess body mass index, low HDL cholesterol levels, and obesity usually exist together [31]. It has been shown that regular aerobic exercise in prehypertensive or hypertensive subjects provides improvement in structural, functional, and biochemical parameters in the cardiovascular system [32].

With regular aerobic exercise significant decrease is ensured in clinical systolic and diastolic BP and daytime average ambulatory BP [33]. In a study conducted in men with stage 1–2 hypertension, a 45-min exercise was followed by decrease in systolic, diastolic, and mean BP levels which lasted for 24 h [34]. Physical activity is as equally important or even more important than pharmacotherapy in reduction of cardiovascular mortality in hypertensive patients. An exercise frequency as once a week is more effective than pharmacotherapy in reducing all-cause mortality in hypertensive subjects [35]. The decrease in BP by exercise is well established by numerous studies. Meta-analyses have shown that aerobic [32, 36–38] and dynamic resistance exercises [36, 37, 39–41] effectively lower BP in hypertensive adults.

In the various studies, BP was shown to be lower in the days of exercise than in the days without exercise, and this was called post-exercise hypotension [42, 43]. Post-exercise hypotension develops in response to exercise which is submaximal, that is, greater than 40% of peak aerobic capacity and in periods between 20 and 60 min in which major muscle groups are used in dynamic exercise such as walking, running, cycling, and swimming. Post-exercise hypotension is observed in both normotensive and hypertensive people, but it is generally more prevalent in hypertensive subjects. Maximum reduction in exercise systolic and diastolic BP related to exercise may reach an average of 18–20/7–9 mmHg in hypertensive people and 8–10/3–5 mmHg in normotensive people. Post-exercise hypotension can develop by various mechanisms such as reduction in peripheral vascular resistance and/or cardiac output, decreased vasodilator response, decreased sympathetic nervous activity, increased parasympathetic modulation, and improved baroreflex sensitivity [36, 43]. Many studies have shown that post-exercise hypotension occurs after aerobic exercise [42, 44–47]. Even after 10 min of short exercise sessions, post-exercise hypotension can be seen [17]. It has also been shown that post-exercise hypotension lasts 24 h [48, 49]. However, there is no post-exercise hypotension approximately in 20–25% of people due to genetic predisposition [50]. In order to have clinical significance, post-exercise hypotension should be of significant size under ambulatory conditions and should be maintained for a long period of time. Post-exercise hypotension is well defined in hypertensive subjects. It has been reported that the degree and duration of BP fall may vary and be influenced by factors such as ACE polymorphism, exercise duration, and continuous or discontinuation of exercise [51].

The most powerful support to the cause-and-effect relationship between hypertension and physical activity is generated from randomized controlled studies. In many studies, positive effects of exercise on the BP have been verified. This effect is more pronounced in hypertensive than in normotensive and prehypertensive [52]. With a decrease of 5 mmHg in systolic BP mortality rate due to coronary heart disease decreases by 4 and 9%, mortality due to stroke by 6 and 14% and all-cause mortality decreases by 3 and 7% in normotensive and hypertensive adults respectively [53]. In addition to aerobic and resistance exercises, there are studies showing that high-intensity exercise is also effective in hypertension [54, 55].

10.2 The Effect of Aerobic Exercise on BP

Aerobic exercise is usually performed in a moderate intensity for 30–45 min in the form of continuous running, cycling, or swimming. The number, duration, and intensity of training per week are important features of an exercise program. In patients with hypertension, there are studies showing that the office and ambulatory BP levels decrease after the aerobic exercise session. It is specified that after each session sympathetic modulation is associated with low BP [34, 36, 56, 57]. In a meta-analysis of 72 studies, in which 4000 people were examined at rest and after regular aerobic exercise; a 3 mmHg decrease in resting BP and 2.4 mmHg decrease in average daytime ambulatory BP were observed. The authors of the study concluded that aerobic

endurance exercise positively affects sympathetic nervous system and renin–angiotensin system, resulting in alleviation of cardiovascular risk factors, reduction in BP, and vascular resistance [32]. Aerobic exercise has beneficial effects in long-term management of BP of hypertensive patients. It is found that a single aerobic exercise session reduces 24-h ambulatory BP levels in hypertensive patients and increases the percentage of patients who has achieved target BP values [58]. In meta-analysis of 54 randomized studies, in which approximately 2400 individuals were examined, it is found that aerobic exercise reduces systolic BP by 3.84 mmHg and diastolic BP by 2.58 mmHg. This effect was observed in the whole study population which included hypertensive, normotensive, underweight, overweight, white, black, and Asian subjects and regardless of the frequency, intensity, and type of aerobic exercise. The authors also emphasized that aerobic exercise-related BP reduction is independent of weight loss [59]. In another meta-analysis which included 24 studies, with aerobic exercise sessions changing from 3 to 8 times a week maintained for 15–60 min for 3 weeks–12 months, systolic BP was reduced by 5 mmHg and diastolic BP by 3.09 mmHg. In this meta-analysis, reduction in BP was more evident in diabetic and hypertensive patients. The authors therefore recommended aerobic exercise especially is in high-risk individuals for both primary and secondary prevention purposes [60]. In another meta-analysis involving 23 studies, included 1226 people and compared individuals who lived sedentary over the age of 60 to individuals 89% of whom exercised as walking and slow running. Exercise duration was 30–50 min and average of three sessions per week. When compared to the control group, with controlled aerobic exercise a net decrease of 3.68 mmHg was observed at DBP and 5.39 mmHg decrease in SBP [61]. According to the results of meta-analysis it is observed that regular aerobic exercise decreased systolic BP by approximately 5 mmHg in and diastolic BP by approximately 3 mmHg.

10.3 The Effect of Resistance Exercise on BP

Dynamic resistance exercise is usually performed by lifting weights or by exercising in the resistance machine. Dynamic resistance exercise involves the movement of joints and muscles against a mutual force, whereas isometric resistance exercise is performed by the contraction of muscles without movement of joints or muscles. In a meta-analysis of 12 randomized controlled trials, it was shown that resistance exercise performed for more than 4 weeks resulted in approximately 3.2 / 3.5 mmHg reduction in systolic and diastolic blood pressure [40]. In a study of more than 4 weeks of progressive resistance exercise, systolic and diastolic BP levels were reduced by 2% and 4%, respectively. It was concluded that progressive resistance exercise was effective method to reduce resting systolic and diastolic BP levels [39]. In a meta-analysis which was related to isometric handgrip exercise for more than 4 weeks also showed a 13.4 mmHg decrease in systolic BP and 7.8 mmHg decrease in diastolic BP. They therefore concluded that isometric handgrip exercise resulted effective BP reduction in adults [62]. In a meta-analysis investigating the effect of isometric exercise on resting BP, it was revealed that about 1 h isometric exercise per week decreased systolic BP by 10.4 mmHg and diastolic BP by 7 mmHg [63]. In meta-analysis of 28 randomized studies; resistance exercise ensured significant BP decrease in normotensive and prehypertensive individuals (3.9/3.9 mmHg respectively) but the decrease in hypertensive patients (4.1/1.5 mmHg) was not significant. When subgroup analysis was performed, it was found that isometric handgrip exercise did provide significant decrease (2.8/2.7 mmHg) whereas the decrease by dynamic resistance exercise (13.5/6.1 mmHg) was not significant. However, subsequent to dynamic resistance exercise, peak VO_2 increased; body fat and triglycerides decreased. The authors emphasized that isometric handgrip exercise is more effective than dynamic resistance exercise

in lowering BP [41]. In a study about effect of isometric resistance exercise on resting BP in adults who exercised for more than 2 weeks, it was found that isometric resistance exercise caused 5.20 mmHg decrease in systolic BP; 3.91 mmHg decrease in diastolic BP and 3.33 mmHg decrease in average BP. The BP reduction was more pronounced in hypertensive, compared to normotensives, over 45 years compared to less than 45 years of age, in man compared to woman and in those who continue exercise more than 8 weeks compared to those who exercise less than 8 weeks [64]. In a meta-analysis of 64 controlled trials, it was found that dynamic resistance exercise resulted in a reduction of 6 mmHg in systolic BP and 5 mmHg in diastolic BP [65]. According to the results of this meta-analysis, the regular isometric handgrip exercise is more effective than the dynamic resistance exercise.

10.4 The Effect of Combined Aerobic and Resistance Exercise on BP

Combined aerobic and resistance exercise corresponds to perform regular aerobic exercise on some days of the week and to perform resistance exercise on other days. In 2004, the American College of Sports Medicine recommended combination of aerobic exercise by resistance training for the purpose of prevention of hypertension [36]. In a meta-analysis of 93 studies, including 105 endurance, 29 dynamic resistance, 14 combined endurance and resistance, and five isometric resistance exercise groups, systolic BP was 3.5 mmHg after endurance exercise, 1.8 mmHg after dynamic resistance exercise, and 10.9 mmHg after isometric resistance exercise. However, it did not decrease after combined exercise. Diastolic BP decreases 2.5 mmHg after endurance exercise, 3.2 mmHg after dynamic resistance exercise, 6.2 mmHg after isometric resistance exercise and 2.2 mmHg after combined exercise. The authors concluded that endurance, dynamic resistance, and isometric resistance training lowered systolic and diastolic BP, and combined exercise reduced diastolic BP only [37]. The effects of combined aerobic and resistance exercise on resting and sub-maximal exercise on BP, arterial elasticity, vascular resistance and vascular impedance were investigated in postmenopausal sedentary women. Group 1 performed aerobic and strength training once a week; group 2 performed aerobic and strength training twice a week; Group 3 performed strength training and aerobic exercise three times a week. In all groups, adequate BP drop was observed in exercise and rest. The authors of the study specify that even 1 day aerobic and strength exercise provides adequate BP decreases [66]. In a study comparing aerobic exercise with combined aerobic and resistance exercise in men aged 65–75 years, the study population was divided into three groups; Group 1 was organized as aerobic exercise, group 2 as combined resistance exercise and aerobic and group 3 as control group. Patients performed exercise 3 days a week for 9 months. In the aerobic exercise group, systolic and diastolic BP decreased by 15 and 6 mmHg respectively and in the combined exercise group by 24/12 mmHg respectively. The authors emphasized that both exercise types provide effective BP reduction, but combined exercise decreases body fat [67]. In a recent study, 12-week combined aerobic and resistance exercise in postmenopausal women with stage 1 hypertension has been shown to reduce arterial stiffness, mean BP, and endothelin 1 levels. Systolic BP decreased by 13.5 ± 1.58 mmHg and diastolic BP decreased by 11 ± 1.34 mmHg [68]. It has been shown that 12-week combined aerobic and resistance exercise in obese prehypertensive women achieved a decrease in BP by 7.3 ± 2.67 mmHg, improvement in insulin resistance and a reduction in central adiposity [69]. According to the meta-analysis results, combined aerobic and resistance exercise provides a significant reduction in BP.

10.5 The Effect of High-Intensity Interval Exercise on BP

This type of exercise consists of low-intensity aerobic exercise interrupted by 1–4 min of high-intensity exercise that reaches 85–95% of maximal heart rate or peak VO_2. With this exercise, it is found that there is a significant reduction in BP compared to that of a continuous moderate exercise, and that the endothelial function improved better, and that arterial stiffness decreased [54]. Aerobic and anaerobic intermittent exercises where maximal oxygen uptake is 70% or above have been shown to significantly reduce office and ambulatory BP of hypertensive individuals [20]. High-intensity aerobic exercise, which is six MET or more than 60% of the aerobic capacity, provides better improvement in diastolic BP, glucose level, and aerobic capacity compared to moderate-intensity exercise, whereas systolic BP, lipid profile and decrease in body fat were not different in terms of the effect [55]. In another study, it was reported that at least 12 weeks high-intensity exercise was required for effective BP reduction [70]. In a study in which high-intensity exercise performed three times a week were compared with moderate-intensity aerobic exercise for 16 weeks, high-intensity exercise was found to be more effective in decreasing BP [71]. Twelve-week high-intensity exercise, continuous running, and strength training were compared to the control group in another study in terms of change in systolic BP, and high-intensity exercise was found to have similar effects with continuous running on BP [72]. Another study where moderate- and high-intensity exercise were compared in adolescents, it was shown that high-intensity exercise provided more reduction in BP [73]. Aerobic and anaerobic intermittent exercise where maximal oxygen uptake of 70% is achieved has been shown to significantly reduce office and ambulatory BP of hypertensive individuals [20]. Interestingly, no significant difference was recorded between high-intensity exercise and moderate-intensity continuous exercise in a recent meta-analysis [74]. Large-scale studies and meta-analyses related to high-intensity exercise are needed.

10.6 The Effect of Accumulated Exercise on BP

Since lack of time to exercise is a major deterrent, performing short durations of aerobic exercise throughout the day can increase the number of people who exercise. In order to achieve a 30-min daily exercise goal, short durations of moderate-intensity physical activity sessions accumulated during the day are called accumulated exercise [75]. There are studies showing that accumulated exercise leads to a significant decrease in BP in prehypertensive and hypertensive subjects. In fact, it is stated that this type of exercise is more effective in prehypertensives compared to the single-session exercise type [57, 76, 77]. In a meta-analysis of the 16 studies, accumulated exercise sessions in total of 30 min per day and single 30 min session were compared, and a similar decrease in BP was found [78]. The evidence suggests that accumulated aerobic exercise during the day (such as three 10-min sessions) is equally effective in reducing the BP. In a study in which continuous exercise that achieves 60% of the heart rate reserve was compared with exercise that achieves 50% of the heart rate reserve in 2 min and 80% of the heart rate reserve in 1 min, there was a significant decrease in ambulatory BP in both methods [79]. When exercise is performed at the time the circadian variation is minimum such as 04:00 to 08:00 a.m. in the morning, it has been reported that the risk of post-exercise hypotension after continuous and intermittent exercise is minimum. It was found that post-exercise hypotension was more significant in intermittent exercise when compared to continuous exercise, and the accumulated exercise in the afternoon hours provided better decrease in BP [80].

10.7 The Effect of Brisk Walking on BP

The brisk walking should be emphasized because it is the most common, inexpensive, feasible, instrument and risk-free type of aerobic exercise which can be recommended for everyone. 10,000

steps per day is an easy method for physical activity. In the meta-analysis of 12 studies with a total of 468 normotensive people, the effect of pedometer use on daily step-count was evaluated and it was found that pedometer use increased the daily physical activity and decreased systolic BP by 3.8 mmHg and diastolic BP by 0.3 mmHg [81]. In a study wherein walking with pedometer for 6 months, a significant decrease in systolic and diastolic BP was observed when the average step count was around 12,000 [82]. In a large study comparing walking and running exercises, the effectiveness of two exercise types were found to be similar in terms of BP lowering effect [83]. In addition, walking and running in hypertensive individuals provides a similar mortality reduction [84]. The brisk walk should be recommended to everyone.

10.8 The Effect of Whole-Body Vibration Exercise on BP

It is a type of passive exercise. However, there are publications related to its effect of lowering BP. In women with prehypertensive and Stage 1 hypertension, 8 weeks of whole-body vibration exercise has been shown to enhance sympathovagal balance and reduce BP [85]. It has also been shown that whole body vibration exercise for 6 weeks reduces central aortic pressure in postmenopausal prehypertensive and hypertensive women [86]. In contrast, it was suggested that the whole body vibration exercise in obese normotensive women leads to an increase in BP [87]. In conclusion, we have insufficient data on the effect of whole-body vibration exercise on BP.

10.9 The Frequency, Intensity, Duration, and Type of Exercise to Be Recommended for Hypertensive Individuals

The frequency of exercise is expressed as how many times it is performed in a week. The intensity of exercise is described as light-, medium-, and high-intensity exercise. The duration of exercise is time or how long an exercise session lasts. The type of exercise can vary from aerobic to resistance to static to dynamic. All these factors inspired the frequency, intensity, time, and type principle (FITT principle) of exercise prescription [88]. On days when exercise was performed, BP was found to be lower than non-exercise days. An exercise session can provide up to 24 h of BP reduction. It is evident that as the number of days of exercise increases, the BP-lowering effect will increase [89].

Seventh Joint National Committee (JNC 7) [8] did not provide a specific recommendation on the number or the frequency of exercise, but it has been proposed to perform aerobic exercise on most days of the week, 30 min or longer per day. There is no information about the exercise intensity. It is stated that exercise described in this way, decreases BP of 4–9 mmHg. The American College of Sports Medicine (ACSM) [36], recommends every day exercise if possible or moderate exercise that achieves 40–60% of the peak on most days of the week. The recommended exercise session is 30–60 min of continuous exercise per 10 min. Although aerobic exercise is the method of recommended exercise, dynamic resistance exercise is also recommended 2–3 times a week. There is a BP decrease of 5–7 mmHg in hypertensive patients. The ACC/AHA Lifestyle Work Group [90] and the Eighth Joint National Committee (JNC 8) [91] recommended moderate- to high-intensity aerobic exercise, 3–4 time per week with 40 min sessions, and a BP decrease of 1–5 mmHg is reported. European Society of Hypertension/European Society of Cardiology (ESC)/(ESH) [92] recommends daily 30 min or longer moderate aerobic exercise, 5–7 days per week. Adding dynamic resistance exercise 2–3 days a week is also recommended. There is a BP decrease of 5–7 mmHg in hypertensive patients. In addition to the usual daily activity, the Canadian Hypertension Education Program (CHEP) [93], recommends accumulated moderate-intensity dynamic aerobic exercise 30–60 min per day, 4–7 days in week. Additionally, dynamic, isometric, or handgrip exercises are recommended but the amount and

the BP lowering effect are not reported. The American Heart Association (AHA) [94] recommends moderate- to high-intensity aerobic exercise on most days of the week. Exercise time is provided as a total of 150 min weekly, and combination of dynamic resistance exercise is recommended, but the amount of resistance training and the amount of BP decrease are not specified.

10.10 How Much Exercise Is Useful?

The greater the exercise density is the greater the BP-decreasing effect is [95]. However, in hypertensive patients with comorbidities such as advanced age, a mild- to moderate-intensity exercise program should be more appropriate. In a study in which 416,000 people were followed for 8 years, it was shown that moderate-intensity exercise for 15–90 min per week may be beneficial for people at risk for cardiovascular disease [96]. In an 8-week exercise study, the subjects were divided into sedentary groups, 30–60 min exercise, 61–90 min exercise, 90–120 min exercise, and above 120 min exercise groups. Systolic BP in 61–90 min exercise group achieved a better drop than 30–60 min exercise group, but there was no further BP decrease with increasing durations of exercise [97]. In a study conducted on approximately 8000 men and 9000 women, it has been reported that the rate of hypertension decreases as exercise intensity increases with mild-, moderate-, and high-intensity physical exercise [98]. In conclusion, the duration of the exercise should exceed 30 min per day as indicated by the guidelines and the intensity should be increased as much as possible.

10.11 Is Excessive Exercise Harmful?

Acute exercise causes a temporary stress. In a study in which approximately 500 men were followed for 8 years, it was shown that moderate exercise was protective for ischemic heart disease, but this effect was not evident in those who had very high intensity when severe exercise. Men who had high-intensity training had higher rates of heart attack than men with moderate activity [99]. In a study of approximately 350 people followed for over 32 years, CVD and HT were found to be highest in groups that spent very low calories per week and in those spent excessive calories and the authors reported that moderate exercise was optimal [100]. It has been shown that there is a J-shaped relationship between physical activity and cardiovascular mortality in patients with coronary artery disease. Both very little physical activity and excessive physical activity increases mortality. It was determined that cardiovascular mortality was increased twofold, and all-cause mortality by fourfold in the least active individuals compared to moderately active individuals. Moreover, mortality was increased by 2.4-fold in overactive individuals [101].

Although there are reports of prolonged life span in athletes with high-intensity exercise [102, 103], cases of intensive exercise-induced arrhythmia and cardiac arrest have also been reported [104]. Excessive exercise leads to volume overload in the atria and right ventricle. Right ventricular ejection fraction temporarily decreases, and cardiac biomarkers increase. This condition returns to normal in 1 week. Repetitive occurrence of this phenomenon by exercise in long run, leads to patchy myocardial fibrosis in some individuals, especially in atria, inter ventricular septum and right ventricle. Fibrosis forms a substrate for atrial and ventricular arrhythmias. In addition to patchy fibrosis, prolonged excessive exercise leads to coronary artery calcification, diastolic dysfunction and stiffening of the great arteries [105].

Exercise test is relatively contraindicated, when BP exceeds 200/110 mmHg. The increase of BP to 250/115 mmHg during the exercise test is a relative indication for termination of the test [106]. Stage 1 and 2 hypertensive patients can perform moderate-intensity exercise without consulting a doctor [107]. This exercise corresponds to walking around 5–7 km/h, cycling at 15 km/h, paddling at about 4 km/h, and swimming at about 2 km/h of a 70 kg person [108]. In hypertensive individuals, exercise

recommendations are the same for the general population. However, before starting an exercise program, exercise test should be done in the control of the health staff in the high-risk hypertensive patient. Stage 3 hypertensive individuals should undergo clinical evaluation before starting exercise [109].

10.12 Exercise in Case of Exercise Induced Hypertension

There is no evidence that hypertension during exercise increases the incidence of adverse events. Therefore, these people should be encouraged to exercise [107].

10.13 Antihypertensive Medicines and Exercise

Antihypertensive drugs such as alpha blockers and calcium antagonists may cause excessive BP drop after sudden cessation of exercise, which is more evident in the elderly. In this case, the exercise should be terminated with a slowdown period instead of sudden stop. Since beta-blockers and diuretics may impair thermoregulation, exercise intensity should be limited in hot or humid conditions, adequate hydration should be provided and refrigerant clothing should be worn [107].

10.14 What Kind of Exercise Is Recommended?

Generally, when starting the exercise, activities such as walking, running, cycling, and swimming are preferred if the individuals are not well conditioned because the energy expenditure of these activities is well known. Competitive sports are not recommended at the early stages but can be included when a minimum of 5 METs functional capacity is reached. Patients with a functional capacity of less than 3 METs due to past surgery or debilitating diseases, should be encouraged to exercise several times a day, usually with sessions lasting only 5 min. Persons with a functional capacity of 3–5 METs can exercise once or twice a day. Individuals with functional capacity of 5–8 METs can exercise on different days, 3 days a week. When the functional capacity reaches 8 METs, more intensive exercise can be done. When a better physical condition is achieved, the heart rate and the degree of perceived effort [RPE) for a given MET level are reduced. Training intensity, duration and frequency should progressively be increased to increase the level of exercise METs by walking, jogging, cycling, or swimming [14].

When physical exercise is continuous, cardiorespiratory fitness improves. It has been shown that those with good cardiorespiratory fitness have less new-onset hypertension compared to those with lower fitness levels [110]. Moreover, it has been reported that new-onset hypertension is more common in patients with deteriorated cardiovascular fitness compared to those with improved cardiovascular fitness [111]. As every 5 mmHg decrease in systolic BP provides reduction by 9% in coronary artery disease-related mortality, 14% in stroke-related mortality, and 7% in all-cause mortality, regular exercise should be prescribed to all hypertensive individuals [53].

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Exercise and Coronary Heart Disease

11

Aydin Akyuz

Abstract

Coronary artery disease (CAD) can be obstructive or nonobstructive. Patients with nonobstructive and stable angina pectoris are usually women. Nonobstructive CAD is caused by endothelial dysfunction at the microvascular level, such as cardiac syndrome X and coronary slow flow syndrome. Even if coronary anatomy is nonobstructive, the presence of myocardial ischemia is a major determinant for the exercise program. CAD is a chronic inflammatory disease, and the progression of the disease can lead to a rapid change in the functional capacity of CAD patients. Exercise training is a major component of cardiac rehabilitation and reduces cardiovascular mortality, morbidity, and rehospitalization as well as improves psychological stress and controls risk factors of CAD, such as diabetes mellitus, hypertension, and obesity. It is possible that the quality of life of patients with CAD can be improved by using appropriate exercise therapy. However, the exercise programs among CAD patients are highly underutilized. This chapter will summarize the research progress of exercise in the prevention and treatment of CAD as well as how to create safe exercise programs and the importance of exercise for patients with CAD. In addition, exercise training has fundamental beneficial effects on ischemic and nonischemic heart failure.

Keywords

Coronary heart disease · Dynamic exercise · Static exercise

11.1 Background

William Heberden, who first described the angina pectoris, noted that "If we give a task of sawing to a patient for half an hour every day, we may cure him." Hippocrates declared 2500 years ago, "the right amount of exercise, not too little and not too much, is the safest way to health." Currently, all CAD patients should be encouraged to regular exercise for long life even though they are symptomatic.

Age, hyperlipidemia, hypertension, cigarette use, diabetes mellitus, and sedentary activity are risk factors for the development of CAD. Some of these factors can be modified such as diet, smoking, and still life activity [1]. Sedentary behaviors increase the risk of cardiovascular mortality [2]. CAD has been reported as a cause of death in one in five people and its annual cost is more than $160 billion [3]. CAD is likely to cause death, especially over the age of 35 [4].

A. Akyuz (✉)
Faculty of Medicine, Department of Cardiology, University Hospital, Namık Kemal University, Tekirdag, Turkey
e-mail: aakyuz@nku.edu.tr

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_11

Acute myocardial infarction (AMI), unstable angina pectoris, cardiac arrest, and heart failure may occur as a result of CAD [5, 6]. Atherosclerosis not only relates to be a cholesterol storage disease characterized by the collection of cholesterol and thrombotic debris in the artery [7], but it also associates with chronic inflammation and endothelial dysfunction [8]. Physical activity levels decrease systemic markers of inflammation, thrombosis, and endothelial dysfunction [9–11]. Genetic inheritance and lifestyle are important determining factors for CAD development [12, 13]. Therefore, physical activity has a key role in preventing CAD development via decreasing endothelial dysfunction and inflammation. Avoiding a sedentary lifestyle during adulthood not only prevents cardiovascular disease independently of other risk factors, but it also substantially expands the total life expectancy and the cardiovascular disease-free life expectancy for both sexes. This effect is seen at moderate levels of physical activity, and the gains in cardiovascular disease-free life expectancy are highly increased at higher activity levels [14]. Franco et al. [14] also found that life expectancy for sedentary people at age 50 years was found to be 1.5 years shorter than for people engaging in moderate daily physical activity and more than 3.5 years shorter than for people with high physical activity levels. These differences were similar for both sexes' CAD severity, and the number of coronary artery vessels' involvement, the degree of myocardial ischemia, the severity of angina, left ventricle function, and general health condition are important determinants of life expectancy and quality in patients with CAD [15]. In the treatment of CAD, many methods are used together, such as physical activity, weight control, smoking cessation, blood pressure control, control of lipid levels in the blood, diabetes control, and drug use (acetyl salicylic acid, beta-blockers, nitrates, etc.) [15]. It is also recommended that patients with CAD receive annual influenza vaccines [16]. Regular exercise is not only beneficial for both CAD prevention and treatment, but it also helps in the modification of CHD risk factors such as diabetes, hypertension, and hyperlipidemia [17–20]. Increased myocardial and peripheral artery perfusion and higher exercise capacity are related to lower mortality and morbidity of CAD [21, 22]. However, the basic mechanism of these positive effects is not fully understood. It is stated that this situation may be due to the improvement of endothelial functions and decrease of inflammation [23–25].

11.1.1 Exercise Definition

While dynamic exercise increases heart rate, static exercise increases blood pressure. For example, running is a dynamic exercise, and weight lifting is a static exercise. However, most of the sports include both dynamic and static exercise (Table 11.1) [26]. The effect of dynamic

Table 11.1 Classification of sports

	Dynamic/static	
1A	Low/low	Bowling, cricket, curling, golf, riflery, yoga
1B	Moderate/low	Baseball, softball, fencing, table tennis, volleyball
1C	High/low	Badminton, field hockey, running (long distance), soccer, race walking, squash
2A	Low/moderate	Archery, auto racing, diving, motorcycling, equestrian
2B	Moderate/moderate	American football, jumping, rugby, surfing, running (sprint)
2C	High/moderate	Basketball, ice hockey, lacrosse, running (middle distance), swimming, team handball, tennis
3A	Low/high	Gymnastics, martial arts, rock climbing, sailing, weight lifting, windsurfing, bobsledding/luge, water skiing
3B	Moderate/high	Bodybuilding, downhill skiing, skateboarding, snowboarding, wrestling
3C	High/high	Boxing, canoeing, kayaking, cycling, decathlon, rowing, triathlon, speed skating

Dynamic: Low (<50%), moderate (50–75%), high (>75%), static low (<10%), moderate (10–20%), high (>20). The estimated percentage of maximal oxygen uptake (VO_2 max) reflects the increasing dynamic exercise and relates to an increasing cardiac output. The increasing static exercise is defined in terms of the estimated percentage of maximal voluntary contraction achieved and leads to an increasing blood pressure

exercise is evaluated by its effect on both maximal oxygen consumption and the percentage of cardiac output. The effect of static exercise is assessed by the increase in blood pressure and its effect on muscle strength. According to dynamic or static exercises' features, the classification of sports was categorized by the American Heart Association and American College of Cardiology (Table 11.2) [27].

11.2 Dynamic (Isotonic-Aerobic) and Static (Isometric-Resistance) Exercise and Cardiovascular Response

The exercise capacity is often consistent with the CAD severity. However, CAD patients may respond to dynamic exercise in various ways, such as myocardial ischemia, irreversible myocardial necrosis, and conduction abnormalities or normal [28–30]. Because the difference in coronary arteriovenous oxygen is unchanged, reduced exercise tolerance is often attributed to the decrease in heart rate and stroke volume. The arterial blood pressure response may be increased, normal, or decreased. A decrease in blood pressure is critical for patients with impaired left ventricular function due to myocardial ischemia. Myocardial lesions may cause left ventricular dysfunction. When left ventricular dysfunction progresses, the increase in heart rate does not fully meet the decrease in stroke volume. If more than 50% of the coronary artery diameter is affected by atherosclerosis, coronary insufficiency is encountered during exercise. The increased oxygen requirement of the peripheral tissue can be supplied by increasing the arteriovenous oxygen difference. Therefore, the absence of symptoms associated with exercise does not mean that there is no atherosclerosis in the coronary arteries [31]. Because the CAD severity increases, the probability of the coronary insufficiency triggered by exercise increases. The number of coronary vessels involved is also important, and as the number increases, the exercise capacity also decreases. Lesion complexity may not be directly proportional with the symptoms. The patient with a single coronary artery stenosis may be more symptomatic during a mild exercise, while a patient with two to three coronary vessel involvement may be asymptomatic at higher work capacity due to having good coronary collaterals. For this reason, functional classifications may be more guiding for the evaluation of patients' exercise capacity [31, 32]. The possibility of ischemia is higher in patients with CAD as the oxygen requirement of myocardium increases during exercise. This happens due to the higher end-diastolic volume and lower left ventricular ejection fraction caused by ischemia. The ST changes in ECG can be seen. Stress nuclear imaging or echocardiography should be performed for the evaluation of ischemia degree. Ischemia usually occurs on a specific exercise threshold in patients with CAD. This threshold can be assessed by the double product response calculated by multiplying the heart rate and systolic blood pressure. Dynamic upper extremity exercises may be useful to increase exercise threshold where ischemia begins [33]. In the supine position exercise, the threshold level decreases due to the increase in the end-diastolic volume of both ventricles. Because static exercises increase diastolic blood pressure and coronary flow in diastole, static exercise may increase threshold of ischemia [34, 35]. Therefore, CAD patients should do both dynamic and static exercises together.

Table 11.2 New York Heart Association classification

	VO_2 max (MET)	Exercise capacity-symptom
Class 1	>6	No limitation in normal physical activity
Class 2	4–6	Mild symptoms only in normal activity
Class 3	2–4	Marked symptoms during daily activities
Class 4	<2	Severe limitations, symptoms even at rest

Canadian Cardiovascular Society grading of angina pectoris is not compatible with VO_2 (MET) in any patient with CAD

11.3 Exercise and Inflammatory Response

Coronary artery atherosclerosis has different stages of the development. These stages include circulating plasma oxidized low-density lipoprotein cholesterol (LDL-C) entering subintimal area in the coronary vessel; upregulation of some adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), E-selectin, and P-selectin; upregulation of some chemotactic molecules, such as monocyte chemoattractant protein-1 (MCP-1); upregulation of metalloproteinases; influx of coagulation proteins; monocyte and T-lymphocyte movement to the arterial vessel wall; expression of some chemokines and cytokines, such as MCP-1, interferon gamma, tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6); migration of smooth muscle cells from media into the intima; vascular endothelial growth factor (VEGF) production; and fibrous cap formation, subsequently [36, 37]. Palmefors et al. [38] have shown in their meta-analysis that physical activity decreases TNF-α, IL-6, VCAM-1, ICAM-1, C-reactive protein (CRP), and VEGF levels in patients with atherosclerosis. Some studies have presented the findings of exercise positive effects on coronary artery atherosclerosis [39, 40].

11.4 Exercise and Brain Natriuretic Peptides

Recently, there is growing interest in the evaluation of the relationship between exercise and ischemia. Plasma levels of brain natriuretic peptides (BNP) significantly increased during acute myocardial ischemia associated with dynamic exercise [41]. BNP levels can show the degree of left ventricular systolic dysfunction [42]. It was reported that BNP is a strong predictor of mortality in acute coronary syndromes and may be a strong prognostic marker in chronic coronary syndromes [43]. BNP show a positive correlation with peak exercise and anaerobic threshold in CAD patients, and it can improve the diagnostic accuracy of exercise testing [44, 45].

11.5 Benefits of Exercise Training and Secondary CAD Prevention

Regular physical activity improves exercise capacity [46]; increases estimated metabolic equivalents (+35%) [47, 48], peak oxygen consumption (+15%) [49], and peak anaerobic threshold (+11%) [49, 50]; decreases total cholesterol (−5%) [51, 52], triglycerides (−15%) [52], and LDL-C (−2%) [51, 52]; increases high-density lipoprotein cholesterol (+6%) [53]; reduces insulin resistance and body mass index (−1.5%) [54, 55], metabolic syndrome (−37%) [56, 57], and high-sensitivity CRP (−40%) [57, 58]; decreases anxiety [59], hostility [59], somatization [59], and mental depression [60]; improves autonomic tone (increased heart rate recovery and variability) [61]; reduces resting heart rate [61]; improves blood rheology [38], and reduces hospitalization costs, morbidity, and mortality [62–64].

11.6 Exercise Training and Cardiovascular Response

Higher intensities of exercise may not be sustainable for longer periods. Therefore, interval training was proposed by physicians [65]. Traditional training methods include continuous training (30–60 min) at moderate intensity (40–80% of VO_2 peak) (aerobic continuous training), leading to gains in VO_2 peak of approximately 20% after 12 weeks of three times-weekly exercise sessions [66, 67]. Even within the high-intensity training zone, exercise intensity was an important determinant for improving VO_2 peak in patients with CAD [68]. An increase of 1 mL/kg/min in exercise capacity yields an almost 15% increase in survival [69]. Villelabeitia et al. [70] have shown that high-intensity interval training (HIIT) results in a significantly greater increase in VO_2 peak

compared with moderate continuous training (MCT). The aerobic threshold increased by 21% in HIIT and 14% in moderate continuous training (MCT). HIIT consists of a repeating series of high-intensity (peak interval) exercises, alternating with periods of low-intensity exercise (recovery interval). MCT program consists of aerobic dynamic exercise and aims at 60–80% of VO_2 peak. The studies on the benefits of MCT exercise have shown a significant improvement in terms of VO_2 peak [49].

11.7 Exercise Programs in Primary and Secondary Prevention of CAD

Both dynamic (aerobic) and static (resistance) exercise mode are proposed for all CAD patients. Dynamic exercise should be at least 20–30 min (preferably 30–45 min), and static exercise should be 10–15 repetitions, 1–3 sets of 8–10 different exercises for all extremities. The frequency of dynamic exercise should include most days (at least 4–5 days/week and preferably 6–7 days/week). The frequency of static exercise should include two to three sessions weekly (nonconsecutive days). The intensity of dynamic exercise should be close to anaerobic threshold: 50–75% peak VO_2, 65–85% of maximal heart rate or 60–80% of heart rate reserve, and 10–15 beats/min below the level of ischemia. Borg Rating of Perceived Exertion (BORG) scale can be used for this purpose. The recommended intensity of walking is a perceived exertion of 11–13 on the BORG scale. The intensity of static exercise should be moderate intensity [46, 71–73]. A CAD patient may have some symptoms during exercise, such as muscle overload, fatigue, muscular pain, dyspnea without oxygen desaturation, dyspnea with desaturation <94%, muscle injury, vasovagal conditions, ischemia, ventricular arrhythmia, or hypertensive emergencies. In these circumstances, exercise program should be reconsidered by the patient's physician.

11.7.1 Telehealth Interventions in CAD Exercise Program

Huang et al. [74] have shown that telehealth (such as the telephone, computer, Internet, and videoconferencing) interventions have a beneficial effect on risk factor reduction and secondary prevention for CAD patients. Telehealth intervention-delivered cardiac rehabilitation does not have significantly inferior outcomes compared to center-based supervised program in low to moderate risk CAD patients. Telehealth models may be helpful for the secondary prevention, especially among CAD patient who do not access cardiac rehabilitation [75].

11.7.2 Exercise-Based Cardiac Rehabilitation After AMI

Patients presenting with AMI should be encouraged for early ambulation (day 1). After early ambulation, the intensity of the exercise program should be quite low. Walking or mild level of gymnastic can be used for this purpose. If extensive myocardial damage, heart failure, hypotension, or arrhythmias exists initially, ambulation should be deterred for clinical stabilization. All AMI patients should be included in the exercise program after AMI [64]. A standard exercise-based cardiac rehabilitation must take account of patients' age, pre-infarction level of activity, and physical limitations. Exercise training, risk factor modification, education and stress management, and psychological support should be major determinants of the cardiac rehabilitation [76]. The best approach is to perform a low-level treadmill test after discharging and decide on the appropriate exercise program. The type, duration, frequency, and severity of the planned exercise should be prescribed for all CAD patients. Static or resistance exercise types such as weight lifting or push-up exercises are not recommended after early discharge. The exercise intensity can be increased after 3 months of AMI or surgery according to the presence of symptoms. Before and after the exercise, the warm-up and cooling periods should be 5–10 min. In this period, it is

recommended to avoid competing sports [31]. An outpatient program should be 2–6 months' duration [77, 78]. Home-based rehabilitation is like centre-based cardiac rehabilitation in terms of the mortality of the patients with a low risk after AMI or revascularization [77].

11.7.3 The Selection of Exercise Program

In the selection of exercise, the risk classification of the CAD patients should be taken into consideration (Table 11.3). In general, the dynamic exercises, in which large muscle groups participate, are well tolerated by patients with CAD. The CAD patients' clinical condition, exercise tolerance, interest, and ability are the important variables influencing the selection of the exercise type. In the period after AMI or revascularization, bicycle ergometer or treadmill can be used. When planning an exercise prescription, it is very important to calculate the appropriate exercise intensity for each patient. Exercise should be intense enough to be beneficial for health fitness and performance, but this intensity should not lead to fatigue or cardiovascular symptoms, such as angina pectoris or dyspnea. The intensity, frequency, and duration of the exercise should be planned appropriately [31]. Heart rate and energy expenditure are directly proportional and very useful in determining the intensity of exercise for CAD patients. The prediction of energy expenditure from heart rate during exercise is possible [79]. Target heart rate during exercise is generally can be calculated with the formula (220 − age), and the target exercise heart rate of 50–80% is an optimal range [80]. The exercise test can be used to determine the appropriate heart rate. For example, if the symptoms of a patient begin at 130 beats/min, the safe interval is less than 130 beats/min. In this case, exercise should be done below the heart rate of 110 beats/min. This heart rate can be increased up to 10% per week according to the presence of symptoms. In patients with low exercise capacity (<5 MET), the exercise should be started with a target exercise heart rate of 40–50%, and the walking will be most useful for the exercise choice. Aerobic and dynamic exercise training sessions should be performed at least 3 days a week, and 250–300 kcal should be spent in one session. The weekly exercise frequency should be increased as much as possible. Approximately 1600 kcal of weekly energy expenditure with a moderate intensity exercise provides significant benefit in patients with CAD [81]. Exercise should not be done more than 5 days per week, which may increase orthopedic problems [31].

Table 11.3 The risk classification of CAD patients in the selection of exercise type

	Risk factors	
Patients with low risk	NYHA functional capacity >8 METs	No exercise-induced ischemia
	Left ventricle ejection fraction >50%	No arrhythmias
Patients with moderate risk	NYHA functional capacity <8 METs	Exercise-induced ischemia (<0.2 mV ST depression in exercise electrocardiogram)
	Left ventricle ejection fraction >30–50%	No severe arrhythmias, such as sustained ventricular tachycardia or fibrillation
Patients with high risk	Left ventricle ejection fraction <30%	Exercise-induced ischemia (>0.2 mV ST depression in exercise electrocardiogram)
	Hypotension at low exercise intensity (systolic arterial blood pressure >20 mmHg)	Persistent severe arrhythmias, such as sustained ventricular tachycardia or fibrillation, or history of cardiac arrest

11.8 Exercise and CAD Patients According to Guidelines

Exercise programs are important for the prevention and treatment of CAD patients, and the American Heart Association, the American College of Cardiology, and the European Society of Cardiology give a Class I recommendation as a fundamental therapy [82–84]. CAD patients

may present their heart disease as asymptomatic (silent ischemia) or symptomatic. However, asymptomatic patients can be documented after exercise testing, stress nuclear imaging, or echocardiography. If necessary, the coronary artery anatomy is evaluated with computerized angiography and calcium score and imaging or coronary angiography in both groups' patients. Stenosis greater than 50% is considered significant. Maximal exercise test is taken under medical treatment in order to determine if there is exercise tolerance, electrical instability, and inducible ischemia in patients with known CAD. Echocardiography should also be performed for the evaluation of left ventricle functions. Patients with CAD should strongly consider deferring their possible return to highly intensive exercise to permit lesion regression and regression of lipid from the plaque. In these patients, statin therapy should be performed well according to guidelines for at least 2 years to reduce the risk of plaque rupture (Class 1; Level of evidence A). CAD patients should undergo an evaluation of left ventricular function (Class I; Level of evidence C). Asymptomatic CAD patients with the left ventricle resting ejection fraction (%) (EF) value of >50% and coronary artery stenosis of less than 50% can do competitive sports or intensive exercises if they are electrically stable during exercise and/or with induced ischemia by exercise (Class IIb; Level of evidence C). Patients should be given detailed information on the sudden outbreak or change of symptoms and should be checked regularly. According to the workforce (MET value) obtained in the exercise test and their clinical features, patients with electrically unstable or EF value <50% during the exercise test can do their exercise programs with 1A (bowling, cricket, curling, golf, riflery, yoga) and 1B (baseball, softball, fencing, table tennis, volleyball) (Class IIB, Evidence level C) sports or at low intensity (20–40% of VO_2 peak). If the patient with symptomatic CAD has undergone a revascularization procedure or has had an acute coronary event, he/she should stay away from any competitive sport within the next 3 months (Class IIb; Level of evidence C). If the duration and frequency of their symptoms increase, their exercise programs should never be competitive (Class IIb; Evidence Level C). Those who have coronary artery spasm and who do not have significant CAD disease can participate in competitive sports or higher-intensity exercise if complete relief is provided by medical treatment, but this indication is weak according to new clinical studies (Class IIb; Level of evidence C). Sports activities should be kept at 1A–B or 2A–B level according to their clinical features in patients with a history of spontaneous coronary dissection [26]. CAD patients with complete revascularization and without ischemia or myocardial depression can do competitive sports or do exercise at higher intensity according to their symptom threshold.

Competing Financial Interests The author declares no competing financial interests.

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Exercise and Peripheral Arteriosclerosis

12

Demet Ozkaramanli Gur

Abstract

Adaptation of a healthy lifestyle including adequate daily physical activity is shown to reduce 80% of cardiovascular mortality and 40% of cancer-related deaths. A large body of evidence exists proving that this relationship is dose dependent, and even half of the recommended normal physical activity yields significant risk reduction. There has been no medical therapy that would provide such high percentages of reduction in mortality to date. The World Health Organization, therefore, has started an initiative to implement exercise into daily life as a primary prevention measure. Herein, we will focus on the effects of exercise on the vasculature, mainly the peripheral vasculature, in the context of atherosclerotic disease. Exercise has a fundamental role in the pathogenesis, diagnosis, and treatment of atherosclerotic vascular disease. It exerts a protective effect against the development of atherosclerosis irrespective of other cardiovascular risk factors. Additionally, exercise induces changes in vascular hemodynamics helping us to elucidate the presence of obscure vascular involvement. Once again, exercise is the main treatment modality in peripheral arterial disease with accumulating evidence to reduce symptoms and improve both exercise capacity and cardiovascular symptoms.

Keywords

Exercise · Peripheral arterial disease · Mortality

12.1 Background

Atherosclerosis is a systemic inflammatory disease of the arterial tree that involves interplay of complex genetic and acquired cardiovascular risk factors on medium to large arteries [1]. The basic concept of atherosclerosis lays on the "response to injury" hypothesis by Russell Ross [2]. This "injury" to the endothelium triggers the cascade of events that result in a plaque composed of lipid, inflammatory cells, smooth muscle cells, extracellular material, and debris [2]. "Injury" is the net effect of cardiovascular risk factors interacting with innate factors. Cardiovascular risk factors include hypertension, hyperlipidemia, smoking, physical inactivity, and diabetes mellitus.

As a modifiable risk factor, physical inactivity is a contemporary public health concern. In addition to its detrimental role in the pathogenesis of atherosclerosis, it is closely associated with various diseases and health conditions. Recently, the World Health Organization has classified physical

D. O. Gur (✉)
Faculty of Medicine, Department of Cardiology, Namik Kemal University, Tekirdag, Turkey

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_12

inactivity as a global health risk, ranking fourth after hypertension, smoking, and diabetes mellitus in the list of risk factors for all-cause mortality (World Health Organization—Health report). Inactivity is estimated to cause 21–25% of breast and colon cancer burden, 27% of diabetes, and 30% of atherosclerotic disease burden [3]. Physical inactivity increases cardiovascular morbidity and mortality not only by its direct effects but also by contributing to other risk factors such as diabetes, hypertension, and hyperlipidemia. Results of the European Prospective Investigation into Cancer and Nutrition Study (EPIC) have shown that the influence in physical inactivity on mortality is much greater than that of obesity [4]. Conversely, epidemiological studies have proved the role of exercise in improving cardiovascular health [5].

The term "peripheral arteriosclerosis" covers the atherosclerotic disease of vascular territories exclusive of coronary arteries and aorta, encompassing involvement of carotid, upper extremity, mesenteric, renal, and lower extremity arteries [6]. Atherosclerosis, however, displays heterogeneity in phenotype. In other words, it causes narrowing or stenosis in some vessels but dilatation or ectasia in others. The pathophysiological basis of these two entities is distinct, but the triggering mechanism that would lead to one or the other is obscure. In this context, peripheral arterial disease (PAD) refers to the atherosclerothic involvement of ≥1 peripheral arteries [7]. The systemic nature of atherosclerosis results in considerable overlap between its manifestations. Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial revealed that almost half of the patients with lower extremity arterial disease (LEAD) had concomitant coronary (CAD) and cerebrovascular disease (CBVD) [8]. Similarly, in REduction of Atherothrombosis for Continued Health (REACH) registry, the proportion of LEAD patients with CAD and/or CBVD was 61% [9]. Either alone or concurrent with other atherosclerotic manifestations, peripheral atherosclerosis is a strong predictor of mortality and morbidity, independent of established cardiovascular risk factors [10, 11].

12.2 Terminology: Physical Activity Versus Exercise

Although frequently used interchangeably, physical activity and exercise represent different concepts. Physical activity can be defined as any movement using skeletal muscles [12] Exercise, on the other hand, is a planned, structured, and repetitive form of physical activity that has the objective of improvement or maintenance of physical fitness [12].

12.3 Exercise Can Broadly Be Classified into Two Types [13]

12.3.1 Dynamic (Isotonic/Aerobic) Exercise

Dynamic exercise involves changes in muscle length and joint movement with rhythmic contractions that develop a relatively small intramuscular force. It consists of movements of large muscle mass in a rhythmic manner. Increased dynamic component of an exercise can be measured by maximal oxygen consumption and is expressed as peak VO_2. Examples of dynamic exercise are walking and running [14]. This is the most studied and recommended modality of exercise [15].

12.3.2 Static (Isometric) Exercise

Static exercise is associated with development of a relatively large intramuscular force with little or no change in muscle length or joint movement. Increasing static component is related to the estimated percent of maximal voluntary contraction reached. Examples for predominantly static exercises are weight lifting and wind surfing [14].

Classification of exercise into two groups provides us ease to understand their effects on the cardiovascular system. Acute cardiovascular response to exercise differs depending on the exercise practiced [14]. Cardiovascular response to exercise differs depending on the exercise

practiced [13, 14]. With dynamic exercise, heart rate and stroke volume increase substantially. This leads to marked increase in systolic blood pressure. Peripheral vascular resistance, on the other hand, reduces with dynamic exercise also reducing the diastolic blood pressure.

With static exercise, such as resistance training, heart rate increases moderately with little or no change in stroke volume and total peripheral resistance. This leads to increase in both systolic and diastolic blood pressures [13]. Classification of exercise as purely dynamic or statics provides easy understanding of the cardiometabolic load of movement. Nevertheless, this also proposes major limitations as sport modalities are usually a combination of static and dynamic exercises.

At rest, most of the cardiac output is directed to renal and splanchnic arteries (40–25%), and only 15–20% of cardiac output reaches to the skeletal muscle. Exercise induces redistribution of blood from splanchnic arteries mainly to the skeletal muscle which is supplied by approximately 70–85% of cardiac output. In patients with peripheral occlusive disease, this redistribution is impaired resulting in leg symptoms on exertion.

12.4 Exercise and Vascular Function: Athlete's Artery

The adaptation of cardiovascular system to exercise can be analyzed in two parts: adaptations in the heart and adaptations in the vascular system. While the adaptation in heart is beyond the scope of this review, the vascular adaptations will further be discussed herein. Green et al. have adopted the term "athlete's artery" to describe the distinct changes in function and structure in the human arteries in response to exercise (Fig. 12.1) [16]. In this context, most common changes induced by exercise are increased muscle capillary density, larger arterial cross-sectional area, and increased nitric oxide bioavailability. There are numerous studies on the mechanism of how exercise influences vascular homeostasis. Green et al. have shown that exercise increases the cross-sectional area of both conduit and resistance arteries (Fig. 12.1). This increase in the vessel diameter allows accommodation of substantial increase in cardiac output that occurs during exercise. Wall thickness of the conduit arteries in patients who train regularly was also shown to be decreased [17]. Moreover, the changes in the wall thickness are systematic rather than localized. Enhanced vessel function is observed in both trained and untrained limbs, suggesting that the effect of exercise is related to patterns of blood flow and shear stress. Upregulation of the vasodilator pathways also contributes to changes in arterial vasodilator capacity [17].

Nevertheless, the type and the duration of the exercise determine the effect of the exercise on vasculature. In a recent meta-analysis, Black et al. showed that resistance training with predominant ischemic muscle contractions and higher magnitude of localized arterial changes tended to exist. They speculated that greater changes in flow pulsatility may be a more powerful stimulus for greater change in arterial size [18].

12.5 Exercise and Peripheral Atherosclerosis

Atherosclerosis is influenced by numerous endogenous and exogenous factors through complex mechanisms. Until recently, it was assumed that genetic predisposition was deterministic in the occurrence of atherosclerotic manifestations [19]. Nevertheless, current evidence supports the theme that genetic risk can be attenuated by adherence to healthy lifestyle. Khera et al. have demonstrated that, among 55,685 participants, those at high genetic risk who adopted a favorable lifestyle including exercise resulted in 50% reduction in cardiovascular risk [20]. Whayne et al. have further suggested that lifestyle changes contribute to reduction of cardiovascular risk through modification of epigenetics [21].

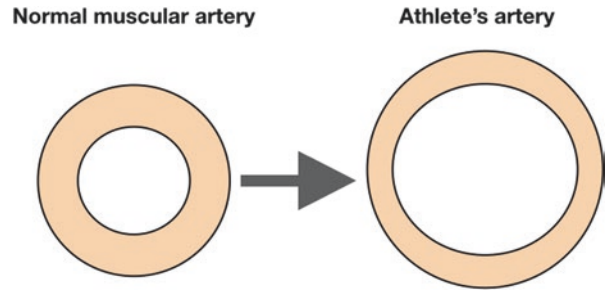

Fig. 12.1 Athlete's artery

12.5.1 Mechanisms by Which Exercise Attenuates Atherosclerosis

There has been vigorous research on the effect of exercise on cardiovascular system, but the exact mechanism by which it promotes cardiovascular health is still elusive. There are several postulated mechanisms, however, that are thought to alleviate the process of atherosclerosis (Fig. 12.2):

1. Alteration of plasma lipid profile: Regular exercise is known to increase the levels of high-density lipoproteins (HDL) and decrease low-density lipoprotein (LDL) in a dose-dependent manner [22].
2. Improvement in vascular homeostasis: Exercise is closely related to improved endothelial function which antagonizes atherosclerosis. Moderate-intensity exercise was shown to increase endothelial nitric oxide synthase expression in atherosclerotic vessels [23]. Increase in laminar shear stress associated with increased cardiac output mediates the effects of exercise on the vascular endothelium [24].
3. Suppression of inflammation: A number of studies have investigated the direct role of exercise in reducing inflammation in LEAD patients. Dopheide et al. reported decreased oxidative burst and sTREM expression in leukocytes of LEAD patients with intermittent claudication after exercise training [25]. Similarly, the gene expression of tumor necrosis factor α and monocyte chemoattractant protein was shown be downregulated with exercise. Regular exercise induces changes in the number and subset composition of macrophages and T cells [26]. Coupled with decrease in pro-inflammatory cytokines, exercise was shown to increase anti-inflammatory cytokines such as interleukin 10 and adiponectin [27].
4. Suppression of oxidative stress: Regular exercise ameliorates the oxidative stress in the arteries and mitochondrial oxidative damage [28].
5. Contribution to reduction in peripheral arterial resistance: Although acute effect of exercise is transient increase in systolic blood pressure, regular exercise has been shown to decrease both systolic and diastolic blood pressures and peripheral vascular resistance. In the early stages, exercise induces a vasodilatory response in arterioles that supply blood to the skeletal muscles. This in turn increases the vasodilatory capacity of vasculature [29].
6. Enhancement of blood rheology: Exercise increases hematopoiesis and hematopoietic progenitor cell counts which increase the oxygen transport capacity of blood [30]. Likewise, the blood viscosity and the coagulability decrease with regular physical activity.

12.5.2 Role of Physical Inactivity in Peripheral Atherosclerosis

Physical inactivity is considered as a pandemic and public health challenge [3]. It is associated with numerous deleterious effects on health, but herein we have focused on the consequences of physical inactivity with regard to peripheral atherosclerosis.

The deleterious effects of physical inactivity on peripheral atherosclerosis should be examined

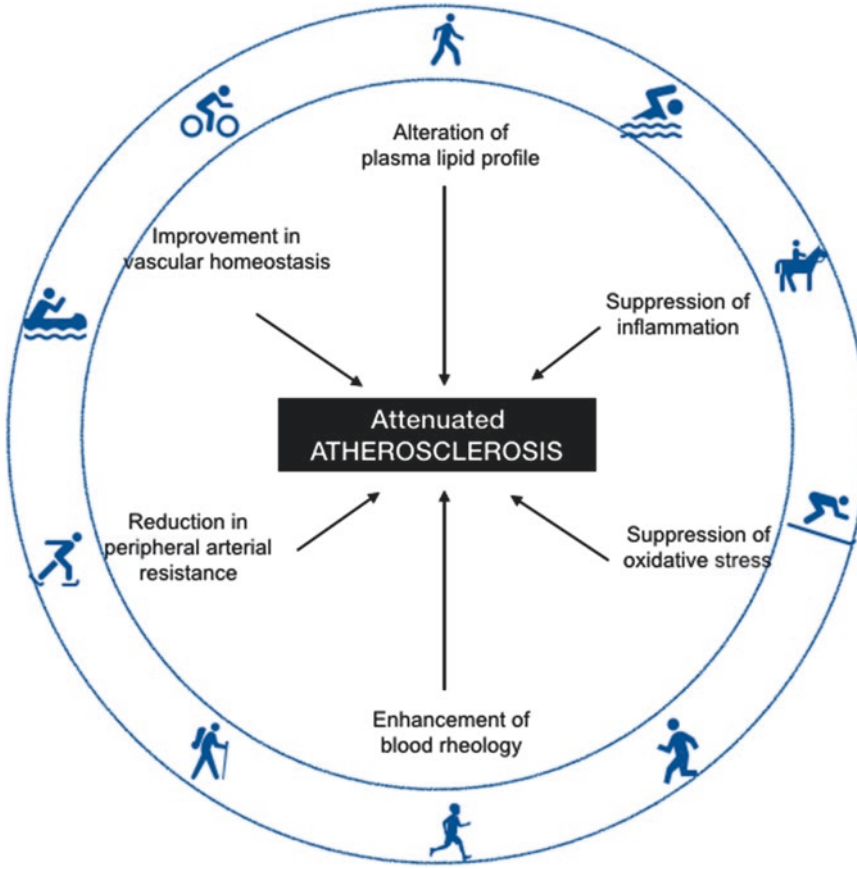

Fig. 12.2 Mechanisms by which exercise attenuates atherosclerosis

under two headings: peripheral vasculature and musculature.

12.5.2.1 Peripheral Vasculature

Studies on the effect of physical inactivity on human vasculature are mainly derived from immobilization due to bed rest, limb fractures, or spinal cord injuries. Physical inactivity causes loss of advantageous effects of shear stress and vasodilatory stimuli which in turn causes adverse arterial remodeling in the affected region. The diameter of superficial femoral arteries of spinal cord injury victims was shown to decrease by 25% by 3 weeks after the accident [31]. Several studies have also evaluated the influence of inactivity on flow-mediated dilatation which is a measure of endothelial nitric oxide-dependent vasodilatation response. They showed that flow-mediated vasodilatation response is impaired in response to even short durations of reduced mobility [32].

12.5.2.2 Skeletal Muscle

The skeletal muscle is one of the early targets of inactivity. The immediate response of the skeletal muscle to reduced activity is decreased protein synthesis [33]. With prolonged periods, this causes muscle atrophy. The reduced muscle mass in elderly population is also thought to result from reduced activity with aging, ultimately leading to a vicious cycle.

The skeletal muscle is also considered as an endocrine organ that secretes myokines, mainly interleukin 6. Myokines are peptides secreted from skeletal muscle upon induction by exercise. They mediate cross talk between the skeletal muscle and adipose tissue [34]. Exercise-induced bouts of high IL-6 exert anti-inflammatory

effects. Conversely, lack of exercise causes low-level increase in interleukin 6, which is pro-inflammatory [3, 35]. Irisin, interleukin 6, interleukin 15, and myostatin are established myokines that together are called the "exercise factor." Exercise factor reduces inflammation and stimulates white adipose tissue to increase insulin sensitivity, thermogenesis, lipid oxidation, and formation of brown adipose tissue [34].

12.5.3 Lower Extremity Peripheral Arterial Disease (LEAD) and Exercise

12.5.3.1 Lack of Exercise as the Causative Mechanism of LEAD

Among all manifestations of PAD, LEAD is the most common form which also bears the poorest prognosis. Fifteen-year survival rate of patients with LEAD is 22% compared to 75% survival rate of patients without this condition. One of the causes for this poor survival is suggested as the underdiagnosis of LEAD which leaves the disease undertreated. The cardinal presenting symptom of LEAD, intermittent claudication, is present in only 15–40% of PAD patients [36]. This condition, therefore, usually goes underdiagnosed and underappreciated both by the patient and by the medical provider [37]. Intermittent claudication is defined as the muscle discomfort provoked by exertion primarily by walking, affecting one or both legs, that is relieved by rest. Muscle discomfort may be described as pain, muscle cramps, or simply fatigue. Fixed obstruction in arterial system supplying oxygen causes supply-demand mismatch in the skeletal muscle metabolism and utilization of anaerobic respiration. Consequently, lactic acid accumulates in the limb causing pain. Depending on the severity and duration of the occlusive disease, this condition might progress to critical limb ischemia and amputation of the affected limb unless the patient dies from a cardiovascular incident such as myocardial infarction. Patients with LEAD thus have reduced functional capacity that further limits their exercise capacity. This forms a negative cycle further aggravating the atherosclerotic process. Hiatt et al. have measured the peak oxygen consumption of LEAD patients with treadmill exercise and revealed that their exercise capacity was reduced by 50% compared to age-matched healthy controls [38]. This is similar to the New York Heart Association functional class 3 heart failure patients.

Several studies showed that there is inconsistent correlation between severity of anatomic stenosis and degree of functional impairment. Limb et al. demonstrated that the calf blood flow measured with magnetic resonance imaging in LEAD patients was only modestly associated with degree of obstructive disease [39]. The most possible mechanism of this discrepancy is postulated as underlying exercise capacity of a patient with atherosclerotic disease.

12.5.3.2 Exercise in the Diagnosis of LEAD

In healthy individuals, the blood pressure at the ankle is slightly higher than that at the site of brachial artery. LEAD causes decrease in the blood pressure distally at the ankle which constitutes the basis of ankle-brachial pressure gradient. In general terms, ABI is the ratio of the arterial pressure in the ankle to that on the brachial artery. This ratio is normally expected to be 1 or above. An ABI of 0.9 or less implies presence of an obstructive lesion on that extremity limiting the arterial pressure at the ankle. Resting ABI is a fast, convenient, and noninvasive method to diagnose LEAD [40]. The sensitivity and specificity of ABI increases substantially when it is measured immediately after treadmill exercise. This is called post-exercise ABI [40]. The current guidelines recommend measurement of postexercise ABI for functional assessment and to reveal moderate stenosis when resting ABI is within normal limits [6, 41, 42].

Exercise has a special place in the pathology of LEAD. Also being one of the causative mechanisms, it is as well used as a diagnostic test and the main mode of treatment. As a diagnostic test, measurement of postexercise ankle-brachial index (ABI) provides invaluable data in patients with LEAD. A postexercise decrease in ABI by >20% or a decrease in ankle SBP by >30 mmHg suggests LEAD. This test is specifically useful in

patients with borderline ABI values (0.9–1). Patients can also be asked to practice heel rising exercise instead of treadmill training to elicit these changes in ABI. Hammad et al. have also shown the association of increase in postexercise ABI with major cardiac events. We can conclude that utilization of exercise into measurement of ABI provides invaluable data for both diagnosis and prognosis of patients with suspected LEAD [43].

12.5.3.3 Exercise for the Treatment of LEAD

Despite advances in the medical and endovascular methods in the treatment of claudication, the principal therapy of LEAD is a formal exercise training program. Current guidelines recommend exercise training in addition to optimal medical therapy as the initial therapy [6, 41]. Beyond increasing the pain-free walking distance, exercise also decreases the cardiovascular disease-related mortality. In this essence, exercise should clearly be defined in terms of intensity, duration, and frequency. Optimum treatment should address all cardiovascular risk factors and include a supervised exercise program, "for a minimum of 30–45 min, in sessions performed at least three times per week for a minimum of 12 weeks" duration [42]. CLaudication: Exercise Versus Endoluminal Revascularization (CLEVER) study, which compared exercise therapy to endovascular treatment, demonstrated that patients on exercise therapy alone had similar improvement in symptoms as patients on endovascular treatment [44]. Pandey et al. have analyzed the randomized controlled trials that compared the efficacy of exercise training, endovascular therapy, and their combination. In 987 patients, they have concluded that endovascular therapy as an initial treatment modality does not improve neither symptoms nor revascularization/amputation [45]. Current guidelines, therefore, prioritize the exercise therapy and suggest endovascular and surgical treatment of LEAD mainly in patients unresponsive to exercise. Aerobic trainings such as walking and stair climbing are the preferred methods of exercise in patients with LEAD. Supervised exercise therapy is more effective than unsupervised exercise [46]. Patients are educated to exercise "walking" until they experience moderate pain and have a period of rest without exercise until the pain is completely eliminated. This procedure is repeated until the target exercise time is achieved. Resistance training can also be used to enhance muscular strength but should not replace aerobic training. Resistance training has been shown to oppose muscle atrophy. Kropielnicka et al. have evaluated and compared three different modalities of exercise on claudication, namely, treadmill training, Nordic walking, and combination of Nordic walking and resistance training. They have concluded that PAD patients benefited most from the combination of dynamic and static exercise (Nordic walking + resistance training) [47]. Although less tested by clinical trials, exercise modalities other than walking can be used for this purpose. Zwierska et al. have used upper limb ergometry in conjunction with lower limb ergometry in LEAD patients and showed that both groups had improved maximal walking distance (29 and 31%, respectively) at the end of 6 months [48]. The effect of exercise training on the LEAD symptoms was irrespective of improvement in other cardiovascular risk factors [49].

How does exercise improve walking distance in patients with LEAD (Fig. 12.3)?

1. Exercise promotes development of collateral circulation and angiogenesis. Exercise increases the density of the capillary network supplying the active muscle. Angiogenic stimuli, such as hypoxia, shear stress, metabolites, and cytokines (vascular endothelial growth factor A), facilitate new vessel formation in PAD [50]. Exercise was shown to induce mobilization of mesenchymal stem cells and the endothelial progenitor cells from the bone morrow [24]. Another key point is the tissue ischemia-mediated stimulation of growth factors such as vascular endothelial growth factor and hypoxia inducible factor 1 which induce angiogenesis [51, 52].

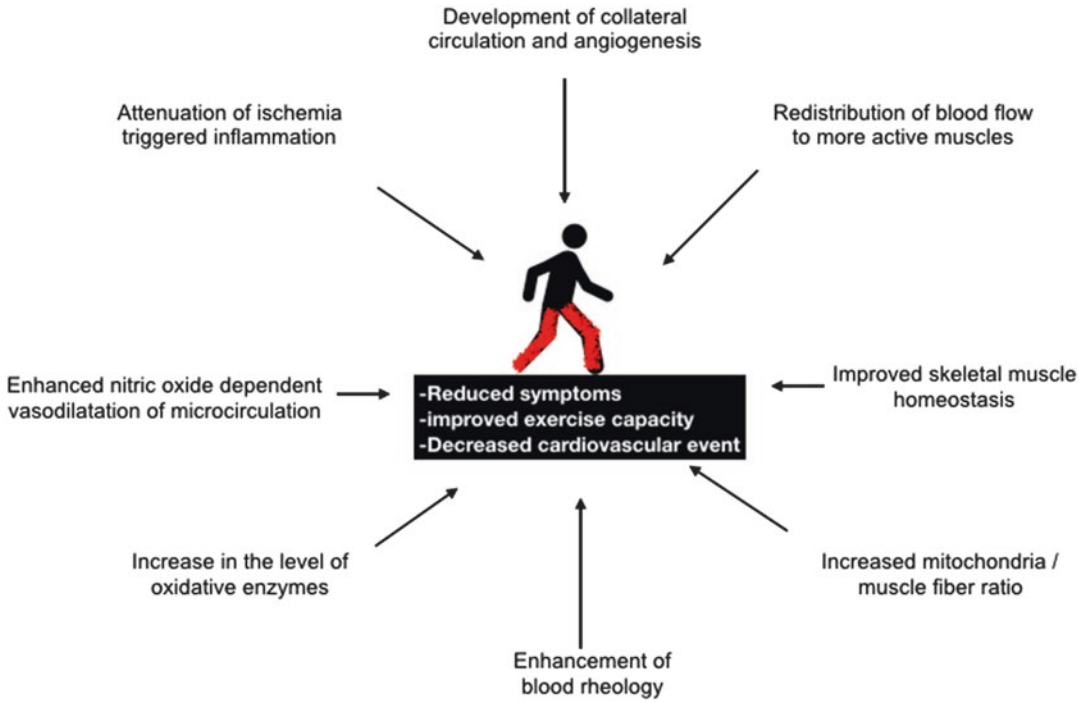

Fig. 12.3 How does exercise improve walking distance in patients with LEAD?

2. Redistribution of blood to more active muscles: Maximal hyperemic blood flow increases in most of the exercise training studies [53].
3. Improved skeletal muscle homeostasis: Exercise training in patients with LEAD reverses sarcopenia, a deleterious condition for cardiovascular health. Balance of energy metabolism within the skeletal muscle promotes preservation of muscle mass, especially in elderly individuals. Resistance training has therapeutic potential particularly for skeletal muscle homeostasis.
4. Increased mitochondria/muscle fiber ratio: The number of mitochondria per muscle fiber and level of oxidative enzymes increase. The energy metabolism shifts further to fatty acid metabolism and less reliance on ATP metabolism [54].
5. Improved blood rheology: Plasma viscosity and red blood cell aggregation are shown to decrease in relation to the exercise program in PAD. Moreover, plasma volume was shown to be increased in LEAD patients who exercise. The aforementioned changes were suggested to result in relation to increased plasma volume and relatively decreased hematocrit [55].
6. Increase in the levels of oxidative enzymes: Exercise restores the carnitine levels in the skeletal muscle. Carnitine is an amino acid that transports fatty acids into mitochondria to produce energy [56].
7. Enhanced nitric oxide-dependent vasodilatation of microcirculation [57]: Healthy endothelium secretes vasoactive substances, mainly nitric oxide, to regulate arterial flow. Nitric oxide is responsible for vasodilatation. Increased shear stress with exercise increases endothelial nitric oxide synthase activity, thus, nitric oxide bioavailability and improvement in endothelial function in LEAD patients [57, 58]. Recent studies have focused on the role of miRNAs in augmenting response to nitric oxide and revealed that miRNA-21 was involved in regulation of endothelial nitric oxide activity [59].
8. Attenuation of ischemia-triggered inflammation and oxidative stress: Several studies have proved that inflammatory markers were

reduced after a period of regular exercise in patients with LEAD [55]. Notably, extended periods of exercise result in downregulation of NADPH oxidase and upregulation of oxygen radical scavengers such as superoxide dismutase and glutathione peroxidase levels [60].

12.5.4 Cerebrovascular Arterial Disease and Exercise

Carotid atherosclerosis is a common manifestation of systemic atherosclerosis. Severe carotid disease is known to present in 20% of patients with LEAD. Cross-sectional studies have provided evidence on the close relationship between carotid disease (expressed by carotid intima media thickness) and the level of exercise. An inverse relationship exists between exercise and carotid intima media thickness [61]. Although a prevalent disease, there are a limited number of prospective studies on the role of exercise on the progression of disease at this site. Buckley et al. have investigated the effect of 12-week physical activity on the attenuation of carotid artery vasoconstriction in response to sympathetic stimulation. In normal subjects, stimulation by sympathetic system causes vasodilatation of carotid arteries, while this response is replaced by vasoconstriction in patients with cardiovascular disease. They showed that after a period of training, vasomotor responses on the central carotid artery during sympathetic stimulation were restored from vasoconstriction to vasodilatation [62]. In parallel with these data, the deleterious effects of sedentary lifestyle (lack of physical exercise) on the carotid atherosclerothic burden were revealed by the Corinthia Epidemiological Study. Within this study, the participants with least activity had most prominent increase in carotid intima media thickness and greatest progression in dimensions of the atherosclerotic plaques [63]. Review of current data shows that physical inactivity is associated with increased intima media thickness [61]. Moreover, in a meta-analysis by Jhamnani, in which the effect of exercise on carotid atherosclerosis was evaluated, it was concluded that exercise improved the carotid intima media thickness [64].

Accumulating evidence has demonstrated that structured exercise programs or even moderate levels of physical activity mitigate carotid atherosclerosis independent of guideline-recommended medical therapies such as lipid lowering statins [61].

12.5.5 Renal/Mesenteric Arterial Disease and Exercise

There are no studies on the role of exercise on the renal or mesenteric arterial disease. Only available data comes from the animal studies which showed that exercise training alleviated endoplasmic reticulum stress-mediated endothelial dysfunction in mesenteric arteries of ApoE knockout mice [65]. Nevertheless, it must be remembered that atherosclerosis is a systemic disease and the data available for coronary or peripheral atherosclerosis should apply for the other sites of involvement.

12.6 Exercise Prescription for the Prevention of Cardiovascular Diseases

Physical activity is the mainstay of cardiovascular protection. With this in mind, general recommendations for the prevention of cardiovascular diseases are at least 150 min of moderate aerobic exercise per week (30 min/5 days a week) or 75 min a week of vigorous physical activity.

Acknowledgment None.

Conflicts of Interest The author declares no conflicts of interest.

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Exercise and Stroke

13

Carmen García-Cabo and Elena López-Cancio

Abstract

Stroke is a leading cause of mortality and morbidity all around the world. Identification of stroke risk factors and protective lifestyles is necessary for optimizing personalized treatment and reducing mortality. Sedentary lifestyle is a well-known modifiable risk factor in primary and secondary stroke prevention. Also, in recent years, exercise has been described as a neuroprotective and neuroreparative factor. Here we summarized the existing available evidence of the relationship between physical activity and stroke.

Keywords

Physical activity · Exercise · Stroke · Neuroprotection

13.1 Introduction and Background

As we have seen in previous chapters, physical activity (PhA) influences prevention, course, and prognosis of multiple diseases (such as certain types of cancer, osteoporosis, type 2 diabetes mellitus, or hypertension). Also, multiple studies show that regular practice of PhA is associated with an overall reduction of the relative risk of premature death from any cause [1]. These studies observed that active men have a reduction in the relative risk of death of up to 50% with respect to the sedentary ones [2] and that middle-aged women doubled their risk of death if they were inactive compared to those who practiced regular PhA.

Cardiovascular diseases (CVDs), including stroke, are the main cause of morbidity and mortality in our environment. There is a large number of systematic reviews and meta-analyses that have analyzed the beneficial impact of PhA in CVD [3–5] and evidenced that regular practice of PhA decreases the incidence and mortality from these diseases regardless of age, sex, or presence of vascular risk factors [6–9]. Furthermore, it has been seen that once CVD is established, PhA slows its progression [10, 11] and reduces the size of atheromatous plaques if they exist [12].

In the specific case of stroke, on the one hand, it is widely demonstrated that PhA plays an important role in primary and secondary prevention of cerebrovascular disease [13–15]. On the other hand, there are preclinical and clinical studies that also show that physical activity has a neuroprotective and neuroreparative effect once the ischemic insult occurs, reducing the final infarct volume and improving the functional prognosis. This is supported by the theory that physical exercise promotes neovascularization and

C. García-Cabo · E. López-Cancio (✉)
Stroke Unit, Department of Neurology, Hospital Universitario Central de Asturias, Oviedo, Spain

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_13

formation of collaterals in the brain through the expression of various endothelial growth factors [16–18]. It should not be forgotten that moderate physical exercise contributes to an early recovery in the stroke rehabilitation period, once the deficits are established. Different intensive activity-based therapy regimens have been studied, targeting motor deficits, aphasia, and other forms of impairment after stroke, in such a way that in these cases PhA would contribute in the interests of neuroplasticity [19–21].

The following sections of the chapter will deal with the role of PhA in stroke prevention, neurorepair, and neuroprotection, as well as its effects on stroke rehabilitation.

13.2 Physical Activity and Stroke Prevention

Stroke is one of the main causes of morbidity and mortality worldwide. Multiple observational studies have reported that the regular practice of PhA reduces the risk of suffering a first stroke as well as the risk of stroke recurrence. Moreover, regular practice of intense physical exercise seems to be inversely related to the risk of stroke. This could be mediated by the beneficial effects on weight, blood pressure, serum cholesterol, and glucose tolerance. Based on these studies, the European guidelines for stroke management [13] include among their recommendations the practice of physical exercise (level of evidence class III-level C), and the guidelines for primary and secondary prevention of American society include sedentary lifestyle as a modifiable risk factor and recommend regular PhA as part of general preventive measures (evidence class I-level B for primary prevention of stroke and class IIa-level C for secondary prevention) [14, 15]. Although the European guidelines do not specify either type or duration of the physical exercise to be performed, the general recommendation in the American guidelines is to perform moderately vigorous aerobic PhA for about 40 min at least three to four times per week to obtain a benefit in cerebrovascular health.

In the next paragraphs, we will try to summarize the evidence existing between physical activity and stroke prevention.

The first meta-analysis on PhA and stroke prevention was published by Lee et al. in 2003 and included 23 studies (18 cohorts and 5 case-control) published between 1966 and 2002 [6]. The major finding in this meta-analysis was that both moderately and highly active individuals had lower risk of stroke incidence and mortality than did low-active and sedentary ones. Overall, moderately active individuals had a 20% lower stroke risk, and highly active individuals had a 27% lower stroke risk than the low-active individuals. This association was observed for both ischemic and hemorrhagic strokes and in both genders. The investigators proposed that there are several plausible ways by which physical activity might reduce stroke risk. For example, hypertension and atherosclerosis of cerebral vessels are major causes of stroke, and hypertension is a risk factor for both ischemic and hemorrhagic strokes. Physical activity lowers blood pressure and improves lipid profiles and also improves endothelial function, which enhances vasodilation and vasomotor function. In addition, PhA may play an antithrombotic role by reducing blood viscosity, fibrinogen levels, and platelet aggregability and by enhancing endogenous fibrinolysis.

The Northern Manhattan Study (NOMAS) is a population-based and multiethnic study designed to evaluate the effects of different medical, socioeconomic, and demographic factors on the incidence of vascular disease. There are several NOMAS sub-studies that address stroke risk factors, and among them, two analyses with regard to physical exercise stand out. In the first study, leisure-time PhA was found to be protective against ischemic stroke in a dose-dependent manner (more protection with higher intensity and duration of PhA) [22]. The second sub-study tries to solve the methodological limitations of the previous one (case-control) with the study of a prospective cohort population [23]. In this second study, investigators found that engaging in moderate- to heavy-intensity physical activity (such as jogging, tennis, or swimming) was

associated with a lower risk of ischemic stroke but that light activity (such as walking) was not. They also found that the protective effect of moderate- to heavy-intensity activity was only present for men. In this study there was a possible dose-response relationship, with a weak trend toward a protective effect in the light-intensity category and a stronger effect for the moderate to heavy intensity categories.

In another meta-analysis, Wendel-Vos et al. included 31 relevant observational studies that analyzed the impact of different types of PhA (recreational or leisure time and occupational) and PhA intensities on the incidence of global stroke and of the two stroke subtypes (ischemic and hemorrhagic) [24]. Their results showed that PhA had a protective effect on total stroke risk, compared with inactivity, and that this effect was observed for both occupational (RR = 0.64) and leisure-time activities (RR = 0.85). Regarding intensities, higher level of occupational PhA protected against ischemic stroke compared with both moderate (RR = 0.77) and inactive occupational levels (RR = 0.57), and high level of leisure-time PhA protected against total stroke (RR = 0.78), hemorrhagic stroke (RR = 0.74), as well as ischemic stroke (RR = 0.79), compared with low level of recreational PhA. They concluded that lack of physical activity is a modifiable risk factor for both total stroke and stroke subtypes and that moderate intensity of PhA is sufficient to achieve risk reduction.

One prospective study that included an extensive number of subjects and a long follow-up is the one carried out in Finland by Hu et al. [25]. It included 47,721 subjects without history of stroke or coronary disease at baseline. A follow-up was performed over 19 years, and the incidence of global stroke and the different types of stroke were calculated (ischemic stroke, parenchymal hemorrhage, and subarachnoid hemorrhage) according to the modality (recreational, occupational, and commuting) and intensity (mild, moderate, and intense) of PhA. It was observed that intense recreational PhA was associated with a lower risk of global stroke and of each of the subtypes, while moderate recreational PhA was only associated with a lower risk of ischemic stroke and intracerebral hemorrhage. In the prospective ARIC (Atherosclerosis Risk in Communities) cohort study, they evaluated the relationship between the level of recreational activity and the risk of total stroke and etiological subtypes of ischemic stroke (lacunar, non-lacunar, and cardioembolic) and observed that those who performed an ideal PhA level had a lower relative risk of total stroke of 22%, total ischemic stroke of 24%, and non-lacunar stroke of 29%, compared with those who performed a low level [26]. Although a beneficial effect of the PhA has been observed in both sexes overall, some studies have observed that the reduction in the stroke risk is higher in men and that perhaps in women a higher level of PhA may be necessary to obtain similar benefits [23, 26–28]. It seems that the performance of PhA decreases stroke incidence in a dose-dependent manner regarding the intensity and frequency of exercise. However, some studies suggest that there may be an upper limit on this dose-dependent effect [29, 30].

In conclusion, regular practice of PhA reduces stroke incidence and recurrence, both in men and women, independent of age, race, and the presence of cardiovascular risk factors. Therefore, sedentary lifestyle is considered an important modifiable risk factor in the prevention of stroke. It has been observed that the relationship between PhA and risk of stroke is dose-dependent, so that the higher level of PhA, the lower risk of stroke.

13.3 Association of PhA with Severity and Prognosis of Ischemic Stroke

Beyond stroke prevention, it has been postulated that PhA may act as an ischemic preconditioning factor that may ameliorate brain injury, exerting a neuroprotective and neuroreparative effect that contributes to improvement when a stroke has already occurred. Animal models of stroke have allowed us to observe that prestroke PhA is associated with a milder severity of stroke, a smaller final infarct, and a better functional recovery [16–18].

The same hypothesis subsequently gave rise to clinical studies in patients. The first study in patients [31] is a prospective study of a single center in which 362 patients were recruited. Prestroke PhA was evaluated with two simple questions (frequency and intensity of PhA) and measured qualitatively as mild, moderate, and intense. Severity of stroke was assessed by the NIHSS scale and functional prognosis by the modified Rankin Scale 8 days after stroke. They conclude that physical activity was associated with milder severity and better functional prognosis. The same group reproduced the same study years later in the minor stroke subgroup with similar results [32]. In two subsequent studies, carried out by Krarup et al. [33] and Stroud et al. [34], same conclusions were reached out, with longer follow-up for stroke functional prognosis (2 years and 3 months, respectively). The abovementioned studies used different questionnaires for PhA measurement, being only PASE validated. In 2011, Rist et al. designed a sub-study of "The Physician's Health Study" including 2128 men in which the data of the cerebrovascular event (transient ischemic attack, ischemic or hemorrhagic stroke) and the functional prognosis were obtained retrospectively by reviewing medical records, after a mean follow-up of 20 years [35]. In the whole sample, practice of aerobic PhA at least two times per week was associated with a lower risk of transient ischemic attack and/or stroke. However, among those who suffered a stroke, the functional prognosis at discharge was not associated with the degree of previous PhA.

The AFRICA study (Prestroke Physical Activity and Functional Recovery in Patients with Ischemic Stroke and Arterial Occlusion) was specifically designed to study the beneficial effects of prestroke PhA on stroke prognosis, including a consecutive sample of 159 ischemic stroke patients with large vessel anterior cerebral occlusion [36]. Investigators confirmed that regular PhA prior to stroke was independently associated with milder stroke severity, smaller final infarct volume, and better functional outcome at 3 months. Also, they observed for the first time that PhA was associated with a higher arterial recanalization rate in those treated with intravenous thrombolysis.

13.4 Biological Mechanisms Involved in the Beneficial Effect of Physical Activity on Stroke

The biological and molecular mechanisms by which the PhA exerts a beneficial effect in the prevention and recovery of stroke have been little studied. It is believed that multiple molecules and metabolic pathways occur and follow each other in a way that is not yet fully defined.

A secondary analysis of AFRICA study [37] evaluated possible molecular pathways studying some angiogenic and neurogenic growth factors at different time points after stroke onset. They studied three angiogenic and neurogenic factors: serum levels of vascular endothelial growth factor (VEGF), granulocyte colony-stimulating factor (G-CSF), and brain-derived neurotrophic factor (BDNF). In logistic regression analysis, both prestroke PhA and increment of VEGF on the seventh day (VEGF on the seventh day-VEGF at admission) were independently associated with good functional outcome at 3 months. They concluded that although there are probably more molecular mechanisms by which PhA exerts its beneficial effects in stroke outcomes, the potential role of VEGF is plausible. In addition, several authors have recently carried out an exhaustive review on the possible role of the PhA in the preconditioning and tolerance to cerebral ischemia. It seems that this effect is the result of multiple processes, among which the following stand out: maintenance of the integrity of the blood-brain barrier (BBB), anti-inflammatory-thorium and antithrombotic effect, neovascularization and optimization of endothelial function, and neurogenesis and optimization of neuronal function. All these processes enhanced by the PhA are also key in neurorepair after cerebral ischemia [16, 17, 38–44].

Finally, PhA induces a series of physiological changes that contribute to control of vascular risk

factors, such as reduction in body mass index, improvement of glucose homeostasis and lipid profile, and control of blood pressure [26–28, 44–47]; all these changes may act as neuroprotective factors once the ischemic insult has occurred.

The biological processes potentially responsible for the benefit of physical activity on stroke, as well as the molecules involved in these processes, are summarized in Table 13.1.

13.5 Physical Activity and Rehabilitation After Stroke

There is no consensus on the specific benefits of physical exercise in patients after a stroke. Stroke subjects can increase their cardiovascular capacity in a similar way to that of healthy adults of the same age following aerobic endurance programs, improve peak force, and reduce spasticity in the hemiparetic side [62]. Studies in this field are divided among those that talk about aerobic physical activity or strength exercises, and they are summarized in the following paragraphs.

In 1999, Smith et al. [62] designed a study to evaluate whether a 3-month-a-week poststroke training program on a treadmill improved spasticity and paresis sequelae to stroke. They concluded that this training improved the maximum force peak and spastic reflexes. Using the treadmill as a physical exercise, in 2005 another study was carried out by Macko et al. [21], who evaluated the effect of the exercise 3 days a week for 6 months and concluded that physical exercise improves cardiovascular capacity and mobility after stroke. Using the same protocol, Ivey et al. showed that physical activity improves glucose intolerance in stroke survivors [19]. Wessel et al. designed a study exercising on a static bicycle at high intensity, and they demonstrated the good tolerance and benefit in stroke survivors [63].

There are studies that support exercise based on strength for functional improvement after a stroke. Although they are scarce and include small samples of patients, they all agree on improving strength and functional capacity by following a nonlinear relationship. Although the studies are limited, evidence shows that a patient with muscle weakness after a stroke can improve strength without negative effects, such as

Table 13.1 Biological processes potentially responsible for the benefit of physical activity on stroke

Process	Effector molecules	Function	References
Action on the control of vascular risk factors	Multiple	Reduces body mass index and prevents obesity. Improves glucose homeostasis by increasing the insulin sensitivity of peripheral tissues. Improves the lipid profile. Optimizes control of blood pressure. Improves cardiac function. Reduces systemic inflammation. Favors an antithrombotic and profibrinolytic state	[1–6]
Maintenance of the integrity of the blood-brain barrier	MMP-9	Lower final volume of infarction and a lower neurological deficit at 24 h after stroke	[48, 49]
Anti-inflammatory and antithrombotic effect	Insulin	The PhA, by decreasing insulin resistance, would reduce the prothrombotic and pro-inflammatory state dysfunction in HF risk stratification	[50–52]
Neovascularization and optimization of endothelial function	Progenitor endothelial cells, nitric oxide, VEGF	Stimulates neovascularization and vasodilation in the ischemic focus, favoring an increase in cerebral blood flow, which would be associated with a lower infarct volume and a better functional recovery	[53–58]
Neurogenesis and optimization of neuronal function	BDNF, NGF	Contributes to less neuronal damage and lower final volume of infarction	[59–61]

MMP-9 metalloprotease-9, *VEGF* vascular endothelial growth factor, *BDNF* brain-derived neurotrophic factor, *NGF* nerve growth factor

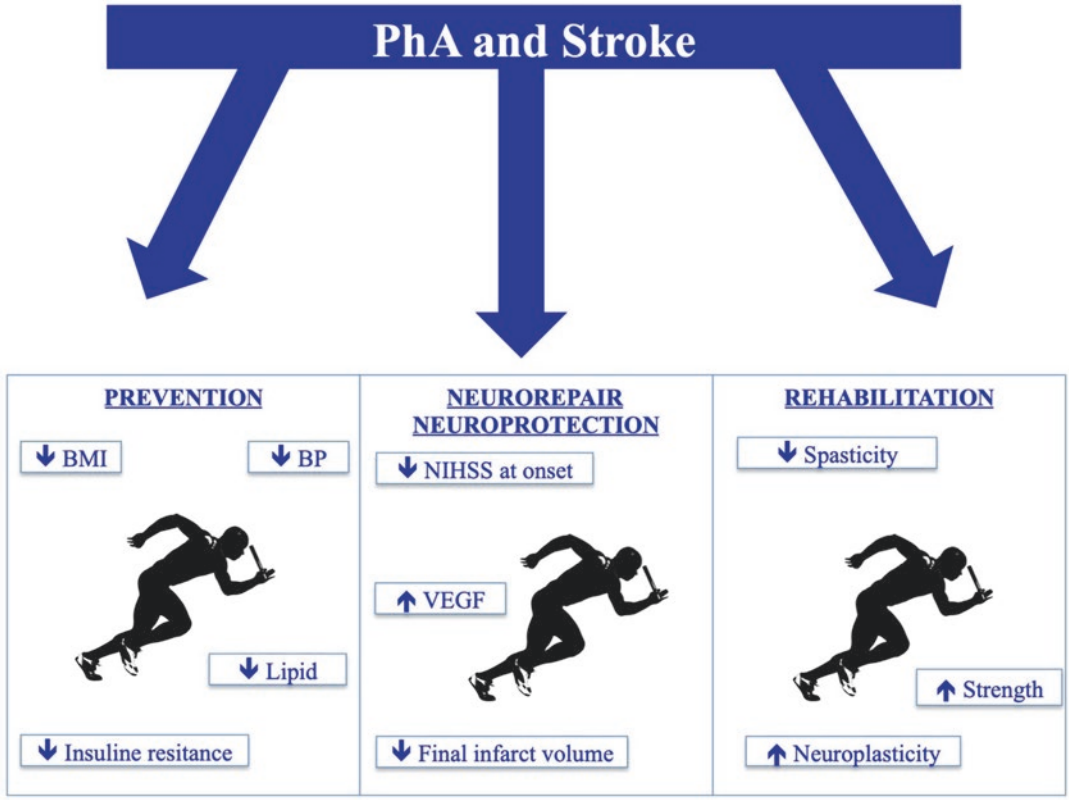

Fig. 13.1 Effects of PhA on stroke

worsening spasticity or hypertonia. In addition, strength improvements may have a transfer in functional capacity. With this regard, one of the most important goals for patients who have suffered a stroke is gait independence. Engardt et al. [64] and Kim et al. [20] observed that working strength in isokinetic machine led to improvements in strength but not in gait. This is due, according to Carr and Shepherd [65], to the fact that strength in this type of patients has to be worked in a functional way (training that implies repetitive practices of the action that is going to improve). Adams et al. [66] examined the voluntary strength of eight muscles of the lower extremities in healthy individuals and the weakened and unaffected lower extremities of stroke patients. On average, one of the most affected groups was the plantar flexor muscle group of the ankle (triceps surae). These authors recommend that the emphasis of strength training should be placed on the muscles of the lower extremity, specifically the extensor muscles such as gluteus maximus, gluteus medius, quadriceps, and sural triceps, since these muscles are responsible for basic support, balance, and propulsive functions during the support phase of the gait.

13.6 Perspective

Regular practice of PhA brings health benefits, especially in the prevention of cardiovascular and cerebrovascular diseases. Beyond stroke prevention, PhA seems to act as a preconditioning factor ameliorating brain damage once a stroke has occurred. Indeed, there are preclinical and clinical studies that have demonstrated the association of prestroke PhA with milder initial stroke severity, smaller infarct volume, and better long-term functional outcomes. Although the exact molecular and cellular pathways by which PhA provides these benefits are not well known, there is a num-

ber of intermediates involved in processes of vasculogenesis, angiogenesis, arteriogenesis, and neurogenesis that appear constantly in the literature such as some neuronal and vascular growth factors that should be more appropriately studied. Regarding rehabilitation after stroke, there is evidence that both aerobic and strength exercise can improve functional capacity and recovery after a stroke. Figure 13.1 summarizes these evidences.

Acknowledgment

Competing Financial Interests The authors declare no competing financial interests.

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Exercise and Cardiovascular Protection

14

Guohua Li, Jia Li, and Feng Gao

Abstract

Accumulating evidence has demonstrated that exercise training not only reduces cardiovascular disease risk but also provides direct endogenous cardiovascular protection. The mechanisms that have been proposed to be responsible for exercise-induced cardioprotection include intrinsic myocardial changes such as increased cytosolic antioxidant capacity and altered mitochondrial phenotype, myokine-mediated metabolic and anti-inflammatory effects in the cardiovascular system, and systemic effects on the cardiovascular system via interorgan cross talk. There remains much to be elucidated in the mechanisms for exercise-afforded cardioprotection. This chapter reviews exercise-induced acute and chronic responses in cardiovascular system, the epidemiological evidence of exercise training and cardiorespiratory fitness in the primary and secondary prevention of cardiovascular diseases, and the current understanding of the mechanisms of exercise-induced cardiovascular protective effects.

Keywords

Exercise · Cardioprotection · Cardiorespiratory fitness · Cardiovascular disease · Exerkine

14.1 Introduction

The benefits of regular exercise or physical activity for the cardiovascular system in settings of health and disease have been well recognized. Exercise training not only reduces cardiovascular risk factors, such as diabetes mellitus and hypertension, to confer protection against cardiovascular diseases (CVD), but also improves status and outcomes in patients with existing cardiovascular diseases. Physical activity levels have been demonstrated to be inversely related with all-cause mortality and CVD mortality [1–3]. High levels of physical activity have also been demonstrated to reduce the mortality of CVD in high-risk populations, including those with type 2 diabetes mellitus and obesity and the elderly [2, 4]. Clinical studies have demonstrated that exercise can improve cardiac function in patients with heart failure. Exercise training has become one of the mainstay clinical interventions for the prevention and treatment of cardiovascular diseases in recent years.

Given that many individuals do not exercise habitually or are unable to exercise, exploiting

G. Li · J. Li · F. Gao (✉)
School of Aerospace Medicine, The Fourth Military Medical University, Xi'an, China
e-mail: fgao@fmmu.edu.cn

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_14

the key mechanisms responsible for exercise-induced cardioprotection represents an active and exciting area of research. Exercise not only has direct beneficial effects on systemic metabolism and promotes numerous cellular adaptations within the heart and blood vessels but also works on other organs or tissues (e.g., liver, skeletal muscle, brain, adipose tissue) which produce secondary effects on the cardiovascular system [5, 6]. This chapter summarizes the known cardiovascular responses to exercise and the underlying mechanisms responsible for exercise-induced cardiac protection.

14.2 Cardiovascular Responses to Exercise

14.2.1 Acute Cardiac Responses to Exercise

To meet the oxygen demands of the muscle in response to exercise, a number of changes take place to allow the heart to pump more blood to increase cardiac output. Cardiac output is about 5 L/min at rest but varies greatly from 20 L/min in healthy untrained individuals to 40 L/min in elite aerobic athletes at maximal exercise. Cardiac output is determined by stroke volume (SV) and heart rate (HR), and both are significantly increased during aerobic exercise. Left ventricular SV is augmented during aerobic exercise by a synergistic increase in end-diastolic volume and myocardial contractility. Although SV is about 50 mL at rest, the augmentation of filling volume and contractility raise SV severalfold during exercise, with large variability that is influenced by many factors, like age, sex, genetics, and exercise training status. The increase in SV during aerobic exercise plateaus at 50% of maximal oxygen consumption (VO_2). Once SV reaches plateaus, it is the continued rise of HR that induces the further increase of cardiac output. During a bout of progressive aerobic exercise to maximal capacity, HR increases at a rate of 10 bpm per 3.5 mL O_2 kg^{-1} min^{-1} in oxygen demand.

14.2.2 Chronic Adaptations of Cardiovascular System to Exercise

Regular aerobic exercise yields a series of favorable morphological and physiological cardiovascular adaptions, and morphological adaptations associated with chronic aerobic exercise are left ventricular dilation and hypertrophy. These left ventricular morphological adaptations enhance cardiac physiological function via increased early diastolic filling secondary to a combination of increased preload and myocardial relaxation, and enhanced contractile function [7]. Although much attention has been paid to the left ventricle, it should be noted that morphological adaptations also occur in the right ventricle that appear to mirror left ventricular adaptations. Cardiac hypertrophy is one of the most significant and characteristic adaptations induced by aerobic exercise. This hypertrophy mainly originates from cellular cardiomyocyte hypertrophy, which may increase in size by adding new sarcomeres either in parallel (concentric hypertrophy), thus increasing cardiac wall thickness, or in series (eccentric hypertrophy), thus increasing chamber volume. In contrast to pathological hypertrophy that is an adverse remodeling process including cardiac fibrosis, electrical remodeling, and activation of a fetal gene program, exercise-induced cardiac hypertrophy is a kind of beneficial remodeling process that commonly exhibits none of these features and is widely believed to be cardioprotective except in extreme conditions such as ultra-elite athletes.

Chronic aerobic exercise also results in a number of positive vascular adaptations and attenuates deleterious adaptations induced by aging, hypertension, diabetes mellitus, or other diseases. Clinical evidence has documented that arterial stiffness is significantly lower in individuals with a higher cardiorespiratory fitness, as well as individuals who have completed an aerobic exercise program recently [8, 9]. The mechanisms underlying the attenuation of arterial stiffness may be related to the alleviation of systemic oxidative stress and inflammation induced by aerobic exercise [9]. Enhanced

endothelium-dependent vasodilation through increased production of NO is also a well-documented aerobic exercise benefit [10, 11].

14.2.3 How Do Exercise-Afforded Acute Responses Translate Over Time into Sustaining Training Adaptation

Most long-term health benefits elicited by exercise training are thought to originate from adaptive changes in proteins involved in specific metabolic or physiological processes. The adaptations are largely due to shifts in gene transcription and protein translation as well as posttranslational modifications, since exercise-induced energetic and mechanical challenges and the ensuing adaptive cellular responses occur primarily during the hours following exercise training [12]. Adaptive increases in any protein during repeated bouts of physical activity will depend on the halftime of the protein, the transient increase in expression that happens during recovery from each exercise session, and the potential decrease in expression that occurs between exercise sessions. Proteins with a fast turnover rate are prone to be expressed at low levels, increase sharply during exercise, and return to the baseline levels before the next training session when the stimulus is removed. In contrast, proteins with a slower turnover rate are prone to be expressed at a relatively high level at baseline, increase mildly during exercise, and retain most of that increase in expression by the time the next exercise session happens due to their longer half-life. Thus, only those proteins with a long enough half-life will accumulate over time [12].

14.3 Cardiorespiratory Fitness and Cardiovascular Disease: Epidemiological Studies

14.3.1 Cardiorespiratory Fitness, Muscular Fitness, and Risk of Cardiovascular Diseases

Cardiorespiratory fitness reflects the integrated ability to transport oxygen from the atmosphere to the mitochondria to perform physical activity. It quantifies the functional capacity of an individual and is dependent on a chain of processes, including pulmonary ventilation and diffusion, ventricular diastolic and systolic function, ventricular-arterial coupling, the ability of the vasculature to accommodate and transport blood from the heart to match oxygen requirements, and the ability of the muscle to receive and use blood-delivered oxygen and nutrients, as well as to communicate metabolic demands to the cardiovascular control center. Low cardiorespiratory fitness is an important risk factor for coronary heart disease (CHD) and CVD mortality, and improving cardiorespiratory fitness can benefit CVD patients [13]. Studies have shown that high levels of cardiorespiratory fitness are associated with reduced prevalence of CHD and many CVD risk factors, including obesity, hypertension, metabolic syndrome, and type 2 diabetes mellitus [14]. Indeed, numerous epidemiological studies have demonstrated that more than half the reduction in all-cause and CVD mortality generally happens when cardiorespiratory fitness is increased from the least fit to the next least fit. More importantly, cardiorespiratory fitness has a good prognostic value in both general population and patients with high risk of CVD, as well as in

CVD populations, such as CHD and heart failure. Although physical activity is probably the most important determinant factor for cardiorespiratory fitness, some studies have indicated that cardiorespiratory fitness is even a more reliable predictor of CVD prognosis than physical activity. Currently, cardiorespiratory fitness is mainly quantified by metabolic equivalents (METs), which are typically estimated from workload on submaximal or maximal treadmill exercise stress tests, and this can be more precisely evaluated by using cardiopulmonary exercise test and assessing peak VO_2. A recent high-profile meta-analysis by Kodama et al. showed that every 1-MET increase in cardiorespiratory fitness was associated with all-cause mortality reduction by 13% and CHD/CVD mortality reduction by 15% [15]. Furthermore, this meta-analysis defined age- and sex-specific normal levels of cardiorespiratory fitness related with lower event rates in both men (40 years, 9 METs; 50 years, 8 METs; and 60 years, 7 METs) and women (40 years, 7 METs; 50 years, 6 METs; and 60 years, 5 METs). Studies have also shown that even in high-risk individuals with metabolic syndrome, prediabetes mellitus, and type 2 diabetes mellitus, higher cardiorespiratory fitness is associated with better prognosis, even better than the prognosis in unfit individuals without these conditions [15]. Moreover, clinical data have indicated the significance of high cardiorespiratory fitness to protect against the lifetime CVD risk [16]. Some studies have also investigated the changes of cardiorespiratory fitness over time and its effect on CVD morbidity and mortality. According to the data from Aerobics Center Longitudinal Study, Blair and colleagues reported that CVD mortality decreased by 52% in those who were classified as unfit at their first examination but fit at their second examination a few years later [17]. As reported by Lee et al., every 1-MET increase in cardiorespiratory fitness over time decreases all-cause and CVD mortality by 15% and 19%, respectively [18].

Together with cardiorespiratory fitness, muscular fitness and muscle strength have also been increasingly recognized in the pathogenesis and prevention of chronic disease, and studies have shown that muscular fitness also has an important impact on CVD risk factors and prognosis [18]. Muscular strength has been shown to be an independent protective factor on all-cause mortality and cancer mortality in healthy middle-aged men, as well as in men with hypertension and heart failure. At the same time, muscular strength was inversely associated with age-related weight and adiposity gains, risk of hypertension, and the incidence of metabolic syndrome. In children and adolescents, higher levels of muscular fitness are inversely associated with CVD risk factors such as insulin resistance and inflammation. Moreover, muscular fitness is the main determinant of frailty and cachexia, both of which are particularly important for advanced heart failure and in the elderly [19].

14.3.2 Effects of Exercise on Cardiorespiratory Fitness

Cardiorespiratory fitness is greatly affected by physical activity and exercise training, though it is mainly determined by genetic hereditability. In general, the greater the activity amount or intensity, the more obvious increase in cardiorespiratory fitness will be achieved. Compared with the duration and frequency of exercise, the increase in exercise intensity is more effective in improving cardiorespiratory fitness. Moreover, the higher the baseline cardiorespiratory fitness, the more intense exercise is needed to produce a clinically significant increase in cardiorespiratory fitness. For instance, in adults with a cardiorespiratory fitness <10 METs, a training intensity that reaches ≈ 50% HR reserve or VO_2R is sufficient to increase cardiorespiratory fitness; when the baseline cardiorespiratory fitness is between 10 and 14 METs, training intensities in the range of 65% to 85% HR reserve or VO_2R are likely more effectively, and among individuals with baseline cardiorespiratory fitness >14 METs, a training intensity that achieves >85% HR or VO_2R may be necessary for most participants to achieve a significant increase in cardiorespiratory fitness [13].

14.4 The Underlying Mechanisms of Exercise-Induced Cardiovascular Protective Effects

Recent studies have shown that exercise training leads to attenuation of insulin resistance, inflammation, autonomic dysfunction, and psychosocial stress that are believed to be involved in the pathogenesis and progression of cardiovascular disease. Epidemiological evidence suggests that the protective effects of exercise on CVD are nearly double that which would be assessed based on changes in traditional risk factors [20]. During the last few decades, a plethora of molecular mechanisms involved in acute and chronic responses to exercise have been elucidated in cardiovascular system and other tissues. Although some breakthroughs have been achieved in unraveling how exercise activates numerous cellular and molecular pathways, direct evidence linking molecular adaptations to specific health, in particular cardiovascular outcomes, remains elusive and a challenge for further research.

14.4.1 Ameliorating Insulin Resistance and Endothelial Dysfunction

Insulin resistance plays an important role in the pathogenesis of obesity- and diabetes-related CVD. In addition to systemic insulin resistance, patients with obesity and diabetes exhibit both endothelial dysfunction and vascular insulin resistance. These two abnormalities always coexist, reciprocally perpetuate, and predispose patients to hypertension and cardiovascular complications [21]. As a vasoactive hormone, insulin acts on large conduit arteries to improve compliance, resistance arterioles to improve tissue blood flow, and precapillary arterioles to increase capillary perfusion [22]. In contrast, chronic metabolic insulin resistance is often associated with arterial stiffness and impaired NO-induced vasorelaxation [23]. The underlying mechanism may be associated with NO production by endothelial cells in response to insulin stimulation [24]. Exercise training attenuates endothelial dysfunction and insulin resistance and reduces obesity- and diabetes-related cardiovascular morbidity and mortality. Substantial evidence has demonstrated that exercise training is capable of improving endothelial phenotype and function in the vasculature possibly via hemodynamic factors such as shear stress and cyclic strain [25]. As reported by a previous study, even moderate daily exercise can significantly increase insulin sensitivity, and a single session of low-intensity exercise is able to improve insulin sensitivity until the next day in obese individuals [26].

14.4.2 Improving Plasma Lipid Profiles

A clear relationship has been demonstrated between CVD risk and elevated blood lipid and lipoprotein levels, and physical inactivity is an important contributor to dyslipidemia. The influence of aerobic exercise on serum lipoproteins has been extensively studied. Although reduction in low-density lipoprotein cholesterol by exercise training is minimal, improvements in triglycerides and high-density lipoprotein cholesterol are more significant (mean changes, −15% and + 6%, respectively) [27, 28]. A 2007 meta-analysis enrolling 25 randomized, controlled exercise intervention trials reported a mean increase in high density lipoprotein (HDL) of 2.5 mg/dL [29]. In this study, the minimal weekly exercise energy expenditure and duration required for these HDL changes were 900 kcal and 120 minutes, respectively. A meta-analysis examining exercise training in an unselected adult population reported reduction in triglycerides of 5 to 38 mg/dL [30]. Although the magnitude of the impact of exercise on lipids at the individual level is small, reduction of total cholesterol by as little as 10% via dietary or pharmacological interventions has been shown to induce a 27% reduction in incident CVD [31]. These data indicated that exercise-induced modest changes in serum lipids may have the potential to decrease the risk of CVD and CVD-related mortality significantly.

14.4.3 Anti-inflammatory Effects

Compelling evidence has demonstrated that inflammation is etiologically involved in the pathogenesis of CVD, and exercise training confers cardioprotection partly through its anti-inflammatory effects [32]. Physical inactivity leads to the accumulation of visceral fat, which is accompanied by adipose tissue infiltration by pro-inflammatory immune cells, increased release of adipokines, and the development of a low-grade systemic inflammation. It has been reported that exercise training reduced levels of high-sensitivity C-reactive protein (hs-CRP) by about 40% in patients with coronary heart disease [33]. Patients with metabolic syndrome had nearly twofold higher levels of hs-CRP compared with those without metabolic syndrome, and both groups achieved significant reductions in hs-CRP after exercise training [34]. The anti-inflammatory effects of exercise may be mediated through both a decrease in visceral fat mass (with a decreased release of adipokines) and an induction of an anti-inflammatory environment with each bout of exercise [35]. The generation of anti-inflammatory environment by exercise may be attributable to the following factors: increased release of cortisol and adrenaline from the adrenal glands, increased production and release of myokines from the skeletal muscle, reduced toll-like receptor expression on monocytes and macrophages and thus inhibition of downstream pro-inflammatory cytokine production, attenuation of adipose tissue infiltration by monocytes and macrophages, reduced circulating numbers of pro-inflammatory monocytes, and increased circulating numbers of T_{Reg} cells [32].

14.4.4 Improving Autonomic Nervous System Health

Activation of the peripheral sympathetic nervous system (SNS) has negative impact on the structure and function of the cardiovascular system, including decreased peripheral blood flow, increased arterial blood pressure, impaired baroreflex function, and hypertrophy of large arteries, which consequently increases CVD risk [36]. Chronically augmented SNS-induced decrease in peripheral blood flow and vascular conductance also play an etiological role in the pathogenesis of metabolic syndrome by increasing glucose intolerance and insulin resistance [37, 38]. Reduced heart rate variability, a noninvasive measure of the autonomic nervous system function, is a marker of autonomic dysfunction that is associated with poorer cardiovascular health and outcomes, as well as increased incidence of coronary heart disease and myocardial infraction [39]. Substantial evidence has demonstrated the beneficial effect of exercise training on autonomic nervous system, and there appears to be a dose-response relationship between exercise training and autonomic nervous system adaptations. Moderate-intensity aerobic exercise for 3 months ameliorated age-related reductions in baroreflex function [40]. Data from a recent meta-analysis showed that exercise training increased heart rate variability in middle-aged or old people, who are either healthy or unhealthy with myocardial infraction, chronic heart failure, coronary artery bypass grafting, or diabetes mellitus [41]. Exercise can also reduce the incidence of lethal ventricular arrhythmias by improving cardiac autonomic balance via increasing parasympathetic activity or decreasing sympathetic activity [42].

14.4.5 Reducing Psychological Stress

As indicated by epidemiological data, the clinical impact of psychological stress has been comparable to many of the important coronary heart disease risk factors, including smoking, hypertension, and physical inactivity [43]. The famous INTERHEART study demonstrated that among the nine major modifiable risk factors for coronary heart disease, psychological stress ranked third, only secondary to lipids and smoking, and is responsible for one-third of acute myocardial infarction events. Importantly, exercise training has a significant impact on psychological stress, including depression, anxiety, and hostility [44]. Exercise training can reduce the

incidence of moderate anxiety (Kellner anxiety score > 7) and high anxiety (Kellner anxiety score > 10) by 56% and 69%, respectively, in patients with coronary heart disease [45]. Exercise can also reduce the prevalence of hostility in both younger and older patients with coronary heart disease by more than 50% [46]. At the same time, exercise can also significantly improve the symptoms of depression in patients with coronary heart disease. Studies have found that patients with coronary heart disease who have less exercise and higher levels of depression have a 3-year mortality rate of about 30%, and exercise training can reduce the 3-year mortality rate of such patients to about 8% [47]. The mechanism by which exercise training improves psychological stress in CVD patients may involve opioids and endocannabinoid systems. For example, long-term running increases levels of β-endorphin (an opioid) and cannabinoids in the serum of CVD patients, resulting in a feeling of "euphoria" with sedative and analgesic effects [48].

14.4.6 Stem Cell Mobilization and Tissue Regeneration

Pluripotent stem cells capable of differentiating into many cell types are considered as valuable therapeutic source, especially in ischemia/reperfusion injury in tissues with low self-repair capacity. Exercise, as a physiological stimulus, can stimulate stem cell proliferation and migration from home tissue to injured tissue to ensure engrafting and cell regeneration. The capacity for vessel wall regeneration and angiogenesis is of great significance for maintaining cardiovascular health, which accounts for exercise-induced cardioprotection [49]. Endothelial regeneration and neovascularization depend not only on cells residing within the arterial wall but also on circulating stem cells. A specific stem cell subset, circulating angiogenic cells (CAC), can differentiate into vascular endothelium, where they can engraft and facilitate the repair and angiogenesis. Low CAC count/function is associated with increased CVD risk and decreases with aging [50], whereas high CAC underlies the association between regular exercise and decreased CVD risk [51]. CAC increase also accounts for exercise-induced improvement in myocardial perfusion and delayed CVD progression [52]. Circulating CAC increase with acute exercise in healthy individuals, individuals with CVD risk factors, and CVD patients, though the effect is attenuated with aging. Furthermore, exercise also potently promotes the release of mesenchymal stem cells (MSCs) into the bloodstream and increases the migratory capacity of MSCs, which may be mediated by the myokine IL-6 [53].

14.4.7 Exerkine

Exercise-stimulated release of peptides and nucleic acids from the skeletal muscle (myokine), adipose tissue (adipokine), and other organs (collectively termed as "exerkine") has been implicated in mediating the systemic adaptations and may confer direct cardioprotection. Exerkines are defined as exercise-induced circulatory humoral factors that are produced and released by tissues and organs to promote cross talk between organs and potentiate the systemic benefits of exercise [54]. The systemic benefits of exercise are probably modulated by exerkines functioning in an autocrine, paracrine, and endocrine manner. As early as 1961, Goldstein has hypothesized that exercise stimulated the skeletal muscle to secrete circulatory "humoral" factors to impart control over glucose homeostasis [55]. Skeletal muscle has been proven to be an endocrine organ in the past decade. In addition to the skeletal muscle, adipose tissue, endothelial cells, and other tissues have been demonstrated to be able to secrete circulatory "humoral" factors in response to exercise stimulus [56–58]. We and others have demonstrated that miRNAs play an indispensable role in modulating exercise-induced cardiovascular protection [59, 60]. Data from basic research have also indicated considerable alterations in several c-miRNA species in response to exercise, and these c-miRNA may function as exerkines to confer health-promoting effect [59]. Furthermore, emerging evidence has

recognized exercise-induced altered circulatory metabolites as regulatory signals with hormone-like functions [61]. Considering that the extracellular milieu is relatively not a hospitable environment for unstable exerkines, a lipid vehicle-based mode of delivery has originated over the course of evolution, including two types of extracellular vesicles, exosomes and microvesicles.

Although the multisystemic effects of exercise are well documented, the complex array of humoral factors and molecular mechanisms promoting cross talk between organs to mediate the health-promoting benefits of exercise has not been fully elucidated. An in-depth understanding of these factors will facilitate the development of therapeutic strategies to improve the quality of life in populations struck by physical inactivity-associated chronic diseases.

14.4.8 ROS-Induced Hormesis

Studies over the past two decades have extended our understanding of reactive oxygen species (ROS). ROS are molecules that not only invoke oxidative stress but serve as signaling molecules to regulate physiological processes. Substantial evidence has demonstrated that acute exercise results in ROS production in an intensity- and duration-dependent manner [62]. More importantly, regular exercise upregulates endogenous antioxidants in the musculoskeletal system, cardiovascular system, and other systems. Although muscle-derived ROS generated during prolonged inactivity facilitates disused muscle atrophy [63], the same stimulus from contracting fibers is necessary for training adaptations to occur [64, 65]. Emerging evidence indicated that exogenous antioxidant supplementation did not mimic but in fact reversed exercise-induced beneficial adaptations [64]. Antioxidant supplementation attenuated acute exercise-conferred increases in mitochondrial and antioxidant gene expression and thus ameliorated endurance exercise-induced enhancement in mitochondrial biogenesis and insulin sensitivity in both humans and rodents [64, 66]. In addition, ROS has also been implicated in the signaling of exercise-induced myogenesis and muscle hypertrophy. This can be explained by the hormesis theory: chemicals and toxic substances that are deleterious at high levels can have a low-level beneficial effect. Therefore, ROS increase elicited by moderate-intensity exercise could consequently lead to beneficial adaptations with increased antioxidant capacity. Another underlying mechanism may be related with the different sources of ROS between working and resting fibers, with mitochondria being the primary source in the latter but not in the former. As a signal molecule, ROS plays an important role in exercise-induced physiological adaptations such as angiogenesis, vasodilatation, mitochondrial biogenesis, and upregulation of the cytoprotective "stress proteins" (heme oxygenase 1, heat shock proteins like HSP60 and HSP90) [64].

14.4.9 Autophagy

Autophagy is a reparative, life-sustaining process by which cytoplasmic constituents are enclosed in double-membrane vesicles and degraded into lysosomes [67]. Emerging evidence indicates that the basal autophagy is an important in vivo process of regulating proper cardiovascular homeostasis and function; either excessive or insufficient levels of autophagic flux may lead to the pathogenesis of CVD [68]. Moreover, environment stress-related stimulus, like exercise, could potently upregulate autophagy in the arterial wall and heart and thus confer cardiovascular protection. As reported previously, acute exercise enhances autophagy activity in the skeletal muscle, heart, and other tissues or organs involved in energy homeostasis in normal mice, while transgenic mice deficient in stimulus-induced autophagy manifest as decreased endurance and altered glucose metabolism [69]. Exercise-induced autophagy facilitates the clearance of protein aggregates and alleviates cardiac proteinopathy, as evidenced by enhanced cardioprotective effect of exercise in mice with an overexpression of autophagy-related proteins. Furthermore, exercise training

attenuates the impairment of autophagic flux to improve mitochondrial bioenergetics in the failing hearts of mice [70].

14.5 Conclusion

In summary, regular exercise training confers cardiovascular protection and plays an important role in the prevention and treatment of cardiovascular diseases. Further elucidation of the mechanisms underlying exercise-afforded cardiovascular benefits holds promise for the discovery of novel therapeutic targets and optimization of physical activity amount to help improve outcomes.

Acknowledgment This work was supported by grants from the National Natural Science Foundation of China (81670253 to F Gao) and Major Basic Science Program of Shaanxi Provincial Natural Science Foundation of China (2016ZDJC-17 to F Gao).

Competing Financial Interests The authors declare no competing financial interests.

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Part V

Exercise and Musculoskeletal Diseases

Exercise and Osteoarthritis

15

Lei Chen and Yan Yu

Abstract

Osteoarthritis (OA) is a degenerative disease of the articular cartilage with subchondral bone lesions. Osteoarthritis etiologies are mainly related to age, obesity, strain, trauma, joint congenital anomalies, joint deformities, and other factors. Osteoarthritis seriously affects the quality of life; however, there is no effective way to cure osteoarthritis. Aerobic exercise refers to a dynamic rhythmic exercise involving the large muscle groups of the body with aerobic metabolism. More and more evidence shows that exercise has become a useful tool for the treatment of osteoarthritis. This chapter will discuss the role of exercise in the prevention and treatment of osteoarthritis.

Keywords

Osteoarthritis · Exercise · Prevention · Treatment

15.1 Background

Osteoarthritis (OA) is a degenerative disease of the articular cartilage with subchondral bone lesions [1]. The etiologies of osteoarthritis are mainly related to age, obesity, strain, trauma, joint congenital anomalies, joint deformities, and other factors [2]. Multiple joints in the body can be affected by osteoarthritis, in particular knee joints which is related to their bearing weight and excessive activity. According to the pathology survey, the incidence rate of osteoarthritis is about 2%–6%, while this rate is more than 50% in people over 65 years old [3]. With the aging of society, the number of patients with osteoarthritis is consistently increasing, which will become the first chronic disease that seriously threatens the health of the elderly [4].

Aerobic exercise refers to a dynamic rhythmic exercise involving the large muscle groups of the body with aerobic metabolism. During aerobic exercise, the oxygen inhaled and the demand by human body reach a physiological balance. Aerobic exercise is generally longer, usually reaching more than 30 minutes, and the intensity is 75%–80% of the maximum heart rate. At this time, the blood can satisfy the oxygen demand of cardiomyocytes [5]. Therefore, aerobic exercise is characterized by low intensity, strong sense of rhythm, and long duration, requiring no less than 30 minutes each time [6]. Aerobics is the main fitness in today's society, which can fully burn off excess sugar in the body and also consume excess

The original version of this chapter has been revised. The erratum to this chapter can be found at https://doi.org/10.1007/978-981-15-1792-1_32

L. Chen · Y. Yu (✉)
Department of Spine Surgery, Tongji Hospital, Tongji University School of Medicine, Shanghai, China

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_15

body fat [7]. Also, aerobic exercise can improve heart and lung function and regulate mental state. Studies have reported that moderate-intensity running exercise promotes the repair of articular cartilage, while high-strength exercise damages it [8]. Here, we will summarize the role of aerobic exercise in osteoarthritis, especially by focusing on its potential in the treatment of osteoarthritis.

15.2 Pathogenesis of Osteoarthritis

It is now widely believed that the occurrence of osteoarthritis is based on genetic susceptibility and changes in the human body environment [9]. Combined with long-term effects of local physical and chemical factors, the occurrence system of osteoarthritis is very complicated which can be related to age, weight, gender, estrogen, autoimmunity, and many other factors [10]. Although different causes are involved, osteoarthritis has similar morphological features, including degeneration of osteoarticular cartilage, subchondral bone exposure, and secondary synovial inflammation [11]. The research on the etiologies of osteoarthritis is summarized as follows:

15.2.1 Age

The prevalence of osteoarthritis is closely related to aging [12]. Age is also considered to be the primary risk factor for osteoarthritis. According to the survey, the incidence of osteoarthritis is about 7.6% in the population aged 18–44 years old, 29.8% in the population aged 45–64 years old, and over 50% in the population over 65 years old [13]. Numerous studies have shown that changes in the expression levels of related cytokines induced by tissue aging can mediate inflammatory lesions in articular cartilage. The expression of Lamin A/C gene decreases with age, which can lead to reduced proliferation activity of osteoblasts, thus causing structural remodeling of the subchondral bone. The aging of chondrocytes is accompanied by an increase in the content of reactive oxygen species (ROS) and dysregulation of growth signals such as transforming growth factor (TGF) [14]. Under pathological conditions, this change is more pronounced which may result in a sharp increase in the number of chondrocyte death, leading to mechanical imbalance of joints. In addition, aging can lead to a decrease in the synthesis and secretion of estrogen, which in turn promotes the development of osteoarthritis [15].

15.2.2 Body Mass Index and Exercise

So far, the effective way to achieve fat loss is mainly through long-term aerobic exercise and resistance training. The mechanism of fat loss of aerobic exercise is to directly consume excess fat in the body [16]. Resistance training is to improve the resting metabolic rate in a quiet state by improving muscle elasticity and mass and activating muscles of the body, thereby achieving the purpose of fat consumption [17]. The basal metabolic rate of obese people can be increased by long-term aerobic exercise, thereby achieving the purpose of weight loss [18]. However, the intensity of exercise is an important issue to be considered. It is currently believed that strenuous exercise can cause damage of the joint, ligament, and muscle and break the mechanical balance. Also, high-intensity exercise can impair the bone hemodynamics, increase the pressure in the initial bone, and cause joint fluid secretion disorder. All these alterations may increase the risk of osteoarthritis [19]. On the contrary, moderate exercise can maintain the joint adduction torque and the biomechanical balance of the muscles around the joints, which is the key factor to reduce joint load and make the surface load distribution of the articular cartilage normal and painless.

Body mass index (BMI) exceeding the standard value was closely related to the occurrence of osteoarthritis [20]. Increasing evidence has shown that the probability of suffering from osteoarthritis is significantly higher in patients with excessive BMI than that in healthy people [21]. Overweight increases the intra-articular load and thus causes the wear and tear of articular cartilage [22]. It may also trigger a sterile inflammatory hyperemia reaction in the joint, which induces micro-damage of the joint. The long-term accumulation of these micro-injuries

eventually leads to irreversible damage of the articular cartilage, destroys the biomechanical balance of joints, and promotes the occurrence of osteoarthritis [23].

15.2.3 Gender and Estrogen

More and more studies have shown that osteoarthritis has little difference between men and women before the age of 50, whereas after 50 years old, women are more likely to suffer from osteoarthritis than men, which is supposed to be related to the physiological structural difference between male and female bones and joints [24]. Compared with men, women have thin cartilage thickness, less cartilage content, and smaller joint area since birth [24]. Particularly, mechanical damage is more likely to occur under load conditions.

Estrogen has a unique role in the pathogenesis of osteoarthritis. Statistics have shown that the incidence of osteoarthritis in postmenopausal women is significantly higher than that in age-matched men [25]. Estrogen can inhibit the formation of osteoclasts in vitro in a coculture system of osteoblasts and pre-osteoclasts; however, this effect is attenuated in the culture of pre-osteoclasts alone, suggesting that the effect of estrogen on bone metabolism is dependent on osteoblasts and secretion of related cytokines [26]. In terms of cytokines, type I collagen N-terminal peptide (NTX-1), osteocalcin, degenerative specific marker CTX-2, and type II collagen degradation fragment C2C are higher in the joint fluid of female osteoarthritis patients [27]. Estrogen can act on type II collagen and affect cartilage metabolism, with increased expression of degenerative specific marker CTX-2 [28]. In addition, estrogen promotes the production of transforming growth factor-β (TGF-β) by osteoclasts which can induce osteoblast formation. Estrogen also promotes insulin growth factor (IGF) production by chondrocytes [29].

When the endogenous estrogen secretion decreases, the body's absorption rate of calcium decreases while the blood uric acid (UA) level increases; this change can promote various inflammatory processes including osteoarthritis [30]. After menopause, the number of estrogen receptors on the surface of chondrocytes is also downregulated, which may trigger osteophyte formation. Estrogen can increase the secretion of glucocorticoids to inhibit the release of IL-1, IL-6, TNF-α, and matrix metalloproteinases (MMPs), and it can also exert an indirect inhibitory effect on osteoarthritis by regulating the immunosuppressive effects of glucocorticoids. Collectively, estrogen deficiency has a great influence on bone formation, bone cell physiological metabolism, and production of inflammatory related factors by chondrocytes [31].

15.2.4 Trauma

According to statistics, the incidence of osteoarthritis in patients with soft tissue injury around the joint is ten times higher than that in healthy people, and the probability of knee osteoarthritis is greatly increased in patients with distal femur fractures [32]. Violence can not only break the intra-articular stress balance by damaging the soft tissue around the joint but also directly damage the articular cartilage with degeneration and necrosis of chondrocytes [33]. In the experimental model of osteoarthritis, common surgical methods are used to destroy the normal anatomy of the joint (e.g., simple meniscal resection and gluteal muscle transection), which leads to the break of joint stress balance [34]. Studies have shown that traumatic stimulation can change the microenvironment of the joint cavity by increasing the chondrocyte inflammatory factors, inducing the necrosis and apoptosis of chondrocytes, and accelerating the degradation of type II collagen fibers and aggrecan. All these pathological processes contribute to the development of osteoarthritis [35].

15.2.5 Inflammatory Factors

The pathogenesis of osteoarthritis is very complicated, with various cytokines and intracellular signaling pathways involved [36]. Although

osteoarthritis has different etiologies, some common inflammatory factors may contribute to the pathogenesis of osteoarthritis, including IL-1 and TNF-α.

IL-1 is synthesized and secreted by macrophages, fibroblasts, chondrocytes, synovial cells, and osteoclasts and participates in various inflammation processes of the body [37]. IL-1 plays an important role in the pathogenesis of osteoarthritis, mainly by stimulating the synthesis and secretion of ADAMTS metalloproteinases by articular chondrocytes and synovial cells and decomposing polysaccharides and type II collagen fibers [38]. Puncture of cartilage and synovial cells produces nitric oxide (NO) and prostaglandin E (PGE2), which causes oxidative damage to the articular cartilage [39]. The activated osteoclasts and inhibited osteoblasts further promote bone catabolism and osteophyte formation in joint cavity and increase the production and secretion of various inflammatory chemokines [40]. Studies have shown that normal articular chondrocytes secrete only a small amount of IL-1, while the synthesis and secretion of IL-1 are greatly enhanced by articular cartilage and synovial cells derived from osteoarthritis patients [41]. IL-1 receptors on the surface of chondrocytes derived from osteoarthritis patients have higher sensitivity to IL-1 compared to normal chondrocytes [42]. In addition, IL-1 has synergistic effect with TNF-α to promote chondrocyte apoptosis [43]. Studies have reported that the addition of IL-1-specific antibodies to the culture medium of osteoarthritic chondrocytes can effectively inhibit the production of other inflammatory factors such as NO and MMPs, suggesting IL-1 as a key factor in the osteoarthritis cascade [44].

TNF-α is widely present in the body and participates in various physiological and pathological processes [45]. In the pathogenesis of osteoarthritis, TNF-α plays a similar role to IL-1, but its efficacy is much lower than IL-1. TNF-α mainly promotes the synthesis and release of MMPs, promotes the catabolism of chondrocytes, and inhibits the repair of chondrocytes after injury [46]. Studies have reported that in animal models of osteoarthritis, TNF-α can significantly inhibit osteogenic activity and reduce bone formation [47]. TNF-α can stimulate synovial cells to synthesize more PGE2 through the cyclooxygenase pathway [48]. In addition, TNF-α can promote the release of IL-6 by osteoblasts [49]. The degree of pain and articular cartilage degeneration in osteoarthritis patients are closely related to the IL-6 levels, indicating that IL-6 may be used to assess the severity of osteoarthritis [50].

In an animal model of osteoarthritis by intra-articular injection of TNF-α and IL-1, molecular targeted therapy against TNF-α and IL-1 has been proven to be a potential therapeutic strategy for osteoarthritis [51]. Targeting the inflammatory factors provides new ideas for clinical molecular targeted therapy for osteoarthritis.

15.2.6 Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) are widely distributed in connective tissues of the body [52]. They are a family of proteases with similar chemical structures and catalytic activity determined by zinc ions [53]. MMPs play an important role in various physiological and pathological conditions of the body, such as bone formation, tissue repair, connective tissue disease, and osteoarthritis [54]. Articular cartilage degeneration is the basic pathological change of osteoarthritis [55]. The damage of the articular cartilage often begins with the destruction of extracellular matrix of cartilage [56]. Multiple MMPs such as MMP-1, MMP-3, and MMP-13 are involved in the pathogenesis of osteoarthritis. The level of MMP-3 in the joint fluid of osteoarthritis patients is high and positively correlated with the degree of disease [57]. In vitro experiments showed that the degradation of type II collagen fibers by MMP-13 was more obvious than that of other types of MMPs [58]. By adding a specific blocker of MMP-13 to the culture medium, the phenotype of the diseased articular chondrocytes tends to be normal, indicating that MMP-13 may be used as a new molecular target for clinical treatment [59].

The expression of MMPs is regulated by a variety of cytokines, such as IL-1, IL-6, TNF-α,

TGF-β, etc. On the contrary, tissue metalloproteinase inhibitor (TIMP) is a strong inhibitor of MMPs [48]. However, these factors play a synergistic role in the development of osteoarthritis. Due to the wide variety and complex mechanism of action, no cytokine has been found to play a decisive role in the pathogenesis of osteoarthritis. The effects of various cytokines are interwoven into the network to promote osteoarthritis progression [60].

15.3 Epidemiology of Osteoarthritis

Osteoarthritis is the most common joint disease, especially in the elderly population. The prevalence rate of osteoarthritis is 50% in people over 65 years old and up to 80% in people over 75 years old [61]. There are a large number of osteoarthritis patients in China. In a large-scale epidemiological survey of more than 17,000 people in 28 provinces across the country, the overall prevalence of osteoarthritis with symptomatic knee arthritis is 8.1% in middle-aged and elderly people aged over 45 years [62]. The distribution of osteoarthritis presents regional and urban-rural differences in China [63]. In areas with high medical levels, the prevalence of osteoarthritis is lower than that in areas with low medical levels [64]. The prevalence of osteoarthritis in southeast coastal cities is lower than that in northwestern regions, and the prevalence in urban areas is lower than that in rural areas [65]. Because farmers in remote rural areas and mountainous areas need to farm and travel, the amount of physical labor is relatively large, and the degree of damage to the knee joints is more serious, which causes increased prevalence of osteoarthritis in these areas [66]. The pain caused by osteoarthritis can be repetitive and difficult to cure [67]. In severe cases, the joint function can be lost, further leading to the loss of work ability [68]. An artificial knee joint replacement brings high financial burden for the patients [69]. Considering that the life of an artificial knee joint is only about 10 years, some people may not only need one operation, so the actual cost will be higher [70, 71]. In addition, long-term osteoarthritis will increase the mortality rate of patients. Although osteoarthritis generally does not directly lead to death, it is often associated with cardiovascular diseases [72]. The reason may be related to reduced exercise and activity of osteoarthritis patients, and the long-term effects of blood sugar and blood pressure lead to increased risk of death from cardiovascular diseases [73]. Therefore, we should pay more attention to the treatment of comorbidities for osteoarthritis patients.

15.4 Theory of Exercise Prevention of Osteoarthritis

Disease prevention and alternative treatment are two main aspects for clinical intervention of osteoarthritis [74]. From the onset to progression of osteoarthritis, obesity, skeletal and muscle injury, and functional muscle decline are usually the main interventional targets for disease prevention [66]. Obesity is an important factor in the development of osteoarthritis. Studies have shown that the obesity rate of adults in China has increased year by year. The prevalence of knee arthritis in obese patients is increased by 30% compared to normal people [75]. Physical exercise helps not only lose weight and but also maintain a healthy weight for a long time, which is important for preventing osteoarthritis [76]. Moreover, scientific training has been proved to protect the muscle and ligaments, thus conveying preventive effect for osteoarthritis. A study of 27,000 subjects showed that neuromuscular training and proprioceptive training can effectively prevent 50% of anterior cruciate ligament injury, thus preventing knee arthritis [77]. Lower extremity muscle dysfunction, especially the weakness of quadriceps muscle, is closely related to knee osteoarthritis. However, lower limb muscles become weakened and smaller in size with aging. Exercise training can effectively promote the growth of muscle fiber volume, thereby increasing muscle strength and slowing down muscle decline [78]. Therefore, exercise is an effective measure for the prevention of osteoarthritis [79].

15.5 Exercise Training Methods for the Treatment of Osteoarthritis

Exercise therapy has been proven to have beneficial effects on osteoarthritis. Relevant guidelines for osteoarthritis at home and abroad recommend exercise therapy to varying degrees. In recent years, sports therapy for knee osteoarthritis (KOA) has also made great progress in China [80]. According to relevant guidelines, sports therapy for treating osteoarthritis mainly includes joint activity training, aerobic exercise, and underwater sports [81].

15.5.1 Joint Activity Training

Osteoarthritis is associated with pain, swelling, and stiffness of the joint [82]. The pain can be increased during joint movement, and joint stiffness can further lead to limited joint activity, which gradually leads to adhesion of fibrous tissue inside and outside the joint and in turn exacerbates joint stiffness and activity [83]. The training of joint mobility can break this vicious circle. Active joints can alleviate tissue adhesion, improve blood circulation, accelerate metabolism, eliminate swelling and pain, and promote the repair and regeneration of articular cartilage [84]. The joint activity training can also promote the circulation of synovial fluid in the joint and reduce the inflammation of synovial membrane, thus preventing joint stiffness [85].

Passive activity training without active muscle contraction is mainly used for osteoarthritis patients who cannot actively move the joint [86]. For patients with knee osteoarthritis, passive activity training can relieve the pain, swelling, and stiffness of the knee joint in a short time and improve local blood and lymph circulation of the joint. It can also accelerate the repair of the articular cartilage, ligament, and tendon and finally increase the range of knee joint activity and improve the balance of the body [87]. In comparison, active activity training is suitable for patients who can actively move the joint. Progressive and slow active activity training can be performed in all axial positions of the joint, ranging from small to large, which aims to stretch the tendon and tissue around the joint [88]. Each activity should be slightly overextended after reaching the maximum possible range to cause mild discomfort, maintained slightly, and then slowly retracted and practiced repeatedly [89]. Active activity may be accompanied by short-term pain, but it has a definite beneficial effect on knee osteoarthritis.

15.5.2 Aerobic Exercise

Osteoarthritis not only leads to decreased muscle strength and range of joint activity but also reduces aerobic capacity which makes patients' dysfunction worse, especially lower limb motor dysfunction [90]. In addition to the promotion of heart and lung function, aerobic exercise has significant effect to improve symptoms such as joint swelling and limited mobility in osteoarthritis patients [91]. At present, domestic and international osteoarthritis guidelines recommend aerobic exercise, including jogging, swimming, cycling, Tai Chi, etc. [92]. Although clinical reports are rare for running exercise in osteoarthritis patients, animal experiments reported that low- and medium-intensity running training on rabbits with osteoarthritis can promote the repair of articular cartilage [93]. Additionally, moderate-intensity running exercise was demonstrated to be beneficial to promote the repair and reconstruction of rat knee articular cartilage. Low-intensity running exercise has limited repair effect, while high-intensity running exercise has destructive effect [94]. In another study using swimming training as aerobic exercise for knee osteoarthritis (KOA), it was found that swimming can not only delay the further destruction of knee joint chondrocytes in KOA rats but also improve the exercise capacity of KOA rats [95]. Moreover, Tai Chi is an effective and safe way to improve joint pain, joint stiffness, and walking speed in KOA patients [96].

At present, there are many reports on aerobic exercise treatment of OA, but most of them are basic animal experiments and lack clinical

large-scale research reports. There is no uniform standard for the type, intensity, frequency, and duration of exercise [97]. It is also noteworthy that repeated excessive exercise will accelerate the destruction of cartilage, cause inflammation of the sliding mold, and eventually exacerbate osteoarthritis [98]. Therefore, the clinical efficacy and safety of aerobic exercise needs further research to find more valuable evidence for the treatment of osteoarthritis.

15.5.3 Aquatic Exercise Therapy

Aquatic exercise therapy uses the buoyancy of water and fluid resistance to perform different exercise trainings on the human body [99]. Importantly, aquatic exercise therapy has the dual role of exercise therapy and warm treatment [100]. Aquatic exercise can promote local and systemic blood circulation in osteoarthritis patients. It can also relieve tissue adhesion and reduce the burden and pressure on joints [101]. At present, hydrotherapy is widely used in clinical practice in developed countries. A randomized controlled trial showed that long-term exercise therapy in water was more effective than general functional exercise to relieve the joint pain during walking in patients with knee osteoarthritis [102]. Water sports is not only useful to reduce pain but also effective to reduce disability [103]. However, it was also reported that hydrodynamic therapy was not effective to relieve joint pain [104]. Although the effect of hydrosport therapy on pain relief is controversial, current research indicates that water sports training has beneficial effect on knee osteoarthritis. In terms of the effect of water pressure on the cartilage, it was also demonstrated that lower water pressure can promote cartilage self-repair [105]. As a noninvasive, easy-to-operate, economical, and less adverse treatment, aquatic exercise therapy is considered to be an effective way to treat osteoarthritis although more investigations are still needed to further clarify its long-term efficacy and safety during treatment.

15.5.4 Muscle Strength Training

Isometric strength training is to fix the limb at a certain angle [106]. Although the muscle fiber length does not change when the muscle contracts, the muscle strength increases and the joint activity does not occur [107]. Isometric training is mainly suitable for patients with obvious joint swelling and pain, weak muscle strength, and advanced age. Quadriceps isometric training has been shown to significantly relieve symptoms and improve joint function, joint stability, and quadriceps muscle strength in the treatment of knee osteoarthritis [108]. At present, the application of multipoint intermittent isometric training is more and more extensive, and its curative effect is more obvious than general isometric training [109]. Because isometric contraction does not produce joint activity, it can avoid joint wear caused by isotonic or constant velocity contraction. So it is especially suitable for knee osteoarthritis patients who cannot move the knee joint due to pain. For these patients, isometric training can improve both muscle strength and muscle function [110].

In comparison, isotonic muscle training is a muscle contraction exercise performed under a constant resistance load. During isotonic training, the muscle fibers become shorter, but the muscle tension does not change [111]. Isotonic muscle training can gradually thicken the muscle fibers and enlarge the atrophied muscles as well as promote the recovery of muscle strength and endurance, which makes the knee joint more stable and improves the function of joint [112]. Meanwhile, isotonic muscle training is able to improve nerve control, local circulation, and articular cartilage nutrition. However, isotonic muscle training is not suitable during the acute inflammation phase of arthritis, because the bright muscle groups may be replaced by the strong muscle groups which then causes the imbalance of muscle strength during training [113].

Isokinetic strength training is a relatively new muscle training technique, which usually needs to be assisted under the instrument [114]. The resistance provided by the instrument is adjusted

according to the patient's muscle strength: when the muscle strength is weak, the resistance is correspondingly reduced; so its safety is better [115]. The isokinetic training can train the active muscles and antagonist muscles at the same time, so the muscles can easily withstand the maximum resistance within the range of motion. Although the safety of isokinetic strength training is obvious, its operation is complicated and the equipment is expensive, which makes it difficult to promote in patients with osteoarthritis.

15.6 Perspective

The layer of cartilage of the bones is very thin, but it plays important roles to reduce the friction of adjacent bones and to cushion the vibrations occurring during exercise. There is no blood supply to the cartilage, and its nutrient supply comes from the joint fluid. With aging, the cartilage will degenerate and shrink. Once the cartilage is damaged, it is not able to repair itself. Thus, it is essential to protect the cartilage and reduce subchondral bone lesions for osteoarthritis patients. There are many ways to treat osteoarthritis, and exercise is considered to be effective in the prevention and treatment of osteoarthritis.

Exercise has been proven to relieve symptoms and improve the function of joints in osteoarthritis patients. However, there is currently no uniform standard for exercise therapy for osteoarthritis. Moreover, it is largely unclear whether exercise therapy has side effects during long-term follow-up and how to avoid further damage due to exercise. The resolution of these problems requires the efforts of both basic and clinical scientists and doctors to clarify the efficacy and safety of exercise therapy for osteoarthritis patients. Moreover, it is important to have guidelines for the recommendation of type, intensity, frequency, and duration of exercise for different osteoarthritis patients. We believe that patients with osteoarthritis will have a more scientific and individualized exercise therapy in the future.

Acknowledgment This work was supported by grants from the National Natural Science Foundation of China (81701218\81873774).

Competing Financial Interests The authors declare no competing financial interests.

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Exercise and Chronic Pain

16

Anna Borisovskaya, Elizabeth Chmelik, and Ashwin Karnik

Abstract

In this chapter, we describe the impact and etiology of chronic pain, the associated changes in the nervous system, and the mechanisms by which exercise may be able to affect and reverse these changes. Evidence for efficacy of exercise in different conditions associated with chronic pain is presented, with focus on chronic low back pain, fibromyalgia, osteoarthritis, rheumatoid arthritis, and migraines. While the efficacy of exercise and level of evidence supporting it vary in different diseases, exercise has direct and indirect benefits for most patients suffering from chronic pain. Effective exercise regimens include education and cognitive restructuring to promote behavioral activation and reconceptualization of what pain means, with the goal of gradually reversing the vicious cycle of pain, inertia, sedentary behavior, and worsening disability. Long-term, consistent, individualized exercise-based treatment approaches are most likely to result in improvements in pain and function.

Keywords

Chronic pain · Fibromyalgia · Low back pain · Migraines · Cognitive behavioral therapy · Exercise · Kinesiophobia · Exercise-induced analgesia

16.1 Introduction: Defining Chronic Pain

Acute pain occurs when a mechanical or inflammatory insult or injury occurs at the tissue level. This pain is described as "nociceptive" pain or pain triggered by a potentially harmful stimulus at the body's periphery [1]. Nociceptive pain is a physiological response to a potentially dangerous stimulus and is the body's warning sign to prevent further damage. It is also a complex process whereby the peripheral nervous system transmits information about the noxious stimuli from the periphery to the spinal cord and ultimately to the brain where the signals are interpreted and experienced as pain [1].

Most people who experience acute nociceptive pain will also experience resolution of pain when the injury or insult heals. Unfortunately, 20–30% of patients will experience persistent pain despite resolution of the initial trigger [2]. In

A. Borisovskaya (✉) · E. Chmelik
Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA

Veterans Administration Medical Center, Seattle, WA, USA
e-mail: anna.borisovskaya@va.gov

A. Karnik
Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_16

this situation, pain is no longer a marker of tissue damage but a perceived need to protect body tissue in the absence of true danger [3].

According to the International Association for the Study of Pain (IASP), when pain lasts beyond 3 months, it is defined as chronic. The 3-month cutoff is the most widely accepted definition of chronic pain, but it's overly simplistic and cannot account for the wide variation in pain disorders [4]. For example, some forms of chronic pain such as osteoarthritis (OA), rheumatoid arthritis (RA), and cancer pain have an identifiable pathology that causes tissue damage. Neuropathic types of pain also have an identifiable pathology that includes damage to peripheral nerves as in the case of diabetes. Other forms of chronic pain such as fibromyalgia, chronic pelvic pain, and chronic low back pain (CLBP) are idiopathic and often without clear physical findings [5, 6]. Interestingly, regardless of the original mechanism of pain, chronic pain can occur in any of these conditions and has been described as a distinct disease entity with similar comorbidities and outcomes regardless of the initial diagnosis [5]. Chronic pain is usually multifocal, imprecise, and also commonly comorbid with other somatic symptoms such as low energy, impaired sleep, memory or concentration problems, and depressed mood [5, 7, 8]. To better capture the complexity of this condition, the IASP has developed a more nuanced taxonomy of pain conditions that classifies pain on these five dimensions:

- Core diagnostic criteria
- Common features
- Common medical comorbidities
- Neurobiological, psychosocial, and functional consequences
- Mechanisms, risks, and protective factors

The goal of this framework is to incorporate neurobiological processes and psychosocial features into the definition of chronic pain, to account for both similarities and differences in various chronic pain conditions, and to guide research and treatment protocols [9].

16.2 Epidemiology of Chronic Pain

The prevalence of chronic pain is reported to range anywhere from 10 to 65% of adults in the United States with most reported estimates in the 30% range [4, 8, 10, 11]. It is also estimated to affect 25–35% of adults worldwide [10, 12]. This translates to approximately 100 million people in the United States and closer to 1.5 billion people worldwide [6].

Generally, pain sensitivity is strongly genetic and occurs in a bell-shaped curve in the general population [1, 5]. Those more sensitive to pain at baseline are understandably more vulnerable to chronic pain conditions [5]. Chronic pain tends to occur more commonly in females and in individuals over age 40 [7]. Some authors have described a "pain-prone phenotype" that includes risk factors of female sex, personal history of trauma, family history of pain, and a cognitive tendency to catastrophize [5].

Though there's little agreement on the best definition of chronic pain [4], the cost of chronic pain is undisputed. CLBP alone is estimated to cost $365–560 billion per year in healthcare utilization, disability, and lost productivity [13]. According to some reports, chronic pain affects more people in the United States than diabetes, cancer, and heart disease combined, which highlights the need to better understand and treat this problem [2].

16.3 Etiology of Chronic Pain

Chronic pain is best described as a "disease of the brain" because it occurs when a person begins to perceive the sensation of pain in the absence of acute nociceptive triggers [11]. A concept known as "central sensitization" is a common underlying process that occurs in most chronic pain conditions, and it describes demonstrable functional changes within the nervous system [5, 11]. Essentially, chronic pain involves a progressive shift from peripheral tissue pathology to central nervous system (CNS) pathology [14].

Central sensitization can be described as an overactive pain neuromatrix that results in a hyperactive nervous system [15]. The peripheral nervous system becomes more likely to send pain signals to the CNS (described as "bottom-up" changes), while the brain and spinal cord develop less inhibitory influence to minimize pain outputs (described as "top-down" change). A complex set of interrelated mechanisms are thought to be responsible for these unfavorable changes [3, 16, 17].

Studies point to both local and systemic inflammation as potential mechanisms for the development of central sensitization and chronic pain. For example, several studies show a shift in the balance of inflammatory cytokines in the chronic pain state that sensitizes peripheral nociceptors and lowers the threshold required to activate them [10, 14]. This results in amplified input to the CNS and promotes persisting adaptations that render a person more vulnerable to experience pain [3, 5]. Pain signals then enter the CNS at the dorsal root ganglion of the spinal cord. There is evidence that afferent nerves in the spinal cord show a potentiated excitatory response in chronic pain [17]. At the brain level, functional imaging demonstrates clear differences in the neuronal activity in areas involved in pain processing compared to healthy controls [5, 17]. For example, neuroimaging shows changes in the amygdala, anterior cingulate, insular cortex, and nucleus accumbens, which are all areas involved in pain modulation [3]. Higher-level brain function is affected too. It is speculated that cortical disorganization alters the sensorimotor homunculus to produce a more pervasive pain experience [13] and those with chronic pain often acquire a maladaptive "pain memory" in which feared movements begin to produce pain without nociception and can worsen and/or sustain chronic pain [18]. Finally, descending pain pathways are vulnerable to maladaptive change. Dysfunctional endogenous analgesia is well-documented in certain chronic pain conditions, and evidence suggests that dysregulated neurotransmission also sustains chronic pain [5, 19]. For example, lower levels of neurotransmitters that inhibit pain (i.e., gamma-aminobutyric acid, serotonin, norepinephrine) and higher levels of neurotransmitters that promote pain (i.e., glutamate, substance P) are found in the cerebrospinal fluid of fibromyalgia patients and can negatively alter pain perception [5].

These mechanisms combine to create a nervous system with reduced threshold to pain induction in combination with an amplified pain response. As pain persists, mechanisms involved in nociceptive pathways become increasingly more sensitive, and the relationship between pain and the need to protect vulnerable tissues becomes more tenuous [20]. Pain is no longer an accurate marker of tissue damage, or danger, and the secondary pathology of "central sensitization" becomes more relevant [20].

16.4 Exercise as a Treatment for Chronic Pain: Mechanism(s) of Action

The nervous system is "neuroplastic", or dynamic, which means that the maladaptive changes that occur in the chronic pain state can be reversed [2, 11]. Exercise is one modality of care shown to improve chronic pain, and the reason for this improvement extends far beyond musculoskeletal health alone [6, 20, 21]. Several studies have demonstrated that exercise improves pain even in the absence of improvements to strength, flexibility, or endurance [20, 21]. Other studies have shown that exercising a non-painful part of the body can have analgesic effects on the painful part, highlighting the fact that chronic pain mechanisms extend beyond a single point of local pathology [19]. Below we describe several proposed mechanisms by which exercise improves chronic pain.

16.4.1 Exercise, Chronic Pain, and Inflammation

Studies have shown that sedentary behavior results in the presence of more inflammatory and fewer anti-inflammatory cytokines in both local and systemic circulation and this imbalance

contributes to the maintenance of chronic pain [2]. Physical activity, on the other hand, has well-documented anti-inflammatory effects, and preliminary studies show that exercise can reduce systemic inflammation, which in turn may reduce chronic pain [22]. Specifically, regular exercise is shown to reduce presence of pro-inflammatory cytokines and increase presence of anti-inflammatory cytokines to normalize neuroimmune signaling in the CNS [14, 22]. This can prevent and even reverse hyperalgesia [22]. Consistency appears to be of importance to achieve this benefit, and so daily activity should be encouraged even if it is of low intensity and short duration [6].

16.4.2 Exercise, Chronic Pain, and Exercise-Induced Analgesia

In healthy adults, physical activity triggers release of endogenous opioids to produce "exercise-induced analgesia" (EIA) that reduces pain perception during and after exercise [22, 23]. Unfortunately, EIA can be dysfunctional or even absent in certain chronic pain conditions such as fibromyalgia and chronic fatigue syndrome [18, 19, 22]. This complicates the application of exercise, because individuals with these conditions are at risk for increased pain severity during bouts of increased activity, which can impact adherence to exercise [19, 23].

16.4.3 Exercise, Chronic Pain, Neurons, and Neurotransmitters

An imbalance in centrally acting neurotransmitters such as serotonin, dopamine, and norepinephrine has been demonstrated in chronic pain [11]. This may be partly related to baseline genetic profiles involved in monoamine metabolic pathways [1] and can also be caused by sedentary behavior. Exercise, on the other hand, is known to trigger stress responses in the neuroendocrine system that can change the balance of these neurotransmitters [19]. For example, exercise is shown to increase serotonin release to promote analgesia by activating this descending inhibitory pain pathway [22]; it can also influence other neurotransmitters such as dopamine and norepinephrine [11].

Molecular and cellular changes in the spinal cord and brain in the chronic pain state are shown to revert in exercise [14]. For example, axonal nerve regeneration occurs with exercise, which can help the CNS to respond more appropriately to pain signals; exercise also induces phenotypic changes in epidermal axons which increase pain threshold [14]. Rodent models show that exercise can increase neuron survival and resistance to brain insults, which can also have a favorable effect on chronic pain [16].

16.4.4 Exercise, Chronic Pain, and the Brain

Chronic pain is often linked to fear of movement which is a common cause for reduced activity compared to baseline. This kinesiophobia can precipitate changes to cortical networks that perceive and regulate motor functions (Puentedura). Increased activity levels can refocus and sharpen the "body schema" maps and reduce pain via cortical reorganization [13].

Many individuals believe pain to be a marker of acute danger, an inaccurate cognition in most chronic pain conditions [15]. Pain is cognitively mediated and can be improved by modifying this and other inaccurate beliefs [3, 15]. Graded exposure targets brain circuitries orchestrated by the amygdala, or fear center, to improve pain [15]. The basic idea is to educate individuals that their pain is no longer a signal of true danger, to expose patient to their feared movements in a controlled and supervised setting, and to alter pain memories in a way that will eventually reduce pain. This is a form of systematic desensitization that promotes development of new memories of safety with previously feared movements [15]. This careful approach to exercise promotes cognitive restructuring by decreasing fear avoidance

and pain catastrophizing and improving self-efficacy [15, 20].

16.5 Exercise for Chronic Pain: The Evidence for Various Pain Conditions

Below, we present the evidence for use of exercise in various conditions associated with chronic pain. Majority of well-designed studies examining exercise for pain focus not only on pain reduction but also on improvement of function and increased quality of life. Wherever possible, we report on all these outcomes. It should be noted that, for the purposes of this chapter, it was impossible to describe the evidence for all conditions associated with chronic pain; we focused on those frequently encountered in clinical practice.

16.5.1 Chronic Low Back Pain and Chronic Neck Pain

LBP is a common problem, affecting at least 80% of all individuals at some point in their lifetime, and is a leading cause of limited activity and work absence [24]. The total costs of healthcare for LBP combined with missed work days exceed $100 billion each year in the United States [25]. In a small percentage of patients, when pain persists for longer than 3 months, CLBP develops. CLBP can be thought of as a symptom, rather than a disease in itself, with a variety of possible underlying conditions, some of which may be more benign than others. Etiologies of CLBP range from muscle strain and disc herniation to spinal stenosis, spondylolysis, vertebral compression fractures, and others [24]. The majority of CLBP, however, is thought of as nonspecific, as the definitive diagnosis of the source of CLBP cannot be made in over 85% of patients [25]. Given the impact of the illness, it's unsurprising that the preponderance of available literature examining nonpharmacological treatments, including exercise, is focused on CLBP.

A systematic review that examined 122 trials to determine the efficacy of exercise on CLBP concluded that it's helpful, even though the overall impact of this intervention may be small to moderate. Exercise was associated with greater pain relief than no exercise. Benefits were found for pain and function. For radicular low back pain, three trials found exercise to be more effective than usual care or no exercise, though the effects were small [26]. Exercise therapy has also been found to be cost-effective for nonspecific neck pain and CLBP while conferring larger effects for quality of life compared with usual care [27]. The authors also found that home exercises combined with manual therapy had lower costs compared with home exercises alone [27].

Various types of exercise have been examined. Two trials found that Tai Chi reduced pain, and one trial found greater improvement in function. Fourteen trials of yoga found it to be associated with reduced pain and better function [26]. Another systematic review of yoga for nonspecific CLBP found low- to moderate-quality evidence that yoga improved function at 3–6 months and was slightly more effective for pain at 3–6 months. It wasn't associated with serious adverse events, although it was associated with more adverse events than non-exercise controls. The authors concluded that it was uncertain whether yoga offered advantages over any other types of exercise in CLBP [28]. A systematic review of Pilates included five high-quality randomized controlled trials (RCTs) and showed improvement in pain relief and function with 6–12 weeks of Pilates compared to usual care, although Pilates didn't offer advantages over other exercise forms that included waist or torso movement [29]. One inexpensive and accessible type of exercise is walking, which has been shown to improve aerobic capacity, reduce blood pressure and triglyceride levels, and decrease fat mass [30]. Two systematic reviews examined the effects of walking on patients with CLBP, both demonstrating efficacy of walking compared to other nonpharmacological interventions (exercise, education, or physiotherapy) in terms of improving pain and decreasing disability [31, 32]. The beneficial effects continued for 3–12 months after the intervention was completed [31]. The quality of evidence substantiating

this conclusion is low to moderate. Core stability exercises were compared to general exercise in 5 studies involving 414 patients with CLBP, and in the short term they were found to be more effective for decreasing pain and improving function [33]. Motor control exercise focuses on the activation of the deep trunk muscles and helps restore their control and coordination. One systematic review found low- to moderate-quality evidence that it was effective for reducing pain compared with minimal intervention in CLBP, but it wasn't more effective than other exercises or manual therapy and didn't have an impact on disability [34]. Another review that focused on patients with CLBP and movement control impairment, defined as alteration of the spinal alignment and movement pattern in a specific direction [35], found motor control exercise to have a positive effect on disability at the end of intervention and after 12 months. Pain intensity was reduced at the end of treatment but not after 12 months [36]. Somewhat poorer quality of evidence exists for Back School, a therapeutic program including education and exercise, although the content of such programs varies widely. At present it's uncertain whether they are effective for CLBP [37, 38]. A systematic review of different types of exercise found something to recommend each intervention examined: moderate intensity aerobic exercise reduced pain and disability by increasing the blood flow and nutrients to the soft tissues in the back; core stability exercises increased the strength of deep abdominal muscles and improved the stabilization of the spine, particularly when combined with muscular strength exercises; flexibility exercises improved the flexibility of the lumbar spine and hamstrings, leading authors to conclude that no single exercise program is optimal for all CLBP patients, especially considering that nonspecific CLBP is a heterogeneous condition with multiple possible etiologies [39].

Because of association between higher fat mass and CLBP, along with associated disability [40], exercise is particularly relevant for overweight individuals suffering from CLBP [41]. Sixteen studies of various exercise programs for CLBP in overweight and obese patients demonstrated that after 4 months of resistance exercise, 2 months of aquatic exercise, or 3 months of Pilates, significant reductions in pain and perceived functional limitations along with increased strength were observed, with all programs being well-tolerated. The highest adherence rate occurred with resistance and aquatic exercise programs [41]. Less is known about older individuals living with nonspecific CLBP, but low-quality evidence indicates that physical therapy and exercise are associated with a small-to-moderate reduction in pain and a small improvement in function [42].

Given the side effects and concerns associated with use of pharmacologic treatments, along with limited evidence of their efficacy, the guidelines for treatment of CLBP emphasize self-management that includes exercise and cognitive-behavioral therapy (CBT) with only limited use of injections and surgery [43].

The body of evidence on prevention of CLBP is inadequate compared to that on treatment; however, existing literature is encouraging, particularly of the role of exercise. A systematic review and meta-analysis of 36 prospective cohort studies demonstrated that participation in sport or other leisure physical activity reduced the risk of CLBP, as it was 11% lower in moderately/highly active individuals, 14% lower in moderately active individuals, and 16% lower in highly active individuals in comparison with those without regular physical activity. However, the studies included in the review were limited: they examined various population groups and may have been influenced by confounding factors [44].

It should be noted that exercise has not been proven helpful for all etiologies of CLBP, where the body of evidence is either too small or has not shown benefit. For example, there is only limited evidence of stabilization exercises for back pain in patients with scoliosis [45]. There is only one trial of exercise described in the treatment of failed back surgery syndrome, which demonstrated reduction in pain [46]. Exercise has not been proven to be more effective than surgical interventions, such as lumbar fusion or total disc replacement, for patients in whom such

interventions were indicated. Analysis of existing literature suggests that while exercise, CBT, physical therapy, fusion, and total disc replacement all conferred benefit, total disc replacement appeared to be the most effective treatment, and physical therapy the least effective treatment for CLBP, although the evidence was limited [47].

Exercise was compared with other nonpharmacological treatment strategies for CLBP by the Agency for Healthcare Research and Quality (AHRQ) in a systematic review of 202 trials that looked at various treatment approaches for chronic pain disorders including CLBP, osteoarthritis, neck pain, fibromyalgia, and headaches [48]. For CLBP, intermediate-term improvements in function were more consistently sustained with exercise than with massage, acupuncture, and spinal manipulation. In the longer term, exercise was comparable to other nonpharmacological modalities except for acupuncture, whose benefits plateaued. In all phases of follow-up, multidisciplinary approaches lead to the greatest and most sustained improvements [48].

Substantially smaller body of literature exists on exercises for chronic neck pain. A Cochrane review found moderate-quality evidence that certain types of strengthening exercises for chronic neck pain were beneficial, although the optimum dosage of exercise was unknown. There was a small benefit for chronic mechanical neck pain with scapulothoracic and upper extremity endurance training immediately posttreatment, a small improvement in pain and function with the use of Qigong, and a large improvement in pain in cervicogenic headaches when combining static and dynamic cervical, scapulothoracic strengthening and endurance exercise [49]. Another systematic review found that low-load craniocervical flexion exercise was particularly effective compared to other types of exercises in improving the strength of deep cervical flexor muscles in patients with chronic nonspecific neck pain [50]. A literature review of long-term effects of exercise on chronic neck pain suggests that long-term interventions of 1 year or more in duration resulted in improvements on body function and structure at 3-year follow-up, although the number of trials included in the review was small, six [51].

16.5.2 Osteoarthritis

Osteoarthritis (OA) is the most common musculoskeletal disease which leads to joint pain and progressive loss of joint function and is a significant contributor to disability worldwide [52]. Etiology of OA varies, from genetic dysfunction of the chondrocytes to trauma, metabolic diseases, nutritional deficiencies, obesity, and hypermobility, among others [53].

The preponderance of literature addressing the impact of exercise on OA is focused on the knee, which is highly prevalent among the aging adults [54]. Modern guidelines recommend therapeutic exercise as part of the multimodal management of knee OA [55]. The American College of Rheumatology recommends aerobic exercises, aquatic exercises, Tai Chi, and weight loss in overweight patients for treatment of OA of the knee and the hip [56]. The body of evidence substantiating this recommendation is strong. A Cochrane systematic review found high-quality evidence that exercise provided short-term benefit sustained at least 2–6 months after cessation of formal treatment in knee OA. Benefit was seen in terms of both reduced joint pain and improvement of physical function, and no injuries were reported in patients who engaged in exercise programs, although there were some instances of knee or back pain [57]. It's important to note that muscle strengthening exercises, as defined by the American College of Sports Medicine, have not been proven to be more effective in decreasing pain and improving function than other types of exercise, despite increases in the knee extensor strength [58]. A recent systematic review of short-term traditional Chinese exercise (such as Tai Chi, Qigong, and Baduanjin) for treatment of OA demonstrated a moderate effect size for pain relief, physical function improvement, and alleviation of stiffness, without serious adverse events in the course of treatment. There wasn't enough evidence to prove long-term effects of traditional Chinese exercise on knee OA [59]. Interestingly, a review assessing the impact of Tai Chi on several chronic health conditions demonstrated improvement of the knee extensor muscle strength in patients with heart failure and chronic

obstructive pulmonary disease (COPD), but only a trend toward improvement in patients with knee OA [60]. Hatha yoga also demonstrated significant improvement for pain relief and physical function [61]. Structured programs combining education and exercise can lead to improvement in pain and physical function and may be a useful intervention to adopt across healthcare delivery systems [62], although no reliable data are available on the cost-effectiveness of these interventions [63].

It's unclear whether running, a popular form of exercise, is a risk factor for the development of knee OA. One recent systematic review and meta-analysis found that recreational runners had a lower occurrence of knee and hip OA when compared with competitive runners and controls; however, it wasn't possible to elucidate whether these associations were causative or confounded by other factors, such as previous injury or occupational workload [64]. Still, the authors felt confident recommending recreational running for general health and as being possibly protective against knee and hip OA. Evidence suggests that running is also protective against surgery due to knee OA—an option utilized when conservative treatment methods fail [65].

Evidence supporting exercise for other joints is less consistent, and recommendations for hip and hand OA are mainly derived from studies of knee OA [66]. However, studies are starting to accumulate, particularly for hip OA, which is highly prevalent among adults, with symptomatic illness reported at 9.2% among adults aged 45 years and older [67]. A systematic review of high-quality RCTs demonstrated that exercise improves pain and physical function; positive results were also seen with combination of exercise therapy and patient education [68]. Therefore, exercise is advocated as part of the treatment, with emphasis on activities that strengthen and stretch the muscles around the hip, and avoidance of activities that involve abduction and rotation of the hip joint, bending, and both prolonged inactivity and prolonged physical activity [67]. It's not known whether exercise is helpful for pain or function in patients who'd undergone total hip arthroplasty for OA [69]. When it comes to hand OA, a Cochrane systematic review found a small number of studies that showed small to moderate benefit of exercise on hand pain, function, and finger joint stiffness [70].

High level of interest exists in elucidating whether exercise combined with other nonpharmacological treatments could offer higher efficacy. One such treatment is self-care, which might include nutrition, adherence to medication regimen, hygiene, exercise, and other things that people might do for themselves to improve their health. A systematic review of existing studies demonstrated short-term benefit for self-care and exercise intervention. There were few studies that looked at long-term efficacy of such interventions, and the majority of these didn't demonstrate statistically significant difference between intervention and control groups [71]. Authors concluded that the potential of combined self-care and exercise interventions has not been maximized; in particular, attention should be given to the type and dose of exercise recommended.

Exercise offers benefits that extend beyond improvement in pain and function. A meta-analysis of 14 RCTs examining exercise for arthritis and other rheumatic diseases found significant reductions in anxiety among participants in regular exercise [72]. Another meta-analysis of 29 RCTs examining exercise in adults with OA, rheumatoid arthritis, fibromyalgia, or systemic lupus erythematosus found significant reductions in depressive symptoms in addition to reduction in pain, with number needed to treat of seven [73]. Exercise therapy with or without other interventions is effective in improving health-related and knee-related quality of life, while cognitive-behavioral therapy (CBT), whether or not it was combined with exercise, improved self-efficacy, depression, and psychological distress in patients with knee OA [74].

The mechanism of exercise-conferred benefit on disease pathology in OA is not yet fully understood. A meta-analysis of RCTs in healthy animals found that a high dose of daily exercise may have a negative impact and a moderate dose of daily exercise may have a positive impact on the composition of the knee joint cartilage [75]. A systematic review of studies that included

humans at risk of knee OA and those who had established OA found that knee joint loading exercise was not harmful for articular cartilage; however, the quality of evidence was low and studies differed in the interventions offered [76]. A meta-analysis in humans demonstrated no change in radiographic disease severity or cartilage morphology with long-term exercise and greater odds of worsening tibiofemoral bone marrow lesions; however, the findings were limited in quality and the population studied was predominantly obese, which may have influenced the results [77]. Stretching exercises are posited to counteract the movement limitations triggered by chronic inflammatory processes resulting in fibrosis of periarticular structures; further, muscle strength improvement is usually accompanied by improvement in coordination and reduction in pain-enhancing evasive movements [53]. Certainly, one of the greatest benefits from exercise in knee OA is potential for aiding in weight loss, since obesity is one of significant contributors to the etiology of this illness [54].

16.5.3 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic disease characterized by persistent synovitis, systemic inflammation, and autoantibodies, which may cause joint damage, disability, decreased quality of life, and possible comorbid pulmonary, ocular, cardiovascular, neurological, and cutaneous manifestations. RA affects 0.5–1% of adults in developed countries and prevalence usually increases with age [78]. While the outcomes in RA have been more favorable in our era due to the better understanding of the disease process and availability of disease-modifying antirheumatic drugs and biological agents, pain related to RA remains a common and persistent symptom. The pain may be caused by inflammation, joint damage, or changes in the CNS signaling [79].

While pharmacological agents have become the mainstay of treatment, there has also been recognition of the importance of staying active. The natural inclination to minimize pain by avoiding movement during acute flare-ups of the disease has not been proven to provide the desired relief [80]. Indeed, evidence is accumulating about the benefits of exercise in RA. A Cochrane review of aerobic capacity and muscle strength training programs that included data from eight RCTs showed that these programs led to some improvement in pain, physical function, aerobic capacity, and muscle strength, with no harmful side effects noted in any of the studies [81]. It should be noted, however, that absolute improvement in pain was slight—6%. Tai Chi has also been examined in patients with RA, and while it helped improve lower extremity range of motion, the majority of studies included in available systematic reviews didn't assess the effects of exercise on pain [82, 83]. Two RCTs that examined pain outcomes didn't demonstrate pain reduction compared with education combined with stretching exercises or the usual activity control [83]. Overall, the available studies that examined efficacy of Tai Chi for RA were of low methodological quality.

RA often affects the joints of the hand, and some studies examined specific exercises for hands in hopes that they would improve pain and function. These exercises included mobility, muscle strengthening, and functional training. So far, the available evidence hasn't demonstrated improved hand function or pain with exercise in the short term, but exercise may offer slightly improved function in the medium and long term; no adverse events were found with exercise programs [84]. A very small body of literature examining benefit of exercise programs on hand function in early arthritis suggested benefit [85].

16.5.4 Ankylosing Spondylitis

Ankylosing spondylitis is an inflammatory rheumatic disease, characterized by chronic pain and reduced mobility. Latest guidelines recommend inclusion of supervised exercise [86], which has demonstrated efficacy in improving quality of life, mobility, and pain. Review of available evidence points to the importance of consistent, preferably supervised exercise and includes axial mobility exercises and exercises that emphasized

stretching, strengthening, pulmonary, and functional fitness [87].

16.5.5 Fibromyalgia

Fibromyalgia is a rheumatic disease characterized by widespread chronic pain, stiffness, fatigue, anxiety, depression, sleep disturbance, and other symptoms. Various treatment modalities have been proven effective, including low-dose antidepressants, CBT, and exercise. A review of available evidence demonstrated that aerobic exercise for 30–60 min at an intensity of 50–80% of maximum heart rate 2–3 times a week for 4–6 months and muscle strengthening exercises (1–3 sets of 8–11 exercises, 8–10 repetitions with a load of 3.1 kg or 45% of 1 repetition maximum) appear most effective in decreasing the pain and severity of fibromyalgia symptoms, while other types of combined exercise including aerobic, stretching exercises and muscle strengthening were most effective in reducing depression, a common symptom and comorbidity of this disease [88]. Another review that evaluated strength training programs found that they had positive effects on reduction of pain, number of tender points, depression and improvement of muscle strength, sleep quality, functional capacity, and quality of life [89]. Authors recommend that strength training program should start at low intensity and gradually increase in intensity and should be performed two to three times a week to exercise the main muscle groups. An umbrella review published in 2014 found that the evidence was inconclusive for modalities of exercise such as yoga, Pilates, and Tai Chi due to paucity of research and quality of research in this area. The same review also recommended light- to moderate-intensity exercise and its duration at 7 weeks or longer [90]. While there's evidence that patients with fibromyalgia have low-grade chronic systemic inflammation, demonstrated by higher concentrations of IL-8 and TNF-α and high expression of IL-10, the effect of exercise on these inflammatory markers in these patients is unclear [91].

Challenges exist in engaging patients with fibromyalgia in a program of exercise. Poor exercise maintenance is associated with high level of stress, older age, higher physical disability as measured by the Fibromyalgia Impact Questionnaire, and disease severity [92]. As patients may be deconditioned, a multimodal exercise regimen consisting of strength training, aerobics, and flexibility training can elicit a flare-up of symptoms. It's recommended that an assessment prior to engaging in a program of exercise should determine the patient's baseline fitness level and a training stimulus that doesn't provoke pain. If pain is provoked by exercise, the intensity of training program should be reduced until the symptoms subside [93].

When exercise for fibromyalgia was compared to other nonpharmacological treatments in the AHQR trial described above, short-term improvements in function were seen with exercise, acupuncture, and CBT, whereas short-term pain was only improved with exercise or CBT. Intermediate-term improvements in function were sustained with exercise, acupuncture, myofascial release massage, CBT, and multidisciplinary rehabilitation. For intermediate-term pain, only multidisciplinary rehab leads to sustained improvement. Long-term improvements in function were only seen with multidisciplinary rehab, and long-term pain was only improved with massage [48].

16.5.6 Chronic Pelvic Pain

Chronic pelvic pain is a noncyclic pain localized to the pelvis, anterior abdominal wall, lumbosacral back, and buttocks that has been present for at least 6 months and is severe enough to cause functional disability. Established treatments include physical therapy, trigger point injections, and neuromodulation techniques [94]. A small body of evidence suggests that exercise may also be a useful treatment, as two RCTs examining a yoga intervention for 100 women with chronic pelvic pain demonstrated significant improvements in pain and quality of life [95, 96].

16.5.7 Migraine

Migraine is a common neurological disorder characterized by nausea, vomiting, sensitivity to light and sound, and head pain, often accompanied by an aura. The most prevalent type of migraine is episodic, characterized by having 14 or fewer headache days per month. It's a common and disabling illness, associated with loss of productivity and reduced quality of life. Medications exist for prophylaxis and acute treatment of migraines, but they're not universally effective and carry a burden of side effects; therefore, high interest exists in effective nonpharmacological treatments. Stress and behavioral patterns such as medication adherence, skipping meals, insufficient or poor-quality sleep, and low levels of exercise are associated with increased frequency of migraines [97]. Evidence is accumulating that regular exercise can be used successfully as prophylactic treatment for migraines, although it should be noted that there is also evidence that exercise can provoke migraines [98]. Most existing studies utilized aerobic exercise or yoga, though intensity and duration of exercise differed, leading authors to conclude that there are still a number of open questions as to the type of exercise program that should be recommended to migraine sufferers. Aerobic exercise may be of particular use since it activates pain inhibition for up to 30 min after exercise, compared to resistance exercise which provides shorter-lasting relief [19]. Another systematic review and meta-analysis that evaluated physical therapy interventions found significant benefit from aerobic exercise for reduction in pain intensity, duration, and frequency of migraines [99]. We still don't know enough about how to exercise to improve migraines, although a slow increase in intensity and duration is important when beginning an exercise program to minimize the likelihood of triggering migraines [19].

At this point, our understanding of the biological processes responsible for exercise decreasing migraine frequency is in its early stages. The proposed mechanisms behind exercise for this condition include changes in vasomotor tone and vasovagal activity; release of endocannabinoids, endorphins, and brain-derived neurotrophic factor; improved hormone regulation and neurotransmitter function; and changes in anti-inflammatory factors [100]. Given that obesity is one of the known comorbid conditions that influence migraines, reduction of weight through exercise is another important mechanism behind reduction of migraine burden [101]. Psychological factor, such as increased perceived self-efficacy in people suffering from migraines, is another important mechanism likely responsible for decreasing the frequency of migraines with exercise [102].

16.6 Exercise Combined with Cognitive-Behavioral Therapy

For decades, CBT has been widely accepted as a first-line treatment for mood and anxiety disorders. While it has the power to change thinking and behavior, it may even lead to physiological changes, as supported by findings that it helps restore a healthy balance of neurotransmitters like serotonin [103]. CBT has also been demonstrated to be an effective treatment for chronic pain conditions [104]. Existing research has led to the theory that exercise and CBT can be combined to produce better outcomes in chronic pain than either treatment modality alone, with the thought that CBT reverses cognitive distortions and exercise promotes behavioral activation [105]. There are several studies that have compared the efficacy of a combined CBT and exercise regimen (CBTEx) to either exercise or CBT alone, as in a recent systematic review and meta-analysis of 30 RCTs that included patients with chronic fatigue syndrome, CLBP, COPD, chronic widespread pain, fibromyalgia, and various cancers in remission [104]. Virtually all trials included in the review had certain features in common in their design. Experimental groups were CBTEx, CBT alone, and exercise alone. CBT involved a therapist using a psychoeducational approach to address dysfunctional thoughts and develop coping mechanisms. Exercise involved structured, repetitive movements—

including walking, running, swimming, or strength and flexibility training—that were either done independently or supervised. The control group, if included, was usual care or waitlist, most commonly defined as self-care, pharmacotherapy, and unstructured physical activities. There were no exclusion criteria for treatment duration, but duration was adjusted for during the analysis. Measured outcomes included depression, anxiety, fatigue, and pain. CBTEx leads to significantly greater improvements in depression, anxiety, and fatigue, especially with longer treatment duration. Impacts were greater for fatigue, especially in studies that included more women. However, CBTEx was only as equally effective as CBT or exercise alone in addressing pain intensity.

Similar results were seen when CBT was administered remotely. One RCT involved 442 patients with chronic widespread pain, which included OA and RA [106]. CBT was administered over the phone to evaluate its promise in a setting where in-person CBT was in low supply. Treatment was administered for 6 months and the measured outcome was a seven-point scale of "very much worse" to "very much better" assessed by a combination of questionnaires at 6- and 9-month follow-ups. All experimental groups (tele-CBT, exercise, and CBTEx) lead to significant and comparable improvements 6 months after the treatment ended. The CBTEx group had slightly better outcomes than tele-CBT or exercise alone, but this difference was not statistically significant.

A recent systematic review of 13 RCTs included patients with CLBP [107]. Outcomes of the studies were compared based on whether treatments were stratified depending on a patient's risk of deficits in pain, mood, functional capacity, return time to work, quality of life, and appropriate healthcare consumption. The review found that outcomes were improved and more consistent for patients whose treatment was stratified based on their risk status. Low-risk patients benefited from education alone, medium-risk patients benefited from education with exercise, and high-risk patients benefited from formal CBT with exercise.

It is possible that the specific approach to CBT may significantly impact efficacy of a CBTEx treatment program. A systematic review of 30 RCTs included patients with fibromyalgia [108]. Measured outcomes included pain, disability, and mood, all assessed by a variety of questionnaires and whose values were standardized for comparison. Results among the included trials were mixed in terms of the comparative efficacy of the experimental groups, but CBTEx was most often found to be only equally as effective as CBT or exercise alone. However, improvements decayed more slowly in the CBTEx group for the two trials that utilized a special multimethod approach to CBT (cognitive restructuring, pain-coping skills, problem-solving techniques, goal setting, stress management, education, and relaxation) as opposed to cognitive restructuring and coping mechanisms alone [109, 110].

In some parts of the world, novel techniques for CBT are studied for their impact in chronic pain disorders. In one RCT, 579 patients with CLBP received a form of CBT called the Alexander technique, which involved mindfulness of body movements and bodily self-care during daily activities [111]. CBT_6Ex (six sessions of Alexander technique plus exercise) was as effective as CBT_{24} (24 sessions of Alexander technique) in reducing pain and increasing quality of life, and both experimental groups were significantly more effective than single treatment regimens of exercise, CBT_6, or massage. There was no significant difference in outcomes between subjects receiving CBT_6Ex and $CBT_{24}Ex$.

Nearly every CBTEx study shares similar limitations. One major limitation was that patients among the different experimental groups didn't experience truly discrete treatments. For example, some patients randomized to CBT alone deliberately increased physical activity because of the treatment, thus creating a "contamination effect" and reducing statistical significance seen between combined therapy groups and single therapy groups [104, 106, 108]. Also, the fact that there was an endpoint to treatment and the follow-up times were relatively short likely limited the potential benefit that could have come from a

combined regimen [104, 106, 108]. In addition, many studies had high dropout rates that were most often due to subjects being too busy to participate in both CBT and exercise, limiting study power [104]. A few studies had lower dropout rates, presumably because treatment intensity and frequency were adjusted to each subject's needs and risk level, so it's possible that in most studies inappropriate treatment intensity led to an underestimation of the benefits of CBTEx [107]. The studies of Alexander technique and other novel approaches to chronic pain are difficult to compare to other CBTEx studies because this form of CBT differs greatly from conventional CBT. In fact, Alexander technique may be considered a unique form of CBTEx since it includes mindful practices in active body movements.

Although most of the studies do not definitively show that CBTEx is superior to CBT or exercise alone in treating chronic pain, the study limitations likely blunt potential statistical significance. Individualized approaches to CBTEx might produce better outcomes in chronic pain than a one-size-fits-all model. Notably, the systematic review of stratified treatments found that CBTEx was more likely to produce better outcomes than single regimens alone in patients with higher risk of dysfunction [107]. Finally, almost every study found that even patients who significantly improved during treatment relapsed after the treatment ended, which indicates that a permanent lifestyle change rather than finite treatment may produce longer-sustained improvement [104, 106, 107].

A reasonable recommendation is to assess each patient's level and nature of dysfunction and design an individualized combined regimen compatible with their schedule, striking the balance between CBT and exercise and ensuring long-term follow-up. This is in line with the National Pain Strategy report, which recommends multimodal, interdisciplinary, and individualized management [112]. One RCT in Germany went so far as to administer 5 weeks of inpatient treatment for patients with fibromyalgia to strictly control and individualize an operant behavioral treatment approach and found very clear improvements that were sustained at a 15-month follow-up [113]. Unfortunately, inpatient rehabilitation for chronic pain disorders is not standard in most parts of the world. Nevertheless, it is reassuring that modified approaches to CBT, such as tele-CBT and the Alexander technique, have recently shown promise in treatment of chronic pain disorders. To optimize clinical application of chronic pain treatment, we need further research investigating patient and environmental risk factors for chronic pain, the neurobiochemical basis of both development of and recovery from specific chronic pain disorders, and risk factors for treatment discontinuation.

16.7 Working with Avoidance: Using Exercise as Treatment for Chronic Pain

Life with chronic pain presents daily challenges. The impact of pain is felt physically, emotionally, and socially. For instance, a synthesis of qualitative research described experiences of people living with CLBP as debilitating and undermining the very sense of a secure self, along with associated loss of function, impaired social roles, and stigma felt from family, friends, and healthcare providers [114]. The task of managing pain is not easy, and the way that people interpret their experience usually leads to avoidance or confronting, two very different styles of coping [115]. Individuals who confront the injury and associated pain as surmountable obstacles engage in physical activity sooner. Avoidance may be adaptive in the short run while the acute injury heals, but ultimately pain catastrophizing and fear of activity lead to disuse, deconditioning, and disability [115]. Research shows that fear avoidance beliefs are associated with poor treatment outcome in patients with LBP, leading to more pain and disability, and decreased chances of return to work [116, 117]. Fear avoidance is also responsible for worse than expected muscle strength changes during exercise programs. For example, during targeted exercise programs, changes in knee extension, elbow flexion force, and handgrip force of women with fibromyalgia were

mediated in part by fear avoidance as well as change in pain intensity [118].

Unfortunately, several studies show that people suffering from chronic pain tend to engage in avoidant behaviors and develop fear of physical activity, ultimately leading to higher degree of disability. For example, when levels of physical activity were compared among people with chronic pain with matched controls in South Africa, the chronic pain group performed worse on several objective measures, such as the 6-min walk test, repeated sit-to-stand test, and 7 days of pedometry. The body mass index (BMI) in the chronic pain group was also significantly higher than in the matched controls [119]. In a population-based study, individuals with chronic widespread pain (a symptom of fibromyalgia) were found to have significantly increased odds of reporting less or much less physical activity compared to people their age [120]. Again, this is understandable since vigorous exercise or an increase in physical activity can trigger a symptom exacerbation in fibromyalgia, and the fear of movement that develops in consequence is prevalent in approximately 40% of patients with this condition [121]. And yet, pain is not an unexpected outcome of physical activity. In fact, painful exercises in the management of chronic musculoskeletal pain offer advantage over pain-free exercises in the short term [122].

Avoidance of physical activity and experience of chronic pain perpetuate each other in a pathological, circular relationship unless the cycle is broken somehow. There are several ways in which patients with chronic pain could be moved toward recovery. One of them is exercise itself, as a positive experience of reduced pain and decreased disability during exercise leads to higher levels of self-confidence and improved motivation for physical activity. For example, an RCT of 67 women with fibromyalgia engaged them in progressive resistance exercises performed twice a week for 15 weeks. At the end of the program, participants had significant decreases in pain and decreases in disabilities associated with recreation, social activity, and occupation [123]. Booster sessions with a physiotherapist assisted older people with hip and knee OA to adhere to therapeutic exercise [124]; it should also be noted that older people were more likely to adhere to exercise when in supervised programs [125]. CBT has been found particularly effective among studies that examined patients with musculoskeletal pain and high levels of pain catastrophizing, although multimodal treatment that involved physical and psychological content showed the strongest effects among all available studies [126]. Graded exposure approach, which encourages a confrontation response by exposing patients to situations in which they are fearful during rehabilitation, has been shown to reduce catastrophizing in the short term [127]. Preliminary evidence shows that motivational interventions can help participants adhere to exercise and have a positive effect on long-term exercise behavior as well as reduce levels of activity limitation [128]. Behavioral graded exercise and motivational interventions lead to improvements in exercise adherence in older adults with LBP and/or hip/knee OA [124].

Education gives people a measure of control over their illness, challenges inappropriate beliefs about health and exercise [129], and potentiates compliance with exercise and weight loss programs [130]. Patients must understand and appreciate the complexity of their condition as well as mechanisms involved in the experience of chronic pain to be successful [3]. Importantly, exercise can seem counterintuitive to patients who still perceive pain to be a marker of damage and is unlikely to be helpful unless patients recognize the need to manipulate the brain in addition to tissue or joints to alter the pain experience [13]. Patients should also understand that improvement can be slow; just as the nervous system took time to develop maladaptive functioning, it will take time to reverse these changes and see results.

It's important to pay attention to the pain itself, as demonstrated by a study of 48 obese adults with knee OA. Authors found that pain in the knee joint affected the capacity to walk and perform weight-bearing exercises and, ultimately, adherence to exercise [131]. Not all patients with chronic pain display expected endogenous analgesic response during exercise, which would be expected in normal individuals and in patients

with OA or RA. For example, muscle contractions may result in increased generalized pain sensitivity in fibromyalgia [18]. Although the benefit of exercise in these conditions isn't questionable, appropriate modifications must be made to suit the needs of individuals engaging in exercise depending on their specific limitations and strengths. Some suggestions include setting a low baseline, exercising non-painful parts of the body, monitoring symptom flares, and discussing the content of the exercise protocol with the patient [18]. Tempering the exercise dosage can help minimize pain exacerbations by reducing the chance that exercise stress will induce hyperalgesia [11]. Over time, regular exercise should normalize the analgesia response by increasing endogenous opioids in central inhibitory pathways to reduce pain [2, 19, 132]. Studies have shown that exercise can upregulate endogenous opioids in the brain to reverse pain perception in areas involved in pain processing [14, 19].

For obese patients with chronic pain, adherence to exercise may be enhanced with modifications to exercise such as the accumulation of several exercise bouts rather than one long session, reducing joint range of motion, and using nonimpact rather than impact activities, to minimize their discomfort [133].

Another concept of importance is recovery from stress, which includes exercise. Strategies for sufficient recovery, including appropriate duration of time to recover, must be employed when working with any human engaging in exercise and especially in patients with chronic pain who are more vulnerable to the effects of stress, physical and emotional [19]. It is suggested that patients with chronic pain could use multiple and long recovery breaks in between exercises [18]. Exercise regimen and intensity must account for chronic medical illnesses, in addition to those that confer pain as a symptom, for example, patients with osteoporosis should avoid bending and rotation of the trunk which could be harmful and aggravate back pain [134].

16.8 Conclusion and Recommendations

- Exercise has a distinct place in the multimodal treatment of most conditions associated with chronic pain, even if direct benefits of exercise may be small. Indirect benefits of exercise such as cardiovascular fitness, healthy BMI, and a sense of well-being are significant contributors to reduced disability in a variety of diseases, including those associated with chronic pain.
- Any exercise program for chronic pain should begin with an individual assessment of the patient's overall health and fitness. Each exercise prescription should include the mode, intensity, and duration of exercise session, frequency of exercise, and increase in level of activity during training. In general, exercise must target flexibility, muscle strength, core stability, cardiovascular fitness, and gait steadiness [134].
- During exercise, individuals with more distress, fear-avoidance, catastrophizing, low mood, and low self-efficacy will benefit from higher levels of supervision [20]. Reassurance that tissues are structurally sound can be helpful, and de-emphasizing pain assessments can reduce unhealthy hypervigilance [20]. Regular follow-up with attention to problem-solving, goal-setting, and rewards for achievements can promote success [12].
- A written exercise prescription can be more effective than a verbal exercise prescription [135]. Each program must include education, including the discussion of the need for lifelong exercise program. People are more likely to adhere to a rehabilitation or exercise program when they're provided with supplementary printed material, supervision, motivation strategies, clinic attendance, positive reinforcement, and goal-setting [136].
- Patients should have as much control as possible in choosing their exercise mode. People are more likely to participate in exercise program designed with consideration of their

circumstances, fitness levels, and exercise experiences [137].

- Individually tailored CBT that assesses and addresses individual's beliefs around pain and physical activity, combined with exercise training, is a promising strategy in patients with fibromyalgia and likely with other chronic pain conditions. If CBTEx is not feasible due to the challenge of time commitment, exercise alone is a strong choice.
- Any amount of movement is preferable to none. Low-intensity programs that progress slowly yield better adherence and outcomes.
- Exercise shouldn't replace pharmacological, surgical, or other nonpharmacological treatment modalities where available and indicated.
- Ultimately, a variety of interventions to decrease avoidance and improve adherence to exercise could be utilized, although the effects of these interventions measured across studies are small. Further research in this area is desperately needed [138].

Competing Financial Interests The authors declare no competing financial interests.

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Exercise and Muscle Atrophy

17

Nana He and Honghua Ye

Abstract

The incidence of muscle atrophy is increasing with each passing year, which imposes a huge burden on the quality of life of patients. It is a public health issue that causes a growing concern around the world. Exercise is one of the key strategies to prevent and treat various diseases. Appropriate exercise is conducive to compensatory muscle hypertrophy, to improve muscle strength and elasticity, and to train muscle coordination, which is also beneficial to the recovery of skeletal muscle function and the regeneration of muscle cells. Sequelae of paralysis of patients with limb dyskinesia caused by muscle atrophy will be significantly alleviated after regular exercise therapy. Furthermore, exercise therapy can slow down or even reverse muscle atrophy. This article aims to introduce the characteristics of muscle atrophy and summarize the role and mechanism of exercise in the treatment of muscle atrophy in the existing studies, in order to further explore the mechanism of exercise to protect muscle atrophy and provide protection for patients with muscular atrophy.

Keywords

Muscle · Atrophy · Exercise · Strength

17.1 Introduction

17.1.1 Muscle

Muscle is an important part of the human skeletal system. The various activities of the human body are driven by the contraction of muscles, pulling the bone lever to move around the joint hub. Human muscles are mainly composed of muscle tissue, and the constituent units of muscle tissue are specially differentiated muscle cells. These muscle cells are slender and appear in a fibrous shape; therefore, muscle cells are often called muscle fibers [1]. According to the morphology, the muscle tissue of the human body can be divided into long muscle, short muscle, platysma, and orbicular muscle; and according to the structure and function, it can be divided into three

N. He
Department of Cardiology, Huamei Hospital, (previously named Ningbo No. 2 Hospital), University of Chinese Academy of Sciences, Ningbo, China

Department of Experimental Medical Science, HwaMei Hospital, University of Chinese Academy of Sciences, Ningbo, China

Key Laboratory of Diagnosis and Treatment of Digestive System Tumors of Zhejiang Province, Ningbo, China

H. Ye (✉)
Department of Cardiology, Huamei Hospital, (previously named Ningbo No. 2 Hospital), University of Chinese Academy of Sciences, Ningbo, China

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_17

categories: smooth muscle, skeletal muscle, and myocardium [2]. Among them, the smooth muscle and myocardium do not contract under conscious control, so they are also called involuntary muscle, while skeletal muscle contraction is rapid, powerful, and easy to fatigue and can contract with conscious control, so it is called voluntary muscle. Smooth muscle is mainly involved in the construction of the viscera and blood vessel, which has the characteristics of slow contraction, long lasting, and not easy to fatigue; myocardium is mainly involved in the formation of ventricular wall; the skeletal muscle is distributed in the head, neck, trunk, and limbs and usually attached to the bone [3–5]. Observing the skeletal muscle under the microscope, it can be found that it is composed of slender cylindrical striated muscle cells, so it is also called striated muscle. Skeletal muscle fibers are composed of cell membrane, nucleus, mitochondria, myofibrils, sarcoplasm, and its inclusions. A variety of regularly ordered protein filaments present in myofibrils are the primary structures for muscle contraction and relaxation. There is a thin connective tissue membrane outside the muscle fibers, and the muscle fibers are bundled into bundles, which are also surrounded by the fascia. Some muscle bundles are wrapped by the outermost fascia to form a whole muscle. The muscle spans one or more joints and attaches to different positions of the bones on both sides of the joint through the tendon or directly to the bone. Skeletal muscle is the motive force of the motor system. Under the control of the nervous system, the skeletal muscle contracts and drives the bone actions. There are more than 600 pieces of human skeletal muscle, which are widely distributed in the human body, accounting for about 40% of the total body weight. Regardless of its size, each skeletal muscle has a certain shape, structure, position, and auxiliary devices, there are abundant blood vessels and lymphatic vessels distributed around it, and it is dominated by nerves. Therefore, each skeletal muscle can be regarded as an individual organ [6–10].

17.1.2 Muscle Strength

Muscle contraction requires energy from the body, and any part of the excitation-contraction coupling can affect muscle activity. The main factors affecting muscle activity are the cross-bridge binding number and the ATPase activity of myosin. The number of the cross-bridge binding is related to muscle strength, and myosin ATPase activity is related to the rate of contraction. The ability of the body to overcome and resist resistance during muscle contraction is measured by muscle strength, which is the essential element affecting the human motor ability. The improvement and development of muscle strength is based on the changes in the shape, structure, function, and physiological and biochemical mechanisms of human muscles and is the result of conditional reflexes established on the premise of full coordination of the excitation and inhibition processes of the nerve center. The strength of the human muscle is restricted by various factors such as development level, gender, body type, muscle structure, characteristics, physiology, biochemistry, and training [11–13].

Muscle strength is determined by the proportion of fast twitch (FT) muscle fibers and slow twitch (ST) muscle fibers. Compared with ST, FT muscle fiber has higher ATPase activity, and its ability to decompose ATP is stronger. When stimulated, the releases rate of Ca^{2+} in FT sarcoplasmic reticulum is more fast than ST. Thus causes more contractile strength [14]. Muscle strength increases with age. In human childhood, water is the major component of muscle tissue. At this stage, the content of protein, fat, and inorganic salts in the muscle tissue is less, so the storage capacity of the muscles is poor and the contraction ability of the muscle is weak. In the adolescence, a great deal of protein and fat are synthesized in the muscle. With the increase of height, the bone grows rapidly. At this time, the development of the muscle is mainly depending on the increase of length. When the growth of the height gradually slows down and tends to be stable, the muscle begins to undergo changes such as muscle fiber thickening, cross-sectional enlargement, and muscle strength increase [15]. Studies

have shown that men usually reach maximum muscle strength at the age of 25, while women usually reach that at the age of 22 years old. Since then, the muscle strength will be maintained to 40–50 years old. After the age of 50, the muscle strength will decline rapidly and decrease by about 12% every 10 years. Although the mechanism of this decline in muscle strength due to aging has not been clarified, studies have suggested that muscle volume also decreases with age, and this process may involve the reduction of the activation of intermediate factors in primary myoblasts, the slowdown of muscle protein synthesis, the inhibition of enzyme activity, and the changes of energy storage systems and mitochondrial function [16–20].

17.1.3 Muscle Atrophy

Muscle atrophy refers to the limitation or extensive reduction of muscle volume in the muscles or imaging findings compared with the same age or their own state or the reduction of the number of muscle fibers or the diameter of the muscles under the microscope, which is a process of loss of muscle mass and strength closely related to age as well as is a normal physiological response to muscle lack of load [21]. Muscle atrophy can be diagnosed when the diameter of muscle fibers in adult males is less than 35 μm or in adult females is less than 28 μm. Muscle atrophy includes two kinds of conditions: dysplasia of muscle fibers and diminution of muscle fibers after normal development [22]. Muscle atrophy is more common in nonphysiological conditions such as fasting, cancer, diabetes, sepsis, and chronic renal failure. According to the primary lesions, muscle atrophy is clinically divided into three categories: neurogenic muscle atrophy, myogenic muscle atrophy, and disuse muscle atrophy.

17.1.3.1 Neurogenic Muscle Atrophy

Neurogenic muscle atrophy is caused by upper and lower motor neurons and peripheral neuropathy innervating muscles. The damaged areas include the brainstem motor nucleus, anterior horn cells of the spinal cord, nerve roots or nerve trunks, and peripheral nerves. The clinical manifestations of this disease are diverse, but it is characterized by fascicular atrophy, loss of transverse muscle, and mild necrosis of muscle fibers on muscle biopsy [23, 24]. Clinical diagnosis is usually performed by typical clinical symptoms, electromyography, and muscle biopsy. Guillain-Barre syndrome is an inflammatory neuropathy that mainly affects the motor nerves of the spinal and cranial nerves; it is mainly characterized by symmetrical flaccid limb paralysis and facial paralysis, disappearance of tendinous reflect, and peripheral sensory disturbances [25]; systemic muscular atrophy will occur after a certain period of development [26]; chronic inflammatory demyelinating polyneuropathy also has limb weakness and diffuse muscular atrophy [27]; the most common cause of muscular atrophy in distal extremities is peripheral nerve damage; amyotrophic lateral sclerosis (ALS) occurs mostly in adults, the disease invades the upper motor neuron and the lower motor neuron, and some patients develop asymmetrical muscle atrophy and muscle weakness at the distal end of the limb, which gradually progress to systemic muscle atrophy, accompanied by extensive fascicular fibrillation [28, 29]. In addition, denervation and recovery of innervation, motor unit remodeling, and loss occur during skeletal muscle aging. This age-related motor unit remodeling involves the denervation of fast muscle fibers and the axons innervating slow muscle fibers to restore nerve innervation, while denervation leads to a significant decrease in the expression of the dihydropyridine receptor (DHPR) and the ryanodine receptor (RyR1). These changes lead to changes in the efficiency of excitation-contraction coupling, which induces a decrease in muscle mass, strength, and endurance [30–32].

17.1.3.2 Myogenic Muscle Atrophy

Myogenic muscular atrophy, which occurs mostly in nonphysiological conditions, is caused by muscular diseases including muscular dystrophy (MD), polymyositis, dermatomyositis, metabolic myopathy, congenital myopathy, myotonia, and so on [33, 34]. MD belongs to X-linked recessive inherited myopathy, and its pathogenesis is related

to the mutation of dystrophin gene and the loss of protein. Defects of this gene will cause dysfunction of myocyte membranes and induce a large amount of free calcium ions and high concentrations of extracellular fluid into the muscle fibers and then induce protein release and complement activation in myocytes, leading to myofibrillar rupture, necrosis, and muscle atrophy. The larger the fragment of the gene deletion, the more serious the disease is [35, 36]. Polymyositis and dermatomyositis are systemic connective tissue diseases that are mainly characterized by inflammation and degeneration of muscle tissue; they often lead to symmetrical muscle strength weakening and muscle atrophy, which are associated with humoral immunity and cellular immunity. Most patients begin with musculoskeletal symptoms; antinuclear antibodies and Jo-1 antibodies can be detected in the serum of some patients, and at the same time, activated T-lymphocyte infiltration in muscle fibers can be detected by muscle biopsy [37, 38]. Metabolic myopathy is a clinical manifestation characterized by repeated muscle weakness and exercise intolerance due to abnormal metabolism of sugar and fat and mitochondrial metabolic disorder. It can be divided into two categories according to the etiology: one is muscle damage caused by endocrine dysfunction such as pituitary gland, thyroid gland, parathyroid gland, and adrenal gland; the other is muscle damage caused by primary inherited metabolic abnormality, including sugar, nucleotide, and lipid metabolism disorders and mitochondrial abnormalities [39–41]. Myotonia syndrome (myotonic myopathies, MM) is a group of hereditary channel disorder characterized by delayed relaxation of skeletal muscle., It is caused by mutations in primary or secondary ion channel proteins. The clinical manifestations of MM include muscle stiffness, muscle atrophy, and muscle weakness; electrophysiology is a typical myotonic potential with or without myopathy potential. According to clinical symptoms, it can be divided into dystrophic myotonia (DM) and non-dystrophic myotonias (NDMs) [42, 43].

17.1.3.3 Disuse Muscle Atrophy

The skeletal muscle has the characteristics of rapid adaptation to external environment changes. When it is under the condition of hypokinesia, external force braking, long-term bed rest, or weightlessness, the body will undergo a typical "use and disuse" change-disuse muscle atrophy. Disuse muscle atrophy is characterized by disorder of the rhabdomyotrophus and thinning of muscle fibers. The main reason for which is the decrease of protein synthesis rate and the increase of protein decomposition rate in the muscle tissue, that is, the body tissue nutrient is redistributed according to the needs of limbs. Clinically, paralysis, muscle strain, postfracture fixation, and long-term weightlessness of astronauts in outer space can cause this pathological condition. Therefore, effective postponement and treatment of disuse muscle atrophy need to be studied and solved in the fields of clinical medicine, sports medicine, rehabilitation medicine, and aerospace medicine and have been receiving widespread attention [44, 45].

The most direct change in muscle structure under disuse state is muscle atrophy, which is manifested by a decrease in muscle volume, a shortening of muscle fiber diameter, and a reduction in muscle mass [46]. In addition, the pathological process of the disease is accompanied by changes in the type of muscle fibers, that is, the number of fast muscle fibers (type II) and mixed muscle fibers gradually increased but the number of slow muscle fibers (type I) gradually decreased while the total number of muscle fibers remained unchanged. Studies have shown that this change mainly occurs in the type I fibers of the antigravity muscles (such as soleus muscle), but not in the gastrocnemius and extensor digitorum longus muscles [47]. After 3 weeks of hind limb unloading in rats, type I muscle fibers in the soleus muscle decreased by 33%, while type II muscle fibers increased by 188%, and the mixed muscle fibers increased by 61% [48]. The ultrastructure of muscle fibers also changes in the disused state. A biopsy of the astronaut's soleus muscle for 17 days of space flight revealed no significant changes in the density and spacing of the thick filaments, while the density of the thin filaments decreased by 26%. The reduction in the density

of the thin filaments promotes the separation of the transverse bridges in the initial state, thereby accelerating the contraction rate of the muscles. These changes increase the strength of each thin filament by 23%, and the atrophic muscle fibers are more susceptible to sarcomere damage during reloading [49]. The ubiquitin-proteasome pathway is the main pathway of protein decomposition in the disused state. Firstly, with the participation of ATP, ubiquitin binds to the protein through ubiquitin activating enzyme and ligase; then the protein bound to ubiquitin is combined with protease and degraded by enzyme catalysis; finally, ubiquitin is separated from protein and enters recycling. It can be seen that the protein can be decomposed only after binding to ubiquitin. The expression levels of ubiquitin protein ligase Muscle Ring Finger 1 (MuRF1) and Atrophy F-box (MAFbx), which reflect the degree of protein decomposition, increased in disused muscle atrophy. Relevant experiments have shown that the reduction of afferent impulses of muscle spindle is also closely related to the occurrence of disuse muscle atrophy. Continuous vibration can excite the muscle spindle, and the increased afferent activity of the muscle spindle can enhance the electromyographic activity of skeletal muscle and effectively counteract muscle atrophy. There is a close relationship between nerve impulse and muscle atrophy; specific nerve impulse can prevent muscle atrophy [50].

17.2 Exercise Benefits to Muscle

Muscle trophic factors existing in the muscle can regulate the normal division, differentiation, and maturation of muscle cells and maintain normal morphology and function of muscle cells [51]. Muscle trophic factors are mainly divided into two major categories: growth factors and hormones, of which growth factors include:

1. Insulin-like growth factor (IGF). IGFs are highly expressed in the skeletal muscle, which promotes the proliferation of skeletal muscle cells and further induces the differentiation of muscle cells [52, 53]. IGF can enhance amino acid and glucose transport between skeletal muscle cells, increase blood supply of skeletal muscle, stimulate myoprotein synthesis, and block myoprotein decomposition to accelerate muscle tissue renewal [54]. IGFs play an indirect role in muscle nutrition through the IGF-neuromuscular pathway and regulate muscle growth caused by various stimuli in an autocrine or paracrine manner [55].
2. Fibroblast growth factor (FGF). FGF exists in the extracellular matrix of damaged muscle tissue and malnourished mouse muscle and has different distribution in the deformed and regenerated areas of striated muscle. The expression of FGFs in the proliferating muscle cells is increased, while the expression of FGFs is decreased during the differentiation in muscle cells [56–58].
3. Ciliary neurotrophic factor (CNTF). CNTF maintains the morphology and function of normal skeletal muscle through direct and indirect nutrient effects on muscles and participates in the repair of neuromuscular injuries [59, 60].

In addition, growth factors such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF), macrophage colony-stimulating factor (M-CSF), and transferrin (Tf) have muscular nutritional effects [55]. Hormone muscular nutrition factors include:

1. Growth hormone (GH): GH participates in the regulation of body growth by promoting muscle protein synthesis, thereby increasing muscle volume and strength, and improving muscle function [61, 62].
2. Insulin: insulin can promote muscle protein synthesis, which is mainly achieved by accelerating the translation of protein synthesis in fast muscle fibers [63, 64].
3. Adrenocorticotropin (ACTH): ACTH can act as a precursor of melanocortin (MSH) to synthesize MSH, which is beneficial to accelerate the neuromuscular development and promote the maturation of nerves and muscles. Under the condition of peripheral nerve injury or pathological, MSH can effectively

promote nerve regeneration and muscle nerve reinnervation [65, 66].

Exercise, as a special kind of stress, can effectively promote the secretion of IGF in the muscle tissue. The increased level of IGF stimulates compensatory hypertrophy of the muscle tissue, resulting in a significant increase in muscle weight, and the number of DNA in hypertrophic muscle increases with the improvement of IGF level [67–70]. Research have shown that an increase in GH level can be observed after 10 min of exercise, and exercise-induced GH increases to a peak around 30 min after exercise, while exercise intensity significantly affects the change in GH level [71–73]. Moderate- and high-intensity push-pull can increase the expression of bFGF in hippocampal neurons of rats [74, 75]. The expression of serum insulin decreases significantly after acute exercise. The mechanism of this change may be that exercise induces blood sugar consumption and stimulates the sympathetic-adrenal system, thereby inhibiting insulin secretion. Reasonable exercise can improve insulin secretion and maintain blood sugar stability [76, 77]. Numerous studies have shown that exercise is conducive to promoting the synthesis and release of muscle nutrient factors, which have proved to be of great clinical value and have been extensively tested in clinical treatment of ALS, muscle dysfunction, and degenerative diseases. Therefore, exercise has important benefits for muscles.

17.3 Exercise Against Muscle Atrophy

Regular exercise helps to improve the adaptability of the skeletal muscle and make it more efficient to synthesize ATP by using intracellular energy substances, thus enhancing the persistence of muscle against fatigue [78]. Long-term exercise training can increase the expression of glucose transporter type 4 (GLUT-4), thereby increasing the activity of mitochondrial enzymes and changing the type of muscle fibers [79, 80]. Exercise and mechanical stimulation are the main ways to improve muscle atrophy at present. Exercise promotes active contraction of the muscle, which causes skeletal muscle hypertrophy to prevent muscle atrophy.

The imbalance of protein metabolism is a typical change of muscle atrophy, which is closely related to ubiquitin-proteasome in the muscle. The ubiquitin ligase MAFbx and MuRF1 are key factors related to muscle atrophy, and their expression has been found to increase in various muscle atrophy models [35, 81–84]. Overexpression of heat shock proteins 70 (HSP70) can inhibit the transcriptional activity of nuclear factor-kappa B (NF-kB) and the activity of MAFbx and MuRF1 promoters, thereby inhibiting the degradation of skeletal muscle proteins and regulating muscle atrophy [85, 86]. The expression of HSP70 is significantly decreased in various muscular atrophy models; HSP70 may be involved in protein degradation and muscular atrophy induced by various conditions as a regulatory protein [87–89]. At the same time, ROS is the main inducement of aging skeletal muscle atrophy, and ROS can activate caspase-9 to form a cascade amplification reaction, which induces skeletal muscle cell apoptosis and leads to skeletal muscle atrophy [90, 91]. Studies have shown that long-term endurance exercise can enhance the degradation of metabolites by autophagy, reduce the accumulation of metabolites in cells, inhibit the production of ROS, and ultimately inhibit skeletal muscle atrophy [92]. Aerobic exercise has also been demonstrated to inhibit the apoptosis of skeletal muscle cells and promote the synthesis of skeletal muscle type IIb fiber, which in turn causes muscle hypertrophy and enhances the mass and strength of skeletal muscle [93].

After the age of 50, the muscle strength of the human body decreases at a rate of 1–2% per year, while it decreases by 3% every year after the age of 60 [94]. A cross-sectional study in the United States showed that the male muscle atrophy rate was 75.5% and the female muscle atrophy rate was 35.4% in the 60-year-old population, and the older the age, the higher the incidence [95, 96]. The damage of muscle satellite cells, decreased number and volume of muscle fibers (especially type II muscle fibers), decreased spontaneous physical activity, and decreased mitochondrial

function of skeletal muscle during aging are closely related to lipid metabolism disorder and insulin resistance [97–99]. Proper exercise can improve or even reverse the mitochondrial reduction in aging skeletal muscle and improve the age-related decline in skeletal muscle mass [100]. Endurance exercise, also known as aerobic exercise, is the most basic and leading exercise prescription. In the study of the elderly and rodents, endurance exercise has been proven to be effective in enhancing the enzyme activity, quantity, and function of skeletal muscle mitochondria in the aging organism and improving the antioxidant capacity of muscle in the elderly [101]. Resistance exercise is a kind of exercise which mainly develops muscle strength; it is characterized by high intensity and short time and belongs to anaerobic metabolism. In another study, the decline of mitochondrial function in the skeletal muscle of normal aging individuals was partially reversed after 6 months of resistance exercise training. Resistance exercise can activate mTOR signaling pathway in the muscle tissue, increase muscle sensitivity to amino acids, promote muscle protein synthesis, activate muscle satellite cells and promote their proliferation and differentiation, induce mitochondrial purine nucleotide transport proteins, and regulate mitochondrial oxygen consumption and aerobic capacity. Therefore, resistance exercise is considered to induce muscle hypertrophy, reduce the rate of mitochondrial DNA deletion mutation in aged muscle, reverse the decline of aging muscle mass, and enhance mitochondrial gene expression level and mitochondrial enzyme activity [102–105]. Patients with end-stage renal failure undergoing hemodialysis are often accompanied by muscle atrophy, which is marked by a significant decrease in the area of type II muscle fibers [106, 107]. The area of type I fibers and type II fibers increased by 26% and 51%, respectively, after 6 months of exercise training, and the atrophic muscle fibers were improved significantly [108]. In type 2 diabetes mellitus (T2DM) patients, the phosphorylation of eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) in the muscle decreased the response to protein and insulin, while ubiquitin-protease binding increased in vivo, resulting in a decrease in muscle protein synthesis. After resistance training, the levels of TNFα and IL-6 in the muscles of patients were decreased, muscle inflammation was alleviated, and muscle strength was improved. Resistance training also increased the CSA of type I and type II muscle fibers of the lateral femur by 18–21% [109–113]. In the case of cachexia such as tumors, muscle strength and quality are significantly impaired, and some patients may undergo muscle atrophy.

The anti-inflammatory effect of exercise has been confirmed clinically. IL-6 is a key pro-inflammatory cytokine in the occurrence and development of cachexia, and combined erythropoietin and exercise training have been confirmed to reduce the IL-6 level in cachexia patients' body [114–117]. During the treatment of tumors, side effects of drugs also include muscle atrophy. A study pointed out that in cisplatin-induced muscle atrophy rat models, treadmill exercise of 20 min per day for 9 days can help muscle fibers in quadriceps femoris and gastrocnemius to become thinner and reduce the expression of MuRF1 and Atrogin-1, which ultimately improved cisplatin-induced muscle atrophy [118]. In the rat model of skeletal muscle atrophy induced by myocardial infarction, the researchers trained rats for 8 weeks with inactivity and interval exercise training (IET). The results showed that IET could protect cell apoptosis and promote cell proliferation. Compared with the non-exercise group, the weight of gastrocnemius and the length of gastrocnemius/tibia increased in IET group, and IET promoted the expression of α-actin and α-myosin in gastrocnemius muscle, suggesting that IET could reverse MI-induced skeletal muscle atrophy. This effect may be achieved by increasing the expression of LIF/LIFR and activating STAT3 in gastrocnemius muscle [119, 120]. Resistance exercise could effectively improve muscle atrophy of quadriceps femoris and triceps brachii caused by bed rest for 29 days [121]. Animal experiments also showed that aerobic exercise could alleviate muscle atrophy in simulated weightlessness rats [122], and aerobic exercise has better inhibition on proteasome activity of skeletal muscle than drug therapy, which can effectively reduce the activity of ubiquitin-proteasome system and improve skeletal muscle atrophy in patients with heart failure [123]. Similarly, individualized

exercise prescriptions have also been found to be useful in preventing and treating glucocorticoid-induced muscle atrophy, but the mechanism of exercise-mediated anti-muscle atrophy remains to be further explored [124].

Exercise against muscle atrophy was also found to be associated with microRNAs (miRNAs). After 6 h of resistance exercise or 1 h of bicycle exercise, the expression of miR-1 in the muscle tissue was increased. The increased miR-1 promotes protein synthesis in the skeletal muscle by activating the IGF-1/Akt signaling pathway and promoted skeletal muscle hypertrophy [125, 126]. In a 12-week resistance exercise study, the increased muscle synthesis was accompanied by increased expression of miR-378, which influenced mediator complex subunit 13 (MED13) and carnitine acetyltransferase (CRAT) by regulating mediator complex subunit 13 (MED13) and carnitine acetyltransferase (CRAT), thereby destroying mitochondrial metabolism [127, 128]. The expression of miR-696 was significantly decreased in the gastrocnemius muscle of mice after endurance exercise for 4 weeks. This change resulted in an increase in the expression of transcription activator PGC-1α in muscle tissue, which is involved in regulating the biological function of skeletal muscle and inhibiting muscle atrophy [129–131]. In addition, the overexpression of miR-410 and miR-433 contributed to the improvement of muscle atrophy in MEF2A knockout mice [132]. Overexpression of miR-486 could reduce the high expression of Atrogin-1 and MuRF1 in atrophic muscles of mice with chronic kidney disease [133]. In view of the therapeutic effect of exercise and the regulatory effect of miRNAs on muscular atrophy, the mechanism of exercise-mediated miRNAs in muscle atrophy needs to be further explored.

17.4 Prospect

In 1969, the World Health Organization officially used the term “exercise prescription” in order to embody the principle of individualization in formulate of appropriate exercise types, time, frequency, indications, and contraindications according to the actual situation and needs of the individual, so as to exercise in a planned way that achieves the purpose of treatment [134, 135]. Exercise is an important means of rehabilitation therapy; aerobic exercise can enhance the blood flow of the body, reduce peripheral vascular resistance and blood pressure, and increase the number of capillaries, mitochondrial density, and oxidase in the metabolic chain, thus providing sufficient oxygen and nutrients for human muscles and promoting the elimination of metabolites. It is conducive to the recovery of various functions of patients, speeds up the recovery of diseases, and has a good rehabilitation effect on the nervous system, cardiovascular system, respiratory system, bone and joint system, and so on [136, 137]. Moderate exercise is one of the internationally recognized gold standards for the treatment of diabetes; exercise can improve the sensitivity of diabetic patients to insulin and the utilization of glucose in vivo, improve lipid metabolism, control body weight, and help prevent complications [138, 139]. The change of muscle strength is of great significance in the course of knee osteoarthritis; exercise therapy can enhance muscle strength and improve the stability of knee joint, so it can be used in the treatment of knee arthritis [140]. Exercise therapy is also the most effective and basic method to prevent and treat osteoporosis; exercise can improve bone density and promote bone formation by enhancing the secretion of sex hormones and the absorption of calcium, increasing blood flow of the cortical bone and muscle strength [141, 142]. Exercise also has a significant effect on various diseases such as chronic obstructive pulmonary diseases (COPD), stroke, hypertension, spondylolisthesis, and other diseases. In recent years, the relationship between exercise and muscle atrophy has been confirmed in numerous animal models and clinical trials, and more and more exercise prescriptions have been used in the clinical treatment of muscle atrophy and have achieved the outcome of improving or even reversing muscle atrophy. The molecular mechanisms of the regulation of exercise on muscle atrophy are continuously being clarified, and ubiquitin-proteasome is involved in the regulation of muscle atrophy, in which MAFbx and MuRF1 are the key factors; HSP70 and NF-kB also play indispensable roles in this process. In

addition, exercise exerts an inhibitory effect on skeletal muscle atrophy by reducing the production of ROS and promoting the degradation of metabolites by autophagy. However, the current understanding of the molecular mechanism of exercise inhibiting muscle atrophy is only the tip of the iceberg, which still needs further in-depth exploration and comprehensive interpretation.

Acknowledgment This work was supported by Ningbo Medical Science and Technology Project, (2016Z01), Ningbo Health Branding Subject Fund (PPXK2018-01), and Ningbo Huamei Research Fund (2017HMKY04).

Competing Financial Interests The authors declare no competing financial interests.

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Part VI

Exercise and Neurological and Psychiatric Diseases

Exercise and Depressive Disorder

18

Javier Bueno-Antequera
and Diego Munguía-Izquierdo

Abstract

Depression is a psychiatric disorder characterized by low mood, loss of interest/enjoyment, and reduced energy and one of the five leading causes of disability and a major contributor to all-cause mortality worldwide. People with depression have, between others, a reduced life expectancy, worse quality of life and cardiorespiratory fitness, and increased risk of type 2 diabetes, compared to the general population. Furthermore, the economic burden of mental disorders including depression is evident, and it is expected to increase to more than double by 2030. Therefore, reducing the growing burden of mental disorders such as depression should be a health priority. Improved prevention and treatment are two key factors that may reduce the burden of depression. Pharmacological- and psychotherapy-based interventions have been traditionally considered for treating depression disorders; however, there is an increasing amount of scientific evidence confirming that physical activity and physical exercise should be highly considered in prevention and treatment of depressive disorders. In this chapter, we aim to summarize and discuss the research progress of physical activity and exercise in prevention and treatment of depressive disorder. Specifically, we summarized and discussed the research progress of the prognostic use of physical activity for incident depression, the importance of sedentary behavior and other outcomes typically improved by physical activity/exercise such as cardiorespiratory fitness for future depression, the research progress of the evidence of the benefits of exercise in people with depression disorders, the resistance training effects in adults and older adults with depression, and the recommendations for the prescription of exercise for people with depression.

Keywords

Depression · Depressive symptoms · Physical activity · Sedentary lifestyle · Physical fitness · Exercise

J. Bueno-Antequera
Physical Performance Sports Research Center, Department of Sports and Computer Science, Section of Physical Education and Sports, Faculty of Sports Sciences, Universidad Pablo de Olavide, Seville, Spain

Research group in development Movimiento Humano, Universidad de Zaragoza, Zaragoza, Spain

D. Munguía-Izquierdo (✉)
Physical Performance Sports Research Center, Department of Sports and Computer Science, Section of Physical Education and Sports, Faculty of Sports Sciences, Universidad Pablo de Olavide, Seville, Spain

Research group in development Movimiento Humano, Universidad de Zaragoza, Zaragoza, Spain

Biomedical Research Networking Center on Frailty and Healthy Aging, Madrid, Spain
e-mail: dmunizq@upo.es

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_18

18.1 Introduction

Depression is a psychiatric disorder characterized by low mood, loss of interest and enjoyment, and reduced energy [1]. Secondary symptoms include impairments in concentration, attention, self-esteem, self-confidence, sleep, and appetite and further include ideas of guilt and unworthiness, pessimism, and ideas or acts of self-harm or suicide [1]. Overall, these symptoms result in serious functional impairment, which substantially interferes with or limits major life activities [2].

Depression is one of the five leading causes of disability [3] and a major contributor to all-cause mortality worldwide [4]. Compared to the general population, people with depression have a reduced life expectancy [4] (with cardiovascular disease being the main contributor [5]), a worse quality of life [6] and cardiorespiratory fitness [7] (defined as to the capacity of the cardiovascular and respiratory systems to supply oxygen to skeletal muscles during sustained exercise [8]), an increased risk of type 2 diabetes [9], an increased risk of metabolic syndrome, an increased risk of hyperglycemia and hypertriglyceridemia [10], a lower serum low-density lipoprotein level [11], an increased risk of hypertension [12], an increased risk of alcohol use disorders [13], and an increased risk of smoking initiation [14]. The global economic burden of mental disorders in 2010 was comparable to that of cardiovascular diseases and was higher than that of cancer, chronic respiratory diseases, and diabetes; it is expected to more than double by 2030 [15]. Therefore, reducing the growing burden of mental disorders such as depression is a global health priority [16].

Pharmacological- and psychotherapy-based interventions have traditionally been considered for treating depression disorders. However, increasing scientific evidence [17–21] confirms that physical activity (defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" [22]) and physical exercise (defined as "a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness" [22]) should be strongly considered for the prevention and treatment of mental disorders such as depressive disorders. These patients have lower levels of physical activity and higher levels of sedentary behavior (defined as "any waking activity characterized by energy expenditure ≤1.5 metabolic equivalents while in a sitting or reclining posture" [23]) compared to the general population [24]. In this chapter, we aim to summarize the research progress of physical activity and physical exercise in the prevention and treatment of depressive disorder.

18.2 Physical Activity and Physical Exercise for the Prevention of Depression

There is ample evidence that physical activity is protective against the onset of depression. One highly cited study on this topic was the systematic review published in 2008 by M Teychenne, K Ball, and J Salmon [25] that examined the association between physical activity and depression. Their evidence suggests that even low doses of physical activity may be protective against depression. Further, vigorous physical activity was more strongly associated with a decreased likelihood of depression than lower intensity physical activity. However, these findings should be interpreted cautiously because of the inclusion of studies conducted in healthy adults and in people experiencing depressive symptoms or clinical depression.

In 2013, G Mammen and G Faulkner [26] published an extended version of the M Teychenne, K Ball, and J Salmon [25], providing updated evidence focusing mainly on longitudinal studies and including study quality assessments. All of the studies included for analysis comprised non-clinical populations, ranging in age from 11 to 100 years, and the majority (25 out of 30 studies) showed that physical activity was negatively associated with the likelihood of future depression. Of interest, of the studies that found a protective role, most were considered to be of modest (n = 6) or high (n = 17) methodologic quality. The authors

also examined the amount of physical activity required to prevent depression and found promising evidence that any level of physical activity, including low levels, can prevent future depression.

Although helpful, both of the aforementioned systemic reviews [25, 26] did not conduct a meta-analysis to study the magnitude of the protective role of physical activity. In this regard, FB Schuch, D Vancampfort, J Firth, S Rosenbaum, PB Ward, ES Silva, M Hallgren, A Ponce De Leon, AL Dunn, AC Deslandes, et al. [27] published a meta-analysis to examine the relationship between physical activity and incident depression in the *American Journal of Psychiatry*, one of the five most impactful scientific journals in the area of psychiatry since 1997. The work included prospective cohort studies evaluating incident depression in participants who were free of depression or depressive symptoms at baseline, searching from database inception through October 18, 2017. The authors found that across 49 studies, higher levels of physical activity were consistently associated with a decreased risk of developing depression in the future. The protective effects of physical activity were observed regardless of age (adolescents, working-age adults, elderly individuals), and sex, and this finding was robust across geographical regions around the world. Regarding dose-response, a higher frequency and intensity of physical activity provided protective effects for incident depression in some but not in all analyses. Additionally, completing the *World Health Organization* recommended physical activity levels (≥150 min weekly of moderate to vigorous physical activity) was protective for incident depression in all adjusted analyses. Despite the robustness of the findings, the authors called for caution when interpreting the results and stated that further studies were warranted. The authors also claimed that the study of the minimum or optimal dosage of physical activity that is necessary to decrease the odds of incident depression should be improved. Although the work of FB Schuch, D Vancampfort, J Firth, S Rosenbaum, PB Ward, ES Silva, M Hallgren, A Ponce De Leon, AL Dunn, AC Deslandes, et al. [27] was an important contribution to the field and the overall study quality was moderate to high (Newcastle-Ottawa Scale score, 6.3), all except one [28] of the studies included in the meta-analysis used self-report questionnaires to measure physical activity, which represents one of the leading limitations.

Below, some interesting prospective studies published later than those included in the meta-analysis of FB Schuch, D Vancampfort, J Firth, S Rosenbaum, PB Ward, ES Silva, M Hallgren, A Ponce De Leon, AL Dunn, AC Deslandes, et al. [27] (i.e., after October 18, 2017) that also investigated the relationship between physical activity and incident depression in people without baseline depression will be discussed.

Two studies using self-report measures showed that engaging in regular physical activity was a significant predictor of future depression in young [29] and older [30] adult populations. The study of XC Zhang, ML Woud, ES Becker, and J Margraf [29] included a sample of 5203 young women (18–25 years) who participated in the Dresden Predictor Study (DPS; for more details see J Trumpf, N Vriends, AH Meyer, ES Becker, SP Neumer, and J Margraf [31]) and were prospectively followed over 17 months. One limitation of this study is that the authors used "several times a week" to categorize individuals as engaging in "regular" physical activity. The use of a fixed number or a range of days per week may better clarify whether there is a minimal or optimal frequency of physical activity to decrease the likelihood of future depression. The second aforementioned study was carried out by S Kanamori, T Takamiya, S Inoue, Y Kai, T Tsuji, and K Kondo [30] and categorized the frequency of physical activity using a more precise criterion. This study included 1422 adults aged 65 years or older who participated in the Japan Gerontological Evaluation Study (JAGES; for more details see K Kondo [32]) and were prospectively followed over 2 years. Specifically, the authors classified "exercisers" into two groups (exercising two or more times a week or exercising less than twice a week) and considered "non-exercisers" those respondents who answered "hardly ever." Those who exercised two or more

times a week had a lower odds ratio for depression compared with the non-exercisers.

Two remarkable issues of the studies described above are that (1) neither used a standardized questionnaire for measuring physical activity and (2) neither explored the influence of the intensity and volume of physical activity on future depression. These two issues were overcome in the study of SB Harvey, S Overland, SL Hatch, S Wessely, A Mykletun, and M Hotopf [33] published in *the American Journal of Psychiatry*. The authors addressed whether exercise provides protection against new-onset depression and, if so, the intensity and amount of exercise required to gain protection using a cohort of 33,908 adults (20 years or older) who participated in the HUNT study (Health Study of Nord-Trøndelag County; for more details see S Krokstad, A Langhammer, K Hveem, TL Holmen, K Midthjell, TR Stene, G Bratberg, J Heggland, and J Holmen [34]) and were prospectively followed over 11 years. Exercise behavior was self-reported at baseline using a questionnaire for which the reliability and validity had been demonstrated against maximal oxygen uptake, objective physical activity using ActiReg, and self-reported physical activity using the International Physical Activity Questionnaire [35]. The authors found that participating in regular exercise was associated with a reduced likelihood of depression, primarily in low levels of exercise, with no indication of any additional benefit beyond 1 h of exercise each week, regardless of intensity. In addition, they suggest that 12% of future cases of depression could have been prevented if all participants had engaged in at least 1 h of physical activity each week.

Concurring with the study of SB Harvey, S Overland, SL Hatch, S Wessely, A Mykletun, and M Hotopf [33], the study of K Kuwahara, T Honda, T Nakagawa, S Yamamoto, T Hayashi, and T Mizoue [36] also showed that the self-reported volume and frequency of exercise was inversely associated with future depression in a sample of 29,052 employees aged 20–64 years who participated in the Japan Epidemiology Collaboration on Occupational Health study (J-ECOH; for more details see [37, 38]) and were followed for a mean of 5.8 years. However, contrary to the study of SB Harvey, S Overland, SL Hatch, S Wessely, A Mykletun, and M Hotopf [33], K Kuwahara, T Honda, T Nakagawa, S Yamamoto, T Hayashi, and T Mizoue [36] suggest that the intensity of physical activity would also contribute to preventing depression. Specifically, the authors found that when compared with no exercise, vigorous exercise alone or combined with moderate-intensity exercise was associated with a 15 or 12% lower risk of developing depression. However, these reductions did not reach statistical significance, and the validity and reliability of the physical activity questionnaire employed (for more details see K Kuwahara, T Honda, T Nakagawa, S Yamamoto, S Akter, T Hayashi, and T Mizoue [37]) were unexplored.

Regarding the importance of meeting the *World Health Organization* recommended physical activity levels (≥150 min weekly of moderate to vigorous physical activity), two recent studies [39, 40] showed a nonsignificant relationship with a reduced risk of future depression. The study carried out by CP McDowell, RK Dishman, M Hallgren, C MacDonncha, and MP Herring [39] used data from 4556 adults aged ≥50 years who participated in two waves of the Irish Longitudinal Study of Ageing (TILDA; for more details see BJ Whelan and GM Savva [41]), where they completed the short form of the International Physical Activity Questionnaire and the Center for Epidemiological Studies Depression Scale at baseline and 2 years later. In brief, the authors found that achieving the *World Health Organization* recommended physical activity levels was associated with a 23% reduced risk of future depression. On the other hand, the study of Hallgren [40] used data from a cohort of 43,863 Swedish adults (18 years or older) from the Swedish National March Cohort study (SNMC: http://ki.se/en/meb/the-swedish-national-march-cohort-nmc) who were followed over 13 years. Physical activity was measured with a questionnaire that was used extensively, and its reliability and validity had been previously published [42–44]; the clinical diagnoses of depression were obtained from a national specialist inpatient and outpatient register. Interestingly, the authors showed that although achieving the *World Health*

Organization recommended physical activity levels could be beneficial, exceeding this level (with at least 300 min/week) significantly reduced the risk of being diagnosed with major depression compared to engaging in less than 150 min/week. Again, the use of self-report methods for measuring physical activity limits the generalization of the findings. Despite this, these results concur with many studies, showing that, overall, engaging in at least 300 min/week of moderate to vigorous physical activity offers more benefits than only 150 min. This fact reinforces the assumption that reaching only the minimum recommended physical activity level is not always the best option for health.

To summarize this point, an extensive amount of prospective studies show that physical activity levels are a strong predictor of future depression. However, there are some issues that might improve the current understanding, for example, using objective measures for measuring physical activity. Another interesting field to explore would be to analyze the prospective influence of sedentary behavior on future depression and to investigate whether sedentary behavior may modulate the association between physical activity and future depression. However, most studies had been focused on the former issue. In fact, the available reviews and meta-analyses [45–48] claim that engaging in sedentary activities for a prolonged time increases the likelihood of depression. The second issue will be discussed in the following section.

18.2.1 The Independent Role of Physical Activity and Sedentary Behavior on Incident Depression

Before discussing the main findings of the prospective studies that explored the independent role of sedentary behavior and physical activity on incident depression, three cross-sectional studies need to be described.

D Vancampfort, B Stubbs, J Firth, T Van Damme, and A Koyanagi [49] explored the association between sedentary behavior and depressive symptoms in 67,077 adolescents from 30 low- and middle-income countries using data from the Global School-Based Student Health Survey (GSHS) developed by the *World Health Organization*, the United States Centers for Disease Control and Prevention, and other United Nations allies (for more details see http://www.who.int/chp/gshs and http://www.cdc.gov/gshs). The main finding is that more than 1–2 h/day of sedentary behavior was associated with a linear increase in the prevalence of depressive symptoms, irrespective of physical activity levels.

Similar results were found in a multi-national study of adults carried out by the same research group [50]. Specifically, the study included a total of 42,469 individuals aged ≥18 years, with oversampling of those aged ≥50 years who participated in the *World Health Organization*'s Study on Global Ageing and Adult Health (SAGE; for more details see P Kowal, S Chatterji, N Naidoo, R Biritwum, W Fan, R Lopez Ridaura, T Maximova, P Arokiasamy, N Phaswana-Mafuya, S Williams, et al. [51]). The authors conclude that higher levels of sedentary behavior (particularly over 11 h/day) were associated with an increased prevalence of depression. Furthermore, the authors highlighted that physical activity between and potential confounders (smoking, alcohol consumption, body mass index, and social cohesion) had little influence in the association.

Although both studies have important findings, due to the novelty and large samples analyzed, neither of them used objective measures for measuring physical activity and sedentary behavior. In this regard, the study of JK Vallance, EA Winkler, PA Gardiner, GN Healy, BM Lynch, and N Owen [52] did so using 2862 adults from the 2005–2006 US National Health and Nutrition Examination Survey (NHANES; for more details see https://www.cdc.gov/nchs/nhanes/index.htm), along with ActiGraph AM-7164 accelerometers to derive both moderate to vigorous physical activity and sedentary time. Both activity behaviors were found to be independently associated with depression.

In contrast to the findings based on cross-sectional studies, recent prospective studies have

shown that sedentary time does not predict depression when using objective [53, 54] and self-report [55, 56] methods for measuring physical activity and sedentary behavior. However, all of these findings related to total sedentary time. When analyzing the impact of specific sedentary behaviors (such as watching TV or office work) on future depression, some interesting results were found. Specifically, some prospective studies based on self-report measures showed that the amount of time engaged in mentally passive sedentary behaviors (e.g., watching TV) was positively related to the risk of depression in adults [56] and in older adults [55, 57, 58]. On the other hand, two of these studies [55, 56] suggest that being engaged in mentally active sedentary behaviors (e.g., office work) may be protective against the onset of depression. Overall, these findings questioned the use of total sedentary time as a depression risk behavior and suggest the importance of differentiating between mentally passive and mentally active sedentary behaviors when measuring sedentary behavior. Nonetheless, there are a limited number of studies that have explored the independent role of physical activity and sedentary behavior on future depression. Therefore, more research, preferentially combining both objectively measured and self-reported sedentary behavior patterns, may clarify the independent role of these exposures and the impact of specific sedentary behaviors on depression.

18.2.2 Other Predictors of Incident Depression Are Typically Improved by Physical Activity and Physical Exercise

Extensive and robust scientific evidence confirms that maintaining an active lifestyle or undertaking physical exercise on a regular basis provides benefits to physical fitness (e.g., cardiorespiratory fitness) and fatness (commonly expressed as body mass index). Furthermore, some studies (e.g., J Joo, SA Williamson, AI Vazquez, JR Fernandez, and MS Bray [59]) suggest that physical exercise appears to motivate people to pursue healthier dietary preferences and to regulate their food intake. These exposures have a potential impact on the development of depression, as shown by recent studies, which will be discussed below.

A systematic review of prospective cohort studies led by FB Schuch, D Vancampfort, X Sui, S Rosenbaum, J Firth, J Richards, PB Ward, and B Stubbs [60] supported the hypothesis that a high cardiorespiratory fitness level may be a protective factor for depression. After searching major electronic databases from inception to January 2016, three studies [61–63] were identified, and data from two studies [62, 63] were pooled, involving over one million people (n = 1,128,290). The low and medium levels of cardiorespiratory fitness were associated with a 75 and 23% increased risk of incident depression, respectively. However, one major limitation is the length of the follow-up period, ranging from 3 to 40 years in the study by MA Aberg, M Waern, J Nyberg, NL Pedersen, Y Bergh, ND Aberg, M Nilsson, HG Kuhn, and K Toren [62] and from 10 to 11 years in the study by X Sui, JN Laditka, TS Church, JW Hardin, N Chase, K Davis, and SN Blair [63].

Two other relevant studies [64, 65] in this field were based on data from the Aerobics Center Longitudinal Study, an ongoing, prospective study at the Cooper Institute in Dallas (USA). These studies reinforced the importance of midlife cardiorespiratory fitness in the primary prevention of depression.

Although all of the described studies controlled for body mass index and other confounders, a study of 2019 individuals compared the role of cardiorespiratory fitness and body mass index with the later receipt of disability due to all and specific causes, including psychiatric disorders and depression [66]. The sample included 1,079,128 male Swedish adolescent individuals aged 16 to 19 years who were conscripted into the military between 1972 and 1994 and were followed over a median of 28.3 years. Although low cardiorespiratory fitness, obesity, and the combination of the two were strongly associated with later chronic disability due to psychiatric reasons (among other reasons), highly fit adolescent individuals with obesity had a

lower risk for disability pension due to psychiatric causes than the unfit adolescents with either obesity or normal weights. Individual associations of both exposures with specific psychiatric disorders (including affective disorders such as depression) are available in the appendix; however, data on the combined association was not available for specific psychiatric disorders. In summary, the findings support the importance of promoting cardiorespiratory fitness and a healthy body weight during adolescence to prevent depression later in life.

Regarding diet, in 2019 J Firth, W Marx, S Dash, R Carney, SB Teasdale, M Solmi, B Stubbs, FB Schuch, AF Carvalho, F Jacka, et al. [67] published a meta-analysis of randomized controlled trials primarily aiming at those designed to decrease the intake of unhealthy foods, improve nutrient intake, and/or to restrict calorie intake to induce weight loss. The meta-analysis found significantly reduced depressive symptoms among the 15 trials in nonclinically depressed individuals. In addition, the combination of diet and exercise interventions had a small positive effect on depressive symptoms compared with exercise alone. However, the latter finding was based only on two studies.

18.3 Exercise for the Treatment of Depression

18.3.1 Evidence of the Benefits of Exercise in People with Depression

In 2018, B Stubbs, D Vancampfort, M Hallgren, J Firth, N Veronese, M Solmi, S Brand, J Cordes, B Malchow, M Gerber, et al. [68] published a meta-review of the evidence and Position Statement from the European Psychiatric Association (EPA), supported by the International Organization of Physical Therapists in Mental Health (IOPTMH), of exercise-based interventions and their impact on health outcomes for people with severe mental illness, including schizophrenia-spectrum disorders, major depressive disorder, and bipolar disorder. This research group searched major electronic databases until January 2018 for systematic reviews with/without meta-analysis that investigated the effect of exercise on any severe mental illness.

In total, ten systematic reviews and meta-analyses reported the benefits of exercise for people with depression. The main characteristics and findings of the four studies were considered to have a high-quality assessment and high-quality evidence, as respectively assessed with the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool [69, 70] and the Scottish Intercollegiate Guidelines Network (SIGN) recommendations adapted from a previous EPA guideline [71], which will be discussed below.

GM Cooney, K Dwan, CA Greig, DA Lawlor, J Rimer, FR Waugh, M McMurdo, and GE Mead [72], in a comprehensive Cochrane review (AMSTAR score 11/11) including exercise trials through March 2013, found that exercise was moderately more effective than a control intervention for reducing symptoms of depression in adults over 18 years of age. However, when compared to other conventional interventions, such as psychological or pharmacological therapies, exercise seemed to be no more effective. Interestingly, P Ekkekakis [73] published a critical appraisal of the aforementioned study and concluded that it had several methodological issues. Indeed, a reanalysis of the same database following rational modifications showed that the effect of exercise was large.

FB Schuch, D Vancampfort, J Richards, S Rosenbaum, PB Ward, and B Stubbs [74] (AMSTAR score 10/11) updated the findings of GM Cooney, K Dwan, CA Greig, DA Lawlor, J Rimer, FR Waugh, M McMurdo, and GE Mead [72], taking into account the issues detailed by P Ekkekakis [73] and using all available randomized controlled trials of exercise-based interventions in adult with depression that compared exercise versus control conditions from January 2013 until August 2015. The authors found 25 randomized controlled trials comparing an exercise and control group and found that the antidepressant effect of exercise increased after adjusting for publication bias. These results questioned previous meta-analyses that were not adjusted for publication bias

and, therefore, might have underestimated the antidepressant effect of exercise. Another interesting finding was that greater effects were found in people with a diagnosis of major depressive disorder who used aerobic exercise at moderate and vigorous intensities and when they were supervised by qualified exercise professionals. The authors elegantly explained why there were differences in the magnitudes of the effects compared with those reported by GM Cooney, K Dwan, CA Greig, DA Lawlor, J Rimer, FR Waugh, M McMurdo, and GE Mead [72]. Three main factors were highlighted: the inclusion criteria, the statistical test used to evaluate the effect size based on the mean change of symptoms of the control and exercise groups, and the inclusion of more recent trials.

FB Schuch, ID Morres, P Ekkekakis, S Rosenbaum, and B Stubbs [75] recently published a selective critical review of relevant studies of exercise as a treatment for adults with depression. The authors explained in detail some methodological issues that should considered to improve the understanding of the role of exercise in depression. One of the issues was the control group responses in exercise interventions. In this regard, FB Schuch, ID Morres, P Ekkekakis, S Rosenbaum, and B Stubbs [75] cited a proper study [76] published in *Sports Medicine*, one of the six most impactful scientific journals in the sports sciences since 1997. The study is a systematic review and meta-analysis of control group responses in randomized controlled trials of exercise from the Cochrane review of GM Cooney, K Dwan, CA Greig, DA Lawlor, J Rimer, FR Waugh, M McMurdo, and GE Mead [72] and included those available in major databases from January 2013 to August 2015. The analyses included 41 studies of adults with major depressive disorder or depressive symptoms that measured depressive symptoms pre- and post-intervention and included a non-active control group. The control groups in the exercise interventions achieved large improvements in depressive symptoms, a finding that was more evident in high-quality studies. In addition, the improvements in the exercise intervention control groups were approximately double when compared with the improvements in the control groups of antidepressant studies [77]. Given this control group response in exercise interventions on depressive symptoms, the same authors carried out a similar study, but this time they focused on the individual's physical and psychological quality of life [78]. This meta-analysis [78] included six randomized clinical trials that compared the effects of exercise on quality of life versus the control condition in people with depression. Contrary to their previous study, the authors did not find a significant response regarding any domain or a change to the overall quality of life in the control group.

Another high-quality meta-analysis was carried out by S Kvam, CL Kleppe, IH Nordhus, and A Hovland [79] (AMSTAR score 10/11), who examined the efficacy of an exercise-based intervention as treatment for unipolar depression, both as an independent intervention and as an adjunct intervention to antidepressant medication. A total of 23 randomized controlled trials published up to November 2014 were included. Exercise-based interventions were found to be more effective in reducing depressive symptoms than either no intervention or the usual care for depression and had comparable effects to psychotherapy and antidepressants. Furthermore, exercise as a co-adjuvant therapy to antidepressant medication showed a moderate effect.

A high-quality meta-analysis was conducted by B Stubbs, S Rosenbaum, D Vancampfort, PB Ward, and FB Schuch [80] (AMSTAR score 10/11), who evaluated whether cardiorespiratory fitness levels improve in people with depression in exercise-based randomized control trials. The authors searched exercise-based randomized controlled trials on depression that were available in major databases from January 2013 to August 2015. A total of seven randomized controlled trials including eight aerobic exercise interventions for depression were eligible. Short-term exercise (~ 12 weeks) was found to moderately improve cardiorespiratory fitness among people with depression. The meta-analysis also suggested that higher baseline depression predicts lower changes in cardiorespiratory fitness.

Although the study of B Stubbs, S Rosenbaum, D Vancampfort, PB Ward, and FB Schuch [80] was not focused on the antidepressant effects of exercise in people with depression, the results are remarkable, as discussed below. The importance of cardiorespiratory fitness for health has been clearly demonstrated. Firmly established evidence [81] shows that a low level of cardiorespiratory fitness is a stronger predictor of all-cause and disease-specific mortality than are traditional cardiometabolic risk factors, such as age, hypertension, hypercholesterolemia, obesity, smoking, family history, elevated glucose levels, and type 2 diabetes. The importance of cardiorespiratory fitness as a predictor of incident depression in people without depression was previously explained in this chapter. The importance of cardiorespiratory fitness in people with depression will be discussed below using two recent studies [65, 82].

First, the study of BL Willis, D Leonard, CE Barlow, SB Martin, LF DeFina, and MH Trivedi [65] showed that a high cardiorespiratory fitness level after a diagnosis of depression was associated with a 56% lower risk of death due to cardiovascular disease compared with a low fitness level. Therefore, cardiorespiratory fitness should be considered as a health risk predictor in people with established depression. Second, the randomized controlled trial of an exercise intervention in people with depression carried out by MS Rahman, B Helgadottir, M Hallgren, Y Forsell, B Stubbs, D Vancampfort, and O Ekblom [82] showed that increased cardiorespiratory fitness was a predictor of reduced depression severity after 12 weeks of exercise. Taken together, changes in cardiorespiratory fitness should be strongly considered as an important health predictor among individuals who are clinically depressed. These results add new evidence to the plethora of robust evidence supporting the prognostic use of cardiorespiratory fitness that led the *American Heart Association* to claim that cardiorespiratory fitness must be routinely assessed in clinical practice as a vital sign [83]. In addition to the importance of improving cardiorespiratory fitness, improvements in the diet, which could occur as a consequence of exercise-based interventions [59], were also associated with reduced depressive symptoms in people with depression [84, 85].

After reporting some important issues of the four high-quality studies included in the recent meta-review of the evidence led by B Stubbs, D Vancampfort, M Hallgren, J Firth, N Veronese, M Solmi, S Brand, J Cordes, B Malchow, M Gerber, et al. [68], the summary of the effects of exercise interventions in people with depression established in this guidance was as follows:

- Consistent evidence that aerobic exercise is effective compared to control conditions at follow-up in reducing depressive symptoms.
- Consistent evidence that exercise has a similar effect as psychological therapy and antidepressant treatment.
- Exercise is effective at improving cardiorespiratory fitness compared to control conditions.
- Exercise improves the overall quality of life in the physical and psychological quality of life domains. There is no evidence for effects on other quality of life domains.
- Aerobic exercise does not improve global cognition or any subdomain compared to control conditions.
- There is no evidence that exercise affects anxiety symptoms.
- There is no evidence that exercise affects body weight, waist circumference, blood glucose, body mass index, or body fat.

Notably, the majority of this evidence is based on aerobic exercise, followed by mixed exercise (aerobic + resistance). Therefore, the literature regarding resistance training as a standalone intervention for depression remains limited. Five of the ten systematic reviews and meta-analyses that reported the benefits of exercise for people with depression [74, 86–89] included the few available studies on resistance training as a standalone intervention for depression. Given the growing interest in the use of this type of intervention as an alternative or complement to other therapies (e.g., physical, pharmacological, psychological), a brief description and discussion of these studies is provided below.

18.3.1.1 Resistance Training Effects in Adults with Depression

Regarding adults, the study of A Pilu, M Sorba, MC Hardoy, AL Floris, F Mannu, ML Seruis, C Velluti, B Carpiniello, M Salvi, and MG Carta [90] included 30 women aged 40 and 60 years who were diagnosed with major depressive disorders (DSM-IV TR) and were resistant to ongoing treatment. They were randomized to pharmacological treatment + two 60-min sessions/week of moderate-intensity resistance training (n = 10) or to pharmacological therapy alone (n = 20) for 8 months (32 weeks). For resistance training, the participants freely chose from among 20 cardiofitness machines for strengthening arms, legs, and postural muscles. After 4 min of exercising, the participants changed to another machine. All exercise sessions were led by a skilled instructor who had a physical education diploma, a psychology degree, and a post-degree diploma in sport psychopathology. The exercise group showed statistical improvements in their depressive and general psychopathological symptoms, whereas the control group did not show any statistically significant differences. Limitations of the study included a small sample size, a poor description of the intervention dosage, and not performing statistical between-group comparisons.

The other study in adults was carried out by J Krogh, B Saltin, C Gluud, and M Nordentoft [91] and consisted of a randomized pragmatic trial for 165 people with unipolar depression, aged 18 and 55 years, who were allocated to supervised resistance (n = 55; 45 women), aerobic training (n = 55; 43 women), or relaxation training (n = 55; 34 women) during a 4-month period (16 weeks). The resistance training included two 90-min sessions/week of progressive intensity (50–75% of repetition maximum) and volume (from two to three sets of 12 repetitions to two to three sets of eight repetitions) training. The training was a circuit-training program with exercises on machines involving large muscle groups and was supplemented with free-weight exercises for small muscle groups. Although the authors did not find any effects on the symptom severity of clinical depression, a tendency toward fewer absences from work at the 12-month follow-up point was found in the resistance training group.

18.3.1.2 Resistance Training Effects in Older Adults with Depression

Regarding older adults, NA Singh, KM Clements, and MA Fiatarone [92] conducted a 10-week randomized controlled trial in 32 adults with major or minor depression or dysthymia, aged 60–84, who were allocated to a supervised progressive resistance training program three times per week (n = 17; 12 woman) or to an attention-control group (n = 15; 8 woman). The resistance training sessions lasted 45 min and included exercises on machines involving large muscle groups, with three sets of eight repetitions at 80% of repetition maximum and increasing absolute loads at each session to maintain this relative load. The progressive resistance training was effective for reducing depressive symptoms, while also improving strength, morale, and quality of life. Notably, this was the first study on resistance training in older adults, which demonstrated its efficacy, feasibility, and safety. Later, the same authors carried out a similar study [93], but this time they focused on the role of the intensity of exercise. In this study, the authors hypothesized that high-intensity progressive resistance training would be more effective than either low-intensity progressive resistance training or standard depression care and that high-intensity training would provide superior benefits regarding quality of life, sleep quality, and self-efficacy. In the study, 60 older adults (>60 years) with major or minor depression were randomized to a supervised high-intensity progressive resistance training group (80% of repetition maximum) or a low-intensity progressive resistance training group (20% of repetition maximum), training 3 days/week for 8 weeks, or to general practitioner care. The main finding was that 61% of the participants in the high-intensity group achieved clinical improvements in their depression (i.e., a 50% reduction in the Hamilton Rating Scale for Depression score), and the improvements were greater than those of the low-intensity (29%) and standard care (21%) groups. Furthermore, muscular strength gain was found to be directly associated with a reduction in depressive symptoms. Overall, these results suggest a higher effectiveness of high-intensity resistance training and a potential prognostic use of

muscular strength for depression among older adults with major or minor depression.

The study carried out by J Sims, M Galea, N Taylor, K Dodd, S Jespersen, L Joubert, and J Joubert [94] in older adults explored whether a progressive resistance training program could reduce depressive symptoms in chronic post-stroke patients with depression. Forty-five eligible people were allocated to resistance training ($n = 23$; 9 women) or to a waiting list comparison group ($n = 22$; 9 women) for 10 weeks. The resistance training was carried out in a community-based gymnasium and was organized in small groups under the supervision of an accredited fitness trainer. There were two sessions/week of three sets of eight to ten repetitions at 80% of the repetition maximum using machine weights for the major muscle groups. A trend for reduced depressive symptoms at the 6-month follow-up was found in the resistance training group.

Although helpful, the three aforementioned studies in older adults were categorized as low-quality studies in the meta-analysis adjusting for publication bias led by FB Schuch, D Vancampfort, J Richards, S Rosenbaum, PB Ward, and B Stubbs [74]. Therefore, more research with higher methodological quality are needed to provide more robust evidence on the effects of exercise in this population group. In this regard, promising results on the efficacy of resistance exercise training for depressive symptoms have been recently found in a meta-analysis and meta-regression analysis of randomized clinical trials in adults, including older adult and clinical (with physical and mental complaints/disorders including depression) populations [95]. In addition, the findings were irrespective of health status, total prescribed volume of resistance exercise training, or significant improvements in strength. Therefore, further research in this field is warranted.

18.3.2 Recommendations for Prescribing Exercise to People with Depression

One of the most well-known studies on recommendations for prescribing exercise to people with depression was the review carried out by CD Rethorst and MH Trivedi [96]. The authors described a summary of the accumulated evidence supporting the use of physical exercise in the treatment of depression and gave recommendations and discussed practical considerations for prescribing exercise in real-world settings. Specifically, the authors focused on the exercise modality, the frequency and duration of sessions, the intensity, the intervention length, and the adherence to exercise. The main recommendations were as follows: aerobic or resistance training (modality), three to five sessions per week (frequency) of 45–60 min (session duration), at 50–85% of the maximal heart rate for aerobic training and at 80% of the repetition maximum for resistance training (intensity), for at least 10 weeks (intervention length), and using psychological strategies to increase adherence to the exercise regime. Regarding practical considerations, they provided some examples of aerobic exercises (walking, running, treadmill, biking) and the muscles group that should be strengthened (all major muscle groups of the upper and lower body), as well as how to calculate the maximal heart rate (220-age) and how to evaluate the intensity of aerobic exercise (Borg scale 6–20 multiplying by 10) and resistance exercise (estimate one repetition maximum using submaximal repetitions and online calculator).

Shortly thereafter, R Stanton, P Reaburn, and S Rosenbaum [97] commented on the recommendations of the study of CD Rethorst and MH Trivedi [96] in a Letter to the Editor. In particular, the authors criticized that the overall recommendations were based on a limited amount of studies, most of which were carried out in older adults with depression. Taking this into account, R Stanton, P Reaburn, and S Rosenbaum [97] recommended following the *American College of Sports Medicine* guidelines for healthy adults [98] when prescribing exercise for the treatment of people with depression until more research supports any particular recommendations in this clinical population. The *American College of Sports Medicine* guidelines for healthy adults [98] include recommendations for individualized exercise prescriptions, differentiating between aerobic, resistance, flexibility, and neuromotor exercise training and between novice (and deconditioned sedentary

populations), intermediate, and experienced exercisers, as well as between adults and older adults. For more details, see a summary of exercise prescription recommendations with their respective evidence statements in Table 2 of the aforementioned study [98].

Finally, the meta-review and Position Statement from the EPA and IOPTMH led by B Stubbs, D Vancampfort, M Hallgren, J Firth, N Veronese, M Solmi, S Brand, J Cordes, B Malchow, M Gerber, et al. [68] also included recommendations for the prescription of exercise in people with depression. Based on all of the accumulated evidence of the systematic reviews with/without meta-analysis until January 2018, the authors recommended two to three sessions of supervised and/or aerobic and resistance training exercise per week of 45–60 min of moderate intensity. Additionally, B Stubbs, D Vancampfort, M Hallgren, J Firth, N Veronese, M Solmi, S Brand, J Cordes, B Malchow, M Gerber, et al. [68] strongly recommended that a physiotherapist and exercise physiologist should deliver, lead, and supervise the exercise-based interventions. In regard to the last recommendation, systematic reviews of meta-analyses have confirmed that when exercise interventions are delivered, led, and supervised by exercise professionals, the outcomes are better [74, 78, 86] and the dropout rate is lower than when they are led by non-professionals and when they are unsupervised. Given this, "these practitioners should be the first choice when considering increasing staff resources to facilitate people with depression engaging in regular exercise" [99].

18.4 Key Points

The following key points summarize the main results on the research progress of using exercise to prevent and treat depressive disorders:

- Depression disorder is a global health issue associated with an increased rate of disability, morbidity, mortality, and economic impact.
- An extensive number of prospective studies have shown that a lower level of physical activity is a strong predictor of future depression.
- An increasing body of evidence demonstrates that a higher level of sedentary behavior, a higher body mass index, and worse cardiorespiratory fitness and diet could also be considered as predictors of incident depression.
- Consistent evidence confirms that exercise interventions are effective in reducing depressive symptoms and have similar effects when compared to psychological and antidepressant interventions.
- There is weak evidence of a dose-response relationship between exercise prescription and people with depression.
- The most consistent evidence is for two to three sessions of supervised, moderate-intensity aerobic and/or resistance training exercise per week lasting 45–60 min.
- The evidence indicates that exercise professionals should deliver, lead, and supervise exercise interventions for depression because this is associated with better outcomes and lower dropout rates.

Acknowledgments The work was funded by Research Group CTS-948, Universidad Pablo de Olavide, Andalusian Government; Universidad Pablo de Olavide, Spain "A2. Ayudas Puente para la Concurrencia al Plan Estatal de I+D"; European University of Madrid, Cátedra Real Madrid, Spain (funding project number P2017/RM08); Biomedical Research Networking Centre on Frailty and Healthy Aging (CIBERFES); and FEDER funds from the European Union (CB16/10/00477). JBA was supported by the Spanish Ministry of Education (grant number FPU13/05130) and by the Departamento de Innovación, Investigación y Universidad del Gobierno de Aragón y el Fondo Europeo de Desarrollo Regional – Programa Operativo FEDER Aragón 2014–2020 "Construyendo Europa desde Aragón" (reference number PUI/2018-337). The funders had no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

Competing Financial Interests The authors declare no competing financial interests.

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Exercise and Parkinson's Disease

19

Simona Bonavita

Abstract

Parkinson's disease (PD) is an aging-related neurodegenerative disorder characterized by progressive motor impairment.

The etiology of PD is poorly understood but likely involves both genetic and environmental factors; the management of the disease is still with symptomatic therapy without any interference on the progression of neurodegeneration. In the past two decades, the results of a series of prospective cohort studies suggested that lifestyle factors likely modify the risk of developing PD. Among these, physical activity is known to reduce the risk of a wide range of diseases and conditions, including cardiovascular disease, stroke, and diabetes.

Recently, a growing body of evidence has suggested that increased physical activity may also reduce the risk of PD and partly improve motor and non-motor symptoms during the disease course.

Here we report the main findings on the effect of physical activity on both mobility and cognition either in animal models of PD or in people with PD. We also highlighted the structural and functional links between gait and cognition by reporting evidence from neuroimaging studies.

Keywords

Parkinson's disease · Exercise · Fitness · Cognition · Magnetic resonance imaging

19.1 Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases worldwide; it is characterized by degeneration of dopaminergic neurons in the pars compacta of the substantia nigra of the midbrain, with loss of axons projecting to the striatum. As a consequence of dopaminergic neuron degeneration, the neurotransmitter dopamine (DA) in the striatum is decreased, leading to PD's primary symptoms including bradykinesia, tremor, rigidity, and postural instability [1].

In the last years, there has been increasing evidence that non-motor symptoms (NMS), such as psychiatric and cognitive dysfunction [2], gastrointestinal disturbances [3], and olfactory dysfunction [4, 5], are associated with this disease, negatively impacting on people with PD's (pwPD's) quality of life [6, 7].

Early symptoms for PD diagnosis are prodromal [8–11]. Olfactory dysfunction, gastrointesti-

S. Bonavita (✉)
II Clinic of Neurology, Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy
e-mail: simona.bonavita@unicampania.it

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_19

nal disturbances, sleep disruption, and mood changes are precocious, followed by motor symptoms and cognitive dysfunction [12, 13]. Although there is no etiological therapy for PD, the motor symptoms are, at least at the beginning of the disease, responsive to pharmacological replacement with administration of the DA precursor levodopa (L-dopa) or to DA receptor agonists.

After a variable number of years, the treatment with L-dopa may complicate with dyskinesias [14, 15], whereas DA agonists may facilitate, even at the beginning of therapy, compulsive disorders and neuropsychiatric symptoms' development [16]. Diagnosis before the motor symptoms' appearance will potentially make early neuroprotective therapies more efficacious and will enhance the clinical prognosis of patients.

Several new therapeutic approaches tried to interfere with the disease progression: (a) neurotrophic factors' intracerebral application, with the purpose of neurorestorative and neuroprotective effects on the nigrostriatal dopaminergic system [17–19], and (b) cell transplantation from fetal midbrain into pwPD's caudate-putamen [20, 21]. However, both neurotrophic factor therapy and cell transplantation require highly invasive stereotaxic surgery, raising safety and feasibility issues.

Therefore, the development of feasible, non-invasive, and effective therapy modifying the disease course is recommendable. Epidemiological research's data suggest that aerobic exercise may reduce the risk of PD development [22–24] and is beneficial to general cognitive and psychiatric health [25].

19.2 Gait and Cognition in PD

In the development of PD, gait worsens [26] and to compensate pwPD rely more on cognition to control gait [27]. Therefore there is a decline in gait automaticity that in normal condition implies minimal demand on cognitive processes while walking. To witness the increased interaction between gait and cognition in pwPD, it has been shown that, when performing automatic movements (such as gait), the activity of brain areas which are important for cognitive processing (the dorsolateral prefrontal cortex) is larger in pwPD than in age-matched controls [28]. As a consequence, cognitive impairment may limit the capability to compensate dysfunctions of gait.

Cognitive impairment in pwPD has a prevalence of 42.5% [29, 30] and includes deficits in working memory, visuospatial processing, language fluency, and verbal learning [31, 32]. It is caused by frontal lobe dysfunction due to both cortical atrophy [33, 34] and Lewy body pathology [35]. Dysfunctions in various neurotransmitter systems, including DA, serotonin, noradrenaline, and acetylcholine, are thought to contribute to the cognitive decline associated with PD [36]; however, the cholinergic deficit is considered to be the most relevant [37].

19.3 Exercise and PD

More and more data show that exercise may rescue motor and NMS (i.e., cognition) of PD [38, 39].

19.4 Evidence from Animal Studies

Animal studies helped to explain the exercise-induced changes in molecular and cellular mechanisms underlying neuroprotection and neurorestoration and its clinical effect on both cognition and motor/NMS in PD.

In particular, many studies on animal models of PD investigated the effect of exercise on cognitive functions.

Exercise-induced improvement of cognitive performances in rodents is associated with changes in the neurocircuitry involved in learning and memory, particularly in the hippocampus [40–42]. The neuronal morphology showed that running wheel exercise increases granule neurons' dendritic spine density in the hippocampus of the rat [43]. Exercise can also increase the

dendritic arborization of immature neurons in the hippocampus of mice in comparison with sedentary mice [44], the number of new neurons in adult rodents' hippocampus [42, 45], as well as neurotrophin brain-derived neurotrophic factor (BDNF), which is important for hippocampal neurogenesis [46–48]. In adult rodents, circulatory and hippocampal levels of the trophic nerve growth factor, fibroblast growth factor-2, insulin-like growth factor-I, and vascular endothelial growth factor are upregulated by exercise and play a role in mediating exercise-induced increases in hippocampal neurogenesis and associated cognition [49–51]. Neurotrophic factors are important to favor the maturation of different subtypes of neurons, comprised of dopaminergic ones; therefore, they have been investigated as potential neuroprotective treatments for PD [19]. It has been shown that exercise upregulates neurotrophic factors in the substantia nigra [52–54], by increasing the expression of the main receptor for glial cell line-derived neurotrophic factor [55]. Moreover, the neuroprotective effects of exercise-induced activation of BDNF on dopaminergic neurons have been demonstrated in animal models of PD [56]. Besides upregulation of neurotrophic factors, there are other potential mechanisms by which exercise can affect neurogenesis and cognitive behavior. For example, exercise is known to significantly increase levels of antioxidant markers in the blood [57, 58]. Oxidative stress and the resulting dysfunction of mitochondria are supposed to be crucial in the PD pathogenesis [59]. Furthermore, recently, studies conducted on animals suggested that exercise dilutes neuroinflammation [60], a significant pathological feature of PD. Exercise decreasing visceral fat and the consequent release of pro-inflammatory adipokines has peripheral anti-inflammatory effects mediated by the production and liberation of anti-inflammatory cytokines from skeletal muscle [61, 62].

Because inflammation negatively impacts on BDNF levels and neurogenesis and boosts oxidative stress in the hippocampus [63, 64], an exercise intervention, able to decrease neuroinflammation and oxidative stress and foster neurogenesis, may benefit either cognitive or motor deficits in PD.

The comparison of animal studies should be done with caution because of inherent variability among the animal models of PD and because of the different exercise protocols (intensity, duration, etc.) in relation to the neurotoxin administration. Likewise, the outcome of a study may be influenced by the type of exercise (aerobic vs. non-aerobic). Furthermore, constraining animals to a forced exercise regimen may provoke stress that may negatively impact on any potential beneficial effects induced by physical exercise on PD symptoms. Indeed, expanding evidence suggests that the benefit from exercise may be prevented by physiological responses of the animal occurring after the exposure to chronic or acute stressful condition, depending on the intervention length [65, 66].

In this regard, it has been shown in studies on rats that high-intensity exercise protocols may worsen cognition and impair synaptic plasticity of the hippocampus [67], while voluntary running has been shown to upregulate neurotrophic factors and to decrease responses to stress in comparison with forced exercise [68]. Interestingly, in rats, long-term (36 weeks) moderate-intensity treadmill exercise decreases pituitary-adrenal stress responses, suggesting a habituation to the treadmill exercise allowing positive exercise-induced effects [69]. Howells and co-workers [70] investigated the relationship between stress and neuroprotective effects of exercise and demonstrated that inducing mild stress by immobilizing the running wheel for 1 h/day prevented the advantageous effects of voluntary running on rat motor deficits. However, considering the different PD animal models, we may conclude that exercise, by increasing brain neurotrophic factor release, by promoting synaptogenesis and angiogenesis, and by decreasing neuroinflammation, induces structural and functional changes in the brain. Furthermore, exercise has effects on the nigrostriatal pathway increasing extracellular DA release by downregulation of the DA transporter expression, reduction of striatal DA loss, and partial preservation of DA terminals [71, 72].

19.5 Evidence from Studies on pwPD

19.5.1 The Effect of Exercise on Cognition

A recent review [73] analyzed the role of exercise on gait and cognition in pwPD. Studies on aerobic training, measuring cognitive performances at baseline and following the intervention, showed improved inhibition activity (at the Stroop or Flanker task) and reaction time [74, 75] after exercise. Other authors reported enhancement in the executive functions evaluated by the Frontal Assessment Battery, set-shifting (Trail Making Test parts A and B), and language [74, 76, 77]. Two resistance training reports evaluated cognitive performances at baseline and after the intervention [78, 79]. In the first study, it was demonstrated that working memory was ameliorated either by resistance training or by control intervention (modified fitness count) after 12 and 24 months. On the other hand, enhanced performance at the Stroop test (inhibition) and at an attention test was observed after 24-month follow-up [78]. In the second study, no changes in Montreal Cognitive Assessment (MoCA) scores were found after resistance training [79].

Out of the 15 studies that concluded the goal-based training, only 3 evaluated cognitive performances at baseline and after the intervention [80, 81]. In particular, after 6 weeks of treadmill training, pwPD had Trail Making Test parts A and B [81] and attention improvements [82]. After dual task training in virtual reality for 2 weeks, pwPD significantly improved in a visual reaction time task [80].To conclude, after treadmill training plus virtual reality, executive functions significantly improved [83].

19.5.2 The Effect of Exercise on Mobility

Timed 7-m walk test, timed 20MWT walk test, 6-min walk test (7MWT), timed 10-m walk test (10MWT), and timed up-and-go (TUG) significantly improved after aerobic training demonstrating a positive effect on mobility and on the capability to go up and down the stairs and turn around a chair [76, 84–89]. However, these results were not confirmed by other investigations [75, 88, 90, 91].

Improvements were also reported in the TUG, 10-MWT, and 6-MWT after training interventions [92–97] except by Morris et al. that did not demonstrate any improvement in the TUG after resistance training [98]. PwPD, after 6 months and 2 years of resistance training, showed better scores on balance and mobility tests.

With respect to goal-based training, under sensory manipulated conditions, the 6-MWT and balance were significantly ameliorated after dual-task exercise [81, 99–101]. Other studies revealed better scores at balance and mobility tests, in terms of self-paced gait speed and time taken to complete a five-time sit-to-stand [82, 99, 102].

At least one cognitive function, such as inhibitory control and set-shifting, was significantly improved in all the studies that measured cognitive performances. Inhibition and set-shifting are executive functions that have been linked to gait in PD; indeed, impairment in executive functions has been associated with higher gait variability and reduced speed in pwPD [103–106]. Thus, it could be hypothesized that enhancements in executive functions after exercise may be associated to improvements in gait in pwPD.

19.6 Structural and Functional Links Between Gait and Cognition: Evidence from Neuroimaging Studies

The areas supposed to be involved in cognitive and gait are particularly the prefrontal cortex, frontostriatal pathways, and the hippocampus. It is well known that the prefrontal cortex has a key role in retaining information in working memory [107] although a volume reduction of the prefrontal cortex has been found in aging adults with gait disturbances [108]. Consistently, neuroimaging in non-PD older adults showed that prefrontal cortex is connected to the basal ganglia through the frontostriatal network [109] impaired in

PD. Worse cognitive performances [110, 111] and freezing of gait [112] have been associated with dysfunction of these frontostriatal networks underlining the common structural substratum of cognition and gait. It is still to be disclosed how different physical trainings might modulate these structures influencing both cognition and gait in healthy subjects and in pwPD. In healthy aging adults, chronic aerobic exercise may increase prefrontal cortex volume [113] and modulate task-related activation of prefrontal areas [114]. It is supposed that in pwPD, the prefrontal cortex has a compensatory role for deficits occurring in the basal ganglia networks (reducing automaticity of gait) [115, 116]. Because decreased prefrontal functioning also occurs in pwPD [117], it is reasonable to hypothesize that exercise-induced prefrontal activation may enhance cognitive performances with consequent improvement in gait control.

The neurophysiological changes determined by resistance training are even less clear than those determined by aerobic training. In healthy subjects [118] as well as in pwPD [119], repetitive force generation leads to increased blood oxygen-level-dependent signal in the basal ganglia and the motor cortex; the difference between the two populations is that in pwPD the amount of signal activation is smaller than in healthy subjects. Because resistance training repeatedly increases force generation, it has been suggested that resistance training may determine increased neuronal activation through basal ganglia loops [120]. As the basal ganglia are intimately connected to the motor cortex through thalamocortical pathways, it is possible that improving this connection could also enhance corticomotor excitability, which is reduced during force generation in PD [121]. In support of this hypothesis, an increased corticomotor excitability has been found in healthy subjects after a resistance training program [122]. All these findings suggest that resistance training may facilitate neuroplasticity in the basal ganglia and corticomotor networks [120] that are crucial to gait performance.

Goal-based exercises provoke proprioceptive feedback through motor networks linking the dorsal basal ganglia with prefrontal cognitive circuits (associated with motor learning) involving the ventral basal ganglia [123]. Therefore, goal-based exercise may induce functional plasticity in networks involved in both cognitive and gait decline thus having as a result the improvement of both cognition and gait.

19.7 Level of Physical Activity in pwPD

Despite the evident benefits derived from exercise and physical activity, many pwPD are sedentary. Indeed at diagnosis—physical activity is rather low when compared to age-matched controls [124] even in pwPD with mild disease (Hoehn and Yahr I, H&Y I) with only 30% spending 30 min/day to walk [125].

There are a few studies investigating the habits to exercise of pwPD; a small sample of pwPD attending their routine visit was asked by Raje et al. [126] to complete a survey investigating what types of exercise they were used to do and whether they exercised regularly, in groups or alone. 71% of patients diagnosed with PD within the past 5 years participated in regular exercise. Walking was found to be the leading form of exercise, followed by stretching, weights, and biking. On average, patients participated in two to three different forms of exercise. Of those that exercised regularly, 28% reported strictly exercising alone, while 65% exercised in groups. These included dance classes and other group settings. Symptomatic improvements due to exercise were found to be significantly greater in patients participating in group exercise compared to patients who exercised alone. These data suggest that group activities can be helpful to patients to maintain adherence to regular exercise, which is consistent with previously published studies examining the differences between individual and group therapies. For example, Westheimer et al. [127] suggested that the social setting of dance therapy promotes continued attendance and improves Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total and gait and tremor subscores. Furthermore, the psychosocial aspects of group

exercise can contribute positively to alleviate psychological as well as physical symptoms in pwPD.

Although higher activity levels have been associated with better quality of life and better motor and cognitive performances [128] and exercise interventions proved to improve muscle strength, balance, motor symptoms, quality of life, and cardiorespiratory fitness [129] in pwPD, it has been shown that patients with mild to moderate PD have less physical activity than age-matched healthy controls (HC), with activity level declining over time [130, 131].

Recently, Amara et al. [132] reported on the impact of physical activity levels on motor and non-motor progression in early PD and described the longitudinal changes (over 2 years of observation) in physical activity. PwPD and HC were assessed for cognitive function with an extensive neuropsychological battery, for motor symptoms (both in ON and OFF condition) with MDS-UPDRS and H&Y stage, and for NMS with Scales for Outcomes in Parkinson's Disease-Autonomic Dysfunction; Geriatric Depression Scale, 15-item version; State-Trait Anxiety Inventory; Epworth Sleepiness Scale; and REM Sleep Behavior Disorder Screening Questionnaire. Participants were also evaluated yearly with the PASE. The PASE is a validated, self-reported questionnaire assessing the frequency, intensity, and duration of activity over the prior week [133]. All pwPD and HC were followed-up for 2 years. Although differences in physical activity measured by PASE at baseline between early pwPD and HC were not significant, only pwPD had decline in PASE scores longitudinally over the years. Because lower levels of physical activity are not a disease characteristic of PD per se, it may be suggested that the disease progression and accumulation of disability may lead to reduction in activity levels. Furthermore, higher physical activity levels at baseline were associated with less progression of disease severity, cognitive decline, and mood disorders in pwPD indicating that interventions to increase physical activity early in the course of PD could have beneficial effects on multiple aspects of the disease, including motor and NMS.

Other factors inducing decreased physical activity over time may be depression, daytime sleepiness, apathy, cognitive impairment, worsening of motor symptoms, fear of falling, and lack of self-efficacy (belief in one's capacity to overcome barriers).

However, it cannot be definitively concluded whether pwPD with more severe disease are less able to participate in physical activity, or if lower activity levels lead to worse motor phenotype. Most likely, this is a bidirectional relationship. In light of the heterogeneity of PD symptoms, exercise/activity prescriptions targeted toward the physical capability of individual patients may increase activity levels across a range of disease severity.

19.8 Effects of Exercise at Behavioral Level

Exercise is associated with neuromolecular, vascular, and structural modifications in the brain, which are supposed to play a part in improving cognitive, physical, and behavioral functions in the aging brain [134]. These changes have been associated with improvements at the behavioral level. Exercise does not take the edge off aging but it alleviates many systemic and cellular effects due to aging thus resulting in substantial therapeutic benefits [135].

Many randomized controlled trials and meta-analytic studies revealed the positive effects of exercise in pwPD at the behavioral level [136]. Multiple forms of exercise have been shown to be beneficial. Exercise programs generally contain four core ingredients: flexibility training, balance, strength, and aerobic/endurance training.

Dance, boxing, and tai chi contain different quantities of the core ingredients effective in improving targeted systems and overall function; furthermore, they provide additional benefit by facilitating social interaction and friendship.

Although it is not yet known which are the underlying mechanisms of exercise-induced benefits in pwPD, pwPD who are physically active or follow a regular exercise program have better outcomes than sedentary patients [128].

19.9 When and How to Exercise

The right timing of intervention with respect to PD onset, the best type of physical exercise (aerobic vs. resistance, group vs. alone, etc.), and the optimal frequency of workout are still an object of investigations.

According to the limited number of trials that have evaluated and examined the optimal dose-response effects of exercise in PD, better disease-modifying effects are obtained with higher-intensity aerobic and strengthening exercise [120, 137]. Similarly, outcomes reached with high-intensity balance exercises are better than those achieved with lower-dosed programs. The exercise program will be sketched out depending on the level of fitness of any individuals. A recent meta-analysis [138], evaluating the influence of the level of physical activity on the incidence of PD, showed that a significantly reduced risk of PD was associated with the highest levels of either total physical activity or moderate to vigorous physical activity, with stronger associations among men than among women. In contrast, light physical activity was not associated with PD risk. The dose-response analysis revealed that for each ten metabolic equivalent of task-hours/week increase in total or moderate to vigorous physical activity, the risk of PD among men decreased by 10 and 17%, respectively. No linear dose-response association was found between physical activity and PD risk among women, indicating that men and women may have different biological responses to physical activity.

In the perspective of modifying the disease course, physical exercise should be started as early as the onset of PD. Although many exercise studies enrolled patients with mild to moderate disability, several years after diagnosis, recently it has been shown that de novo pwPD may benefit from a 6-month high-intensity aerobic exercise in terms of a greater slowing down of motor symptom progression (as compared to patients in the control condition) [137].

Because physical, behavioral, and psychosocial barriers as well as low self-efficacy and poor outcome expectation may hold back pwPD from engagement in physical activity [139], personalized exercise programs may help in getting over these barriers and in facilitating engagement in physical activity and exercise.

Exercise programs must be readjusted regularly based on the disease course to ameliorate the benefit. The recent introduction of mobile health (mHealth) technologies may help in engaging pwPD in physical activity and exercise while staying connected to a physiotherapist or healthcare professional [140]. In regard to these technologies, the RIoT, a set of home-based Rehabilitation Internet-of-Things, has been shown to optimize exercise uptake and to increase physical activity [141]. A RIoT could include wearable devices with activity recognition sensors and instrumented rehabilitation devices (i.e., virtual reality systems) that send out data about quality and quantity of exercises to a smartphone or tablet. Telerehabilitation approaches allow healthcare professionals to regularly monitor the results obtained and to timely adapt the exercise intervention [142]. Exercises may be uploaded through smartphone applications ("apps") so that the exercise program could be set up to give the right challenge for each patient based on the level of performance reached. Strategies to motivate adherence such as goal setting, rewards, and feedback could be provided through apps to encourage a sound and active lifestyle.

19.10 Conclusions

There are enough evidence to suggest that exercise may positively influence the course of PD; however, new trials should be designed to account for the multisystem nature of PD, and further studies are needed to investigate the pathophysiological mechanisms underlying the effects of exercise on both cognition and mobility in pwPD. A better knowledge about these mechanisms would permit to embed personalized exercise programs in pwPD lifestyle since the early stage of the disease; furthermore, taking into account patients' preferences and ability will probably improve adherence. The support of digital technologies may pave the way for a precocious delivery (at the earliest stage) through later

stages of PD, modifying exercise protocols according to the evolving individual's needs.

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Exercise and Dementia

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Zahra Gholamnezhad, Mohammad Hossien Boskabady, and Zahra Jahangiri

Abstract

Several experimental and human studies documented the preventive and therapeutic effects of exercise on various diseases as well as the normal physiological function of different systems during aging. The findings of several basic animal studies and clinical investigations identified the advantageous effects of exercise as non-pharmaceutical intervention on dementia and Alzheimer's disease (AD). The main positive effects suggested for exercise are less cognitive and behavioral impairment or decline, development of health-associated conditions (stress, sleep), reduction of dementia risk factors including chronic non-communicable disease (diabetes, cardiovascular disease), increase in neurotrophins, enhancement of brain blood flow, angiogenesis, neurogenesis, synaptogenesis and synaptic plasticity in the brain memory-related region (e.g., hippocampus), and reduction of neuroinflammation and apoptosis. However, regarding the controversial evidence in literature, designing standard clinical and experimental studies to reveal the correlation between physical activity and dementia sign and symptom including biomarker alternation, brain supramolecular and molecular changes, and neuropsychological manifestation is necessary for preparation of effective guidelines and recommendations.

Keywords

Exercise · Physical activity · Dementia · Alzheimer · Prevention · Treatment

20.1 Background

Impairment of cognitive abilities and memory is known as dementia, which is a distressing disease with a high economic burden for aged population and health organizations. Alzheimer's disease (AD) is a main and common type of dementia, and by now there is no any approved treatment for this neurodegenerative disease. The fast-growing incidence of non-communicable chronic disease and the increasing geriatric population have elevated the number of AD patients in recent years, which is predicted to reach 95 million by the year 2030 [1]. Although several hypotheses have been proposed to explain the pathophysiology of AD, however, there is no confirmed etiology for the pathogenesis of this disease. Brain Aβ deposition is one of the

Z. Gholamnezhad (✉) · M. H. Boskabady · Z. Jahangiri
Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

Department of Physiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
e-mail: gholamnezhadz@mums.ac.ir

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_20

hallmarks of AD. Several factors, including excessive reactive oxygen (ROS) formation, impaired Aβ metabolism and hyperphosphorylation of protein tau, chronic low-grade neuroinflammation, vascular disorders, impaired metabolism and insulin resistance, abnormal basal autophagy, and mitochondrial dysfunction are indicated as pre-Aβ deposition in the pathogenesis of AD [2]. There is also cause and effect relationship between these etiological factors. For instance, chronic neuroinflammation as a main factor inducing neurodegenerative process could be the cause or effect of tau abnormal metabolism [3].

Therapeutic or preventive strategies for the management of AD disease should target these etiological factors. There is growing evidence about the beneficial effects of exercise in brain health promotion and slowing the AD-induced cognitive decline. Physical activity (PA) and exercise leads to circulatory and tissue elevation of catecholamines [4], endorphins [5], and neurotrophic factors such as brain-derived neurotrophic factor (BDNF) concentrations [6], improvement of cell metabolism and mitochondrial activity, and reduction in inflammatory mediators [7] and oxidative stress-induced neural damage [8], which are demonstrated as memory and cognitive enhancer factors. In addition, the effect of moderate exercise in reducing the risk of non-communicable chronic disease can result in healthy brain function during elderly years [9]. Similarly, moderate exercise can increase nerve growth in the hippocampus, thereby enhancing memory and learning ability [10]. However, effects of different loads (mild, moderate, or severe) and durations (acute or chronic) of exercise training on long-term memory have been unclear. According to researches of a human systematic review, acute exercise has more effect than chronic exercise on long-term memory. The mechanism of improving long-term memory induced by acute exercise is related to both encoding and consolidation of new information. Also, chronic exercise mostly affects the signal transduction of memory processing and had a small effect on long-term memory [4]. However, both human and animal studies demonstrated that chronic exercise has an effect on long-term memory and cognition. The improving effects of chronic exercise on molecular mechanism, including mitogen-activated protein kinase (MAPK), N-methyl-D-aspartate (NMDA)-receptor, BDNF, and cAMP response element binding (CREB, long-term neuronal plasticity critical factor), as well as behavioral hippocampal-related memory tasks offer gross support of chronic exercise on long-term memory [11, 12].

The beneficial effects of exercise on brain biochemical, structural, and cognitive functions related to dementia were summarized in Fig. 20.1.

20.2 Exercise and Amyloid-β, the Role of Neuroinflammation

Although genetic defect has a key role in the pathology of early-onset AD, late-onset AD is not induced by amyloid precursor protein (APP), presenilin-1 (*PS1*), *PS2*, and *tau* mutant genes. Instead, in late-onset AD progression, amyloid-β formation followed by neurofibrillary tangles deposition is a chronic condition. It is believed that there is a close interaction between tau formation and chronic inflammation. It means that not only there is activation of immune system components (microglia and astrocytes) in the brain but also systemic or neuroinflammation may result in amyloid-β formation and AD induction. Recently bioinformatics and genetic data have supported the clinical and preclinical findings regarding the increase in circulatory and brain tissue concentrations of immune system mediators such as chemokines and inflammatory cytokines [13]. In addition, activation of microglia in the aged brain might lead to increase in messenger RNA (mRNA) expression of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor α (TNFα) [14].

It was showed that mitochondrial lysates of a mouse microglial cell line induced the production of pro-inflammatory transcription factor nuclear factor κ of B cells (NFκB) which activated the signaling pathway related to p38

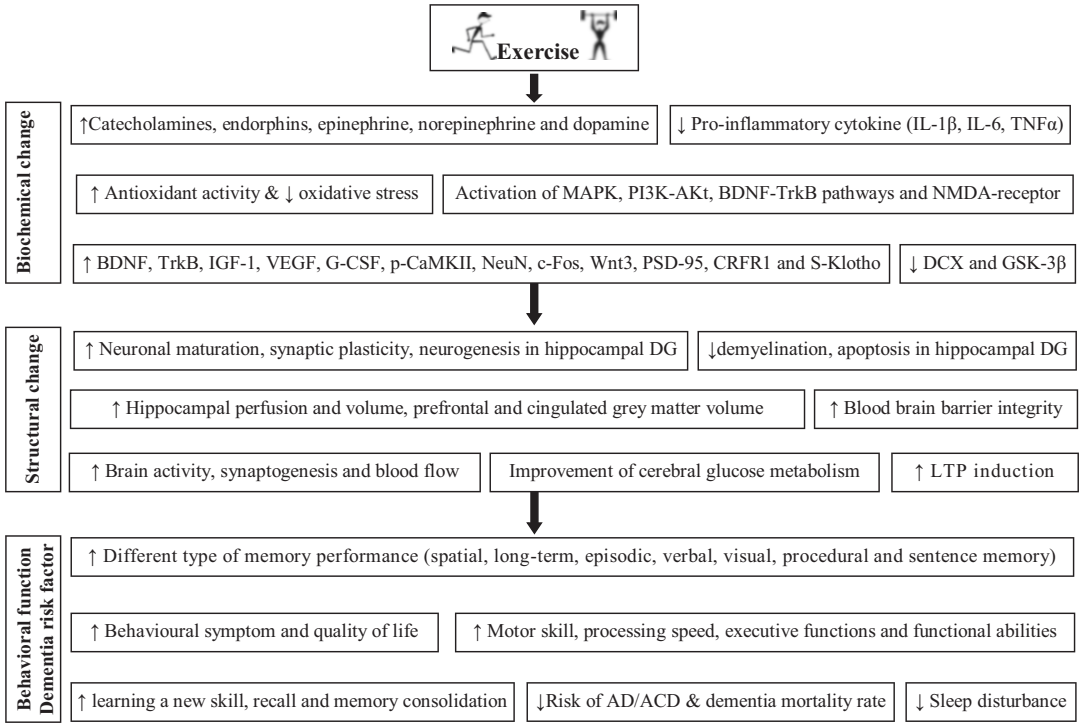

Fig. 20.1 Beneficial effects of exercise on brain biochemical, structural and cognitive functions related to dementia. *IL* interleukin, *TNFα* tumor necrosis factor α, *MAPK* mitogen-activated protein kinase, *PI3K* phosphoinositide 3-kinase, *Akt* protein kinase B, *BDNF* brain-derived neurotrophic factor, *TrKB* tropomyosin-related kinase, *NMDA* N-methyl-D-aspartate, *IGF-1* insulin-like growth factor, *VEGF* vascular endothelial growth factor, *G-CSF* granulocyte-colony stimulating factor, *CaMK* Ca_2^+/calmodulin-dependent protein kinase, *NeuN* neuronal nuclei, *PSD-95* postsynaptic density protein 95, *CRFR1* corticotropin-releasing factor receptor 1, *S-Klotho* Klotho secreted protein, *DCX* doublecortin, *GSK-3β* glycogen synthase kinase 3 beta, *DG* dentate gyrus, *LTP* long-term potentiation, *AD* Alzheimer disease, *ACD* all cause dementia

MAPK. Therefore, it leads to increase in the cytokines TNFα and IL-8 and matrix metalloproteinase 8(MMP-8) mRNA expression, while reducing the mRNA level of triggering receptor expressed on myeloid cells 2 (TREM2) which code inhibitory protein for cytokine production [15]. Exercise reduces neuroinflammation and neural tissue oxidative stress through inhibition of pro-inflammatory cytokine (IL-1β, IL-6, TNFα) local and systemic production [16, 17] and enhancement of antioxidant activity of plasma [18, 19]. Recent systematic review and meta-analysis findings indicated that exercise alleviates TNFα and IL-6 expression, while increasing BDNF expression, which attenuated the memory impairment and cognitive decline in mild cognitive impairment (MCI) and AD patients [20].

APP and PS1 gene mutant mouse is an experimental model of AD. Long-term treadmill exercise alleviated cognitive impairments through reduction in activated microglia and increase in BDNF-positive cells of the cerebral cortex and the hippocampus [21, 22]. Neurodegeneration in the amygdala and hippocampus as the most important temporal lobe structures has been considered as the quick onset of AD indicator [23]. In APP/PS1 transgenic mice, treadmill exercise increased neuronal function in CA1 and CA3 of the hippocampus and amygdala-associated long-term memory by improvement of BDNF signaling pathways and clearance of Aβ [24].

There is controversial result regarding the effect of exercise on Aβ formation in human studies. It was suggested that moderate- to high-intensity physical exercise including ergometer

bicycle, cross trainer, and treadmill (70–80% maximum HR, 10 min for 12 weeks) could not modulate Aβ and tau concentrations in cerebrospinal fluid (CSF) of patients with mild Alzheimer's disease. So, the beneficial effect of physical exercise on cognition might not be associated with modulation of Aβ and tau in CSF of Alzheimer's patients [25].

20.3 Exercise and Memory-Related Brain Signaling Molecules

Signaling pathways related to BDNF and insulin-like growth factor (IGF-1) are main regulators of learning and memory function improvement. BDNF has a key role in neural plasticity and brain neurotrophic signaling pathways [26, 27]. Moreover the regulatory effect of this CNS neurotrophic factor in peripheral metabolism and homeostasis has been shown. BDNF cell signaling mediators, including tropomyosin-related kinase B (TrKB) receptor, Ras mitogen-activated protein kinase (Ras-MAPK), phosphoinositide 3-kinase (PI3K), and phospholipase Cγ (PLC), are promoters of neuronal proliferation, differentiation, synaptic activity, and survival. In addition, PLC induces inositol-1,4,5-trisphosphate (Ins-1,4,5P3) and diacylglycerol-mediated protein kinase C (PKC) activation, resulting in Ca_2^+/calmodulin-dependent protein kinase (CaMKII, CaMKK, and CAMKIV)-mediated CREB stimulation and long-term potentiation (LTP) that induce synaptic plasticity [12].

IGF-1 is the other main mediator of brain neural plasticity, neurogenesis, and apoptosis, and its receptor is distributed in most regions of the brain, while IGF-1 mRNA is expressed in a particular section of the brain like the hippocampus [28]. Activation of IGF-1 pathway acts as a neurotrophic and neuroprotective mediator by inhibiting neural, fibroblast, and other cell apoptosis. Moreover insulin receptor substrates (IRSs) are Ras-MAPK and PI3K/AKT pathway activators as well as regulators of neural function and development [29].

In experimental animal models of memory deficit, the protective effects of exercise on inhibition of BDNF and its related signaling pathways have been indicated [30]. Exercise induces neurogenesis and ameliorates the toxic effect of Aβ injection in rat via stimulation of the expressions of BDNF and TrkB in the hippocampal dentate gyrus, elevation of BDNF and p-CaMKII, and inhibition of the upregulation of calcineurin during early long-term potentiation (E-LTP) [31, 32]. In an animal model of ethanol-induced memory impairment, exercise increased LTP induction and the hippocampal dentate gyrus BDNF concentration [33]. In LPS-induced neural toxicity and low-grade inflammation, the protective effect of exercise may be through the PI3K-AKt pathway activation and inhibition of double-cortin (DCX) expression as well as increase of the BDNF, TrkB, and neuronal nuclei (NeuN) expressions and cell proliferation, synaptic plasticity, and neurogenesis in the hippocampal dentate gyrus [34–36]. Exercise alleviates scopolamine-induced mice amnesia by activation of BDNF-TrkB pathway and increasing hippocampal cell proliferation [37].

Central or peripheral injection of streptozotocin is a common animal model of diabetes and brain metabolic dysfunction. It has been shown that treadmill exercise might ameliorate diabetes-induced memory deficits and neurodegenerative disorders through modulation of several mechanisms. Exercise increases the expression of immediate-early gene *c-Fos*, *BDNF*, *TrkB*, and *Wnt3*, astrocytic proliferation, neurotrophic factor production, blood-brain barrier integrity, and suppression of *GSK-3β* expression, which lead to the hippocampal neural plasticity and inhibition of apoptosis in the hippocampal dentate gyrus [38, 39].

In an ischemic model of stroke, the preventive effect of mild exercise on spatial memory and synaptic plasticity impairment through increasing the BDNF and postsynaptic density protein 95 (PSD-95) levels and enhancement of neuronal maturation and cell proliferation has been indicated [40–42].

The protective effect of exercise in autoimmune encephalomyelitis-induced memory deficit

might be mediated by suppression of demyelination and apoptosis and elevation of cell proliferation and BDNF expression in hippocampal dentate gyrus [43].

It was also reported that exercise increases the central corticotropin releasing factor receptor 1 (CRFR1) expression in the amygdala, prefrontal cortex, and hypothalamus, which leads to improvement of spatial memory impairment of post-traumatic stress disorder [44].

Those mentioned experimental animal studies have been approved in human clinical trials. It was indicated that a single bout (35 min) of three types of PA, including moderate physical aerobic exercise (using the interactive Xbox Kinect™ application), cognitive training (using a computerized working memory training program, Cogmed™), and mindfulness practice (using the Mindfulness application), increased the serum level of BDNF in healthy older persons. However, the effect of moderate physical exercise on serum BDNF level was higher than two other types of activities. This study also indicated the correlation between post-single bout of exercise elevation of serum BDNF and working memory improvement [45]. Skriver et al. reported that an intense bout of cycling increased the plasma levels of IGF-1, epinephrine, norepinephrine, dopamine, and lactate immediately and 15 min following exercise as well as enhanced the concentration of plasma BDNF and vascular endothelial growth factor (VEGF) immediately after exercise in healthy young people. Thus, acute exercise improved motor skill in adults through increased peripheral biomarkers involved in memory and learning processes [4]. However, the results of Maass et al.'s study showed that long-term aerobic treadmill exercise (3 months) did not affect the levels of neurotrophic and angiogenic growth factors, such as BDNF, VEGF, platelet-derived growth factor-C (PDGF-C), and IGF-1, in the blood of healthy older humans but increased hippocampal fitness-related vascular plasticity levels. The latter effect was associated with increase in hippocampal perfusion and volume that could be mediated by exercise-induced angiogenesis effect [46].

It had been reported that low-intensity gymnastics exercise (30–40% of maximal exertion) and medium-intensity Nordic walking (50–60% of maximal exertion) had the similar positive effect on increase of episodic memory performance in Auditory Verbal Learning Test (AVLT) of healthy elderly individuals. However, moderate-intensity aerobic exercise increased prefrontal and cingulated region gray matter volume (assessed by magnetic resonance voxel-based morphometry) and BDNF levels compared to low-intensity aerobic exercise [47]. In another study a short-term intense aerobic exercise on a bicycle ergometer (60 min, 3 times a week for 6 weeks) improved verbal memory performance in verbal learning and memory test (VLMT) as well as BDNF levels in young and healthy male [48].

Results of a randomized controlled trial (RCT) reported that older adults walking (60–75% maximum HR, 40 min for 7 weeks) improved spatial memory (using computerized spatial memory task) as well as increased the serum levels of BDNF as mediator of neurogenesis and neuroplasticity [49].

A cross-sectional study of older community-dwelling individuals showed that high PA led to better performance in AVLT and increased the levels of neurotrophin granulocyte colony-stimulating factor (G-CSF). So, exercise had a beneficial effect on cognitive functions in healthy older adults [50].

It had been reported that combined exercise including high-intensity interval training (90–95% maximum heart rate (HR), 20 min, 3 times a week for 6 week) and cognitive training (training on a computerized version of the concentration memory task, 20 min, 3 times a week for 6 weeks) improved performance on a high-interference memory task and had synergistic effects on hippocampal function through increased proliferation and survival of new cells as well as supported their survival in the hippocampal dentate gyrus of healthy young adults. Also, exercise training increased serum levels of BDNF and IGF-1 in adults and led to improved memory performance [51].

It was also reported that an acute bout of post-learning aerobic exercise on a stationary bicycle (70% VO_2R, 6 min) increased the endogenous level of norepinephrine of salivary alpha-amylase, activated noradrenergic system, and enhanced recall and memory consolidation in both healthy and MCI aged participants [52].

Recent evidence identified the *klotho* gene expression in the brain and the role of its secretory protein (S-Klotho) in brain functions, including hippocampal neural progenitors, and Purkinje cell number (klotho, the key to healthy brain aging). The protective effect of this gene against aging-induced neurodegenerative disease has been demonstrated in both mutant mouse model and human correlational study. Lower level of CSF klotho was identified in older adults with AD, and it was more pronounced in women than men [53]. PA is showed to be involved in signaling pathways related to the regulation of the S-Klotho circulatory levels. In a FIT-AGING program, the effects of different exercise modalities (high-intensity interval training and electromyostimulation) on plasma levels of S-Klotho and other biomarkers, physical fitness, and cognitive and metabolic parameters were evaluated in healthy adults (45–65 years). The results showed association between PA and plasma levels of S-Klotho [54].

20.4 Exercise and Memory-Related Brain Structures

Functional brain imaging techniques, including magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), and positron emission tomography using 18F-fluorodeoxyglucose (FDG-PET), provide important information about functional and structural situation of different brain regions. Volumetric MRI helps to diagnose regional brain atrophy patterns, fMRI measures brain blood oxygen level and also hemodynamic activity, and by the FDG-PET results, the posterior cingulate cortex and precuneus hypometabolism is detectable in the early stage of dementia and AD [1].

The results of 6-month aerobic or stretch exercise training (40 min, 3 times/week) in MCI people showed an improvement of [^{18}F] FDG-PET measurement of cerebral glucose metabolism in the important brain region of interest, which might explain the positive effect of exercise on memory [55]. In addition, the advantageous effect of 3-month aerobic and strength training (90 min, 3 times/weeks) on result of [^{18}F] FDG-PET in elderly women (75–83 years old) was showed as enhancement of brain activity of specific regions, including the precuneus and entorhinal cortex [56]. High PA in older community-dwelling individuals increased the levels of prefrontal and cingulate gray matter volume which were assessed by magnetic resonance voxel-based morphometry [50].

The exercise (12-week moderate-intensity treadmill walking) improved the cognitive function in the MCI patients which has been supported by task-activated fMRI changes but elevation in fMRI activation was not significant [57]. A cross-sectional study of older adults with MCI reported that moderate physical activity (aerobic exercise, 6 min at 70% VO2 max on a stationary bicycle) was positively associated with an increase in hippocampal volume during structural MRI. Data showed that increase in the duration of moderate physical activity led to greater hippocampal volume and activation of the noradrenergic system in older adults. Hippocampal volume was also directly correlated with memory in humans [58]. Walking in older adults increased the hippocampal perfusion and volume in MRI measurement [49]. Moreover, short-term intense aerobic exercise on a bicycle ergometer increased left anterior hippocampal activation in fMRI in young and healthy males [48].

In MCI patients and older adults, there was a positive correlation between cardiorespiratory fitness and white matter integrity which was measured by diffusion tensor imaging [59, 60]. Improvement in white matter integrity has been related to the development of cognitive performance [59]. However, it was shown that 16 weeks of moderate- to high-intensity aerobic training in individuals with mild to moderate AD did not affect the whole or regional cerebral blood flow

which was measured through imaging techniques, including T1-weighted magnetization-prepared rapid gradient-echo, pulsed arterial spin labeling, and fluid-attenuated inversion recovery [61].

20.5 Exercise and Dementia Risk Factors

Despite the fact that some studies had not approved the preventive effects of PA in dementia, most of them reported a negative association between exercise and dementia risk factors. Recently a systematic review and meta-analysis investigated the effects of leisure-time PA on all-cause dementia (ACD), AD, and vascular dementia (VD) risk factors. The authors found a dose-response association between PA and AD or ACD, but not for VD. The impact of the higher intensity of PA was more than that of lower intensity. The specific range of effective exercise was 0–2000 kcal/week or 0–45 MET-h/week, and increasing it to 10 MET-h/week or 500 kcal/week was accompanied with lower risk of AD and dementia (~13% and ~ 10%, respectively) [62]. It was also proposed that the effect of PA is more pronounced in AD prevention than ACD, and it has no effect on VD [63]. In a cohort study of Norway, the association of dementia with psychological distress and leisure-time PA was evaluated. There was a negative association between leisure-time PA and risk of mortality rate related to dementia, but psychological distress increased this risk. Interestingly, the leisure-time PA impact on dementia mortality rate was equal in the absence or presence of psychological distress. These findings emphasized the importance of leisure-time exercise in elderly and middle-aged adults [64].

Another prospective cohort study evaluated the impact of leisure-time PA on risk of dementia improvement among individuals with MCI. Moderate PA and not mild or severe exercise, during middle age of life, decreased the incidence of dementia in aging. Moreover mild and moderate exercise had no significant effect on this risk. These results show the dose-response effect of exercise on dementia risk factors [65].

20.6 Exercise and Cognitive or Behavioral Response

The advantageous effects of exercise on the behavioral responses in various animal models of AD have been shown [30]; these experimental findings also have been approved in clinical studies.

Results of a systematic review investigating the core outcome set of clinical studies evaluating the effect of exercise on dementia showed the following outcomes as the most important, common, and frequent among 133 domains of outcome which were measured through 267 different tools. The most frequent outcome was functional abilities and independence which had been improved by PA. Despite the heterogeneity of studies making the cognitive function results inconclusive, this outcome was the most commonly measured. The positive effects of exercise on this outcome may be mediated through increase of brain synaptogenesis and blood flow and suppression of inflammatory process. Exercise-induced reduction in falling risk (balance) is another desirable outcome [66]; however, there is a report mentioning it as a side effect. Improved behavioral symptoms and quality of life are the other important outcomes; however, there is limited and controversial evidence about them, and future investigation is needed for developing clinical recommendations and guidelines [67].

20.6.1 Effect of Exercise on Quality of Life

Previous studies' outcomes showed controversial findings regarding the impact of exercise on quality of life in patients with dementia. However, a recent study indicated that PA in patients with dementia reduced the sleep disturbance [68].

The beneficial effect of exercise for increasing the quality of life in patients with dementia was

evaluated in a systematic review. The results of interventional studies showed non-significant and small effect of exercise on patient's quality of life [69]. In another scoping review, the outcomes of 20 kinds of PA in 48 evaluated articles showed large, medium, and small effects in 50% of the studies. The recommended PA in old people with mild to moderate dementia are isometric strength, 6-min walk test, repeated chair stand tests, timed up-and-go, short-distance gait speed, and Berg balance scale training [70].

20.6.2 Effect of Exercise on Executive Functions

Deficit in executive functions, including memory, attention, planning, reasoning, and cognitive flexibility, is a hallmark of dementia in patients with AD disease [71]. Evidence from an RCT had showed that the acute combination training including aerobic exercise (60–80% maximum HR, 24 min, 3 times a week for 4 weeks) and strength training (6 min, 3 times a week for 4 weeks) led to improvement of different types of cognitive functions. After exercise, there was improvement in executive functions (tested by Stroop test and verbal fluency task), episodic memory (tested by logical memory and first and second names), and processing speed (tested by digit symbol coding and symbol search) of healthy elderly people [72]. The post-interventional results of 12-week exercise on psychomotor speed, episodic memory, working memory, and executive function were assessed in an RCT of three groups, including exergame (exercise combination with cognitive stimulation) training, aerobic training, and an active control. Aerobic and exergame training improved psychomotor speed of patient with dementia compared to control group, while the exercise and exergame had no significant effect on other cognitive assessments [73]. The beneficial effect of regular and long-term physical exercise at home (1 h, twice a week for 12 months) was indicated in an RCT. Exercise improved the executive function and had positive results on the clock drawing test in older people with Alzheimer's disease [74]. In addition, physical exercise habit had beneficial effects on cognitive performance and daily living activities in a community sample. It had been shown that prolonged exercise habit (more than 5 years of exercise) leads to better cognitive and functional ability in the Cantonese version of the mini-mental state examination and the Chinese version of disability assessment in dementia of Chinese older adults [75].

A systematic review evaluated the results of six eligible clinical studies and showed the effectiveness of exercise on improvement of executive function in community-dwelling older adults with AD [76]. Moreover, the results of a systematic review with meta-analysis emphasized the effects of both aerobic and resistance exercise on cognitive function improvement in individuals older than 50 years without considering their cognitive status [77].

However, there are also controversial studies. The evaluation of the perceptions of aged people with or without dementia toward the Wheelchair-Bound Senior Elastic Band exercise program showed no difference between groups. Therefore, a long-term exercise program might be done in these patients using self-rating survey and participants' feedback [78]. It was also reported that persons with dementia could benefit from a moderate exercise composed of balance and strength activities [79]. Findings of an RCT reported that a bout of progressive high-intensity treadmill exercise (15 min) before memory encoding was more effective in increasing long-term memory performance (measured using the Rey auditory verbal learning test) compared to treadmill training during memory encoding or consolidation in young adults. But, the differential temporal effect of exercise had no effect on short-term and prospective memory in adults [80]. It had been suggested that an acute high-intensity interval training (80% reserve HR, 3 min) improved the performance effect on selective attention (assessed by the Victoria version of the Stroop test), but had no effect on short-term memory (assessed by the digit span test), in healthy middle-aged adults [81]. Another randomized controlled study reported that 12 weeks of

different training exercises including resistance (high-intensity strength training on isotonic machines), cardiovascular (moderate- to high-intensity treadmills, cycle ergometers, and step ergometers), and postural training (low-intensity postural and balance exercises) had similar effects on improvement of memory complaint questionnaire (MAC-Q) scores in aged people with memory complaints. However, it did not have any effect on objective memory performance (measured using the prose test and Rey test) in aged adults [82]. Another study suggested that physical activity had a positive influence on performance related to neuropsychological tests of visual episodic memory and experimental face-name learning test of visual episodic memory in the older adults. However, it had no effect on the performances in younger adults. Performance was also positively associated with physical activity intensity (step rate) that was assessed by an accelerometer [60].

It had been also reported that intense exercise prior to encoding led to better performance of procedural memory (assessed by serial order task) and sentence memory (assessed by text memory task) and improved long-term memory, but it did not have any effect on paired-associate learning. Therefore, exercise might have an effective role in learning a new skill or recalling new information [83].

20.7 Perspective

Health benefit effects of exercise training and PA are a well-known matter among people. However, adults' (especially middle-aged and old individuals) participation in PA program is poor. There are contradictory recommendations to encourage individuals for PA performance. In general, self-reporting and self-regulation behavior change technique is suggested in adults [84], but this approach is associated with lower participation of adults older than 60 in PA [85]. In a recent systematic review, a combination of goals, including social support, communication, and goal setting (behavior), is recommended in older people with dementia [86]. In addition, there is heterogeneity among outcomes of present clinical investigations and few of them have a well-defined outcome. Moreover, there are several types of dementia with different stages of disease, and the therapeutic potential and preventive effect of different modalities and durations of exercise training and their brain-specific action need to be more elaborated. Taken together, designing standard clinical and experimental studies with reliable measures is necessary for preparation of the effective guidelines and recommendations. These studies should reveal the correlation between physical activity and dementia signs and symptoms, including biomarker alternation, brain supramolecular and molecular changes, and neuropsychological manifestation.

Acknowledgments *Competing financial interests*: The authors declare no competing financial interests.

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Exercise and Schizophrenia

21

Javier Bueno-Antequera
and Diego Munguía-Izquierdo

Abstract

Schizophrenia is a psychiatric disorder characterized by distortions of thinking and perception, with no strictly pathognomonic symptoms that can be divided into positive, negative, and cognitive symptom domains. People with schizophrenia have, between others, a reduced life expectancy and cardiorespiratory and muscular fitness and increased risk of cardiovascular disease, metabolic syndrome, obesity, hypertension, and hyperlipidemia compared to the general population. Furthermore, the economic burden of mental disorders including schizophrenia is evident and it is expected to increase to more than double by 2030. Therefore, reducing the growing burden of mental disorders such as schizophrenia should be a health priority. Improved prevention and treatment are two key factors that may reduce the burden of schizophrenia. Pharmacological- and psychotherapy-based interventions have been traditionally considered for treating schizophrenia disorders; however, there is an increasing amount of scientific evidence confirming that physical activity and physical exercise should be highly considered in prevention and treatment of schizophrenia disorders. In this chapter, we aim to summarize and discuss the research progress of physical activity and exercise in prevention and treatment of schizophrenia disorder. Specifically, we summarized and discussed the research progress of the prognostic use of physical activity for incident schizophrenia; the importance of other outcomes typically improved by physical activity/exercise such as obesity and fitness (cardiorespiratory and muscular fitness) for future schizophrenia; the research progress of the evidence of the benefits of exercise in people with schizophrenia disorders differentiating between effects of exercise on varied health outcomes, cognitive functioning, and cardiorespiratory fitness; and finally the clinical practice recommendations.

J. Bueno-Antequera
Physical Performance Sports Research Center, Department of Sports and Computer Science, Section of Physical Education and Sports, Faculty of Sports Sciences, Universidad Pablo de Olavide, Seville, Spain

Research Group in Development Movimiento Humano, Universidad de Zaragoza, Zaragoza, Spain

D. Munguía-Izquierdo (✉)
Physical Performance Sports Research Center, Department of Sports and Computer Science, Section of Physical Education and Sports, Faculty of Sports Sciences, Universidad Pablo de Olavide, Seville, Spain

Research Group in Development Movimiento Humano, Universidad de Zaragoza, Zaragoza, Spain

Biomedical Research Networking Center on Frailty and Healthy Aging, Madrid, Spain
e-mail: dmunizq@upo.es

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_21

Keywords

Schizophrenia · Psychosis · Physical activity · Obesity · Physical fitness · Exercise

21.1 Introduction

Schizophrenia is a psychiatric disorder characterized by distortions of thinking and perception, with no strictly pathognomonic symptoms that can be divided into positive, negative, and cognitive symptom domains [1]. Overall, these symptoms result in serious functional impairment, which substantially interferes with or limits major life activities [2].

Schizophrenia is 1 of the 20 leading causes of disability worldwide [3] and is a major contributor to all-cause mortality and reduced life expectancy [4–8]; this is mainly due to physical health comorbidities, such as cardiovascular, metabolic, and respiratory diseases [9, 10]. Compared to the general population, people with schizophrenia/psychosis have an increased risk of cardiovascular disease [11]; metabolic syndrome and cardiometabolic abnormalities [12]; diabetes mellitus [13, 14]; obesity, hypertension, and hyperlipidemia [15]; high smoking prevalence [16]; impaired lung function, pneumonia, chronic obstructive pulmonary disease (COPD), and chronic bronchitis [17]; and multimorbidity (i.e., two or more physical health conditions) [18]. The global economic burden of mental disorders in 2010 was comparable to that of cardiovascular diseases and was higher than that of cancer, chronic respiratory diseases, and diabetes, and it is expected to more than double by 2030 [19]. Therefore, reducing the growing burden of mental disorders such as schizophrenia [20, 21] is a global health priority [22].

Pharmacological- and psychotherapy-based interventions have been traditionally considered for treating schizophrenia disorders. However, there is an increasing amount of scientific evidence [23–27] confirming that physical activity (defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" [28]) and physical exercise (defined as "a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness" [28]) should be strongly considered in the prevention and treatment of mental disorders such as schizophrenia. These patients have lower levels of physical activity and higher levels of sedentary behavior (defined as "any waking activity characterized by energy expenditure ≤1.5 metabolic equivalents while in a sitting or reclining posture" [29]) than the general population [30]. In this chapter, we aim to summarize the research progress of physical activity and physical exercise in the prevention and treatment of schizophrenia.

21.2 Physical Activity and Other Outcomes as Predictors of Incident Schizophrenia

21.2.1 Physical Activity as a Predictor of Incident Schizophrenia

As in other mental disorders, such as depression [31–37], low physical activity has been suggested to be a predictor for schizophrenia. However, compared with depression, the accumulated evidence of the prognostic use of physical activity for incident schizophrenia remains scarce. Some prospective studies will be described and discussed below.

A study published in 2010 carried out by J Koivukangas, T Tammelin, M Kaakinen, P Maki, I Moilanen, A Taanila, and J Veijola [38] evaluated the level of physical activity in a relatively large cohort sample of adolescents (15–16 years of age) who participated in the Northern Finland Birth Cohort 1986 (NFBC; for more details see [39]) by responding to a postal inquiry that used a single question about the time engaged in moderate to vigorous physical activity outside of school. The respondents were then invited to participate in a clinical examination that included the assessment of prodromal symptoms of psychosis using the PROD-screen that consists of 29 questions assessing performance and symptoms and has been developed to be used in clinical

settings [40]. In addition, the Finnish Hospital Discharge Register was used to ascertain the parental and adolescent's psychosis status. The adolescents who developed psychosis were 3.3 (CI 95% 1.4–7.9) times more likely to be physically inactive (defined as not at all active or approximately half an hour of moderate to vigorous physical activity per week) compared to those who did not develop psychosis. Interestingly, the familial risk for psychosis was not associated with physical inactivity. The main limitation of this study was that the findings were based on self-reported data on both physical activity and risk for psychosis. Additionally, the number participants who had a future psychosis was very low (N = 33; 14 boys and 19 girls) compared with those who did not have this risk (N = 6946; 3349 boys and 3597 girls). Despite these limitations, this study suggested that low levels of physical activity in adolescence may increase the risk of schizophrenia onset and can be considered as one of the early pieces of evidence on physical activity as a predictor of schizophrenia.

In 2016, A Okkenhaug, T Tanem, A Johansen, UK Romild, HM Nordahl, and B Gjervan [41] published a study investigating whether there were specific patterns of physical activity in the premorbid phase of schizophrenia and whether these participants differed from those with bipolar disorder and healthy controls. The study was composed of adolescents who participated in the Young-HUNT1 1995–1997 study and the Nord-Troendelag Health study (HUNT study; for more details see S Krokstad, A Langhammer, K Hveem, TL Holmen, K Midthjell, TR Stene, G Bratberg, J Heggland, and J Holmen [42]). All participants self-reported their levels of physical activity using a two-question survey to measure the hours and days spent on exercise or sports during the previous week. There were also questions concerning the types and levels of activity. The participants who later developed schizophrenia and bipolar disorders were identified through the patient administrative system of the Nord-Troendelag Health Trust Department of Psychiatry in Levanger Hospital and Namsos Hospital. Fifteen participants (11 boys and 4 girls), with a mean age at data collection of 17 years (ranging from 13 to 18), and 18 participants (10 boys and 8 girls), with a mean age at data collection of 16 years (ranging from 13 to 18), later developed schizophrenia and bipolar disorder, respectively. The healthy control group consisted of 120 adolescents, with the same sex and age distribution as the baseline cases. The adolescents who later developed schizophrenia were less physically active, with fewer days and hours per week of activity compared to those who later developed bipolar disorder and compared to the healthy control group. In addition, the adolescents who later developed schizophrenia also participated less in team sports than the control group. Although having few cases of schizophrenia, this study again suggests that a low weekly volume and frequency of exercise/sports during adolescence is associated with future schizophrenia.

The study carried out by Suetani [43] examined the association between physical activity at age 14 and mental health outcomes at age 21 using a large birth cohort study conducted in Queensland, Australia, between 1981 and 1983: the Mater-University of Queensland Study of Pregnancy (MUSP; for more details see [44, 45]). A total of 3493 participants (1641 boys/men and 1852 girls/women) were analyzed. At the 14-year-old follow-up, participants self-reported their frequency of physical activity using a single question: How often did you exercise or play sports in the last week? At age 21, some mental health-related outcomes were recorded, including measures of common mental disorders and psychosis-related outcomes. Although no significant association was found between participation in exercise/sports at age 14 and having a psychotic disorder diagnosis at age 21, the authors found significant associations between participation and several psychosis-related outcomes. Specifically, they found positive relationships between no participation in exercise/sports at age 14 and an increased number of delusional experiences and auditory and visual perceptual disturbances at age 21 compared to those in the frequent participation exercise/sports group (4–7 days/week). These results suggest that a low level of

physical activity is associated with an increased risk of future schizophrenia.

The study of Sormunen [46] examined whether physical activity levels in childhood and adolescence independently predict the later development of non-affective psychosis using data from the Cardiovascular Risk in Young Finns study (YFS; for more details see [47]). In total, 3596 children and adolescents from 6 different age groups (3, 6, 9, 12, 15, and 18 years) were randomly selected from the national register from 5 Finnish population centers (Helsinki, Turku, Tampere, Kuopio, and Oulu) and reported their levels of physical activity in 1980, 1983, and/or 1986. Half of the individuals participated in all three study visits (1980–1986), and the rest participated in either two visits (25%) or one visit (25%). Physical activity was assessed with a self-report questionnaire that included questions about the following activities: frequency of 30 min or more of leisure time physical activity per day, intensity of physical activity and sport, frequency of training sessions at a sports club, participation in sport competitions, and the main activity during leisure time, with three possible answers—(1) indoors or reading, (2) indoors/outdoors and walking or spending time with friends, and (3) outdoors and exercising a lot. All questions had a score, and the sum of all measurements was used to calculate a physical activity index. The authors reported that this questionnaire had been previously validated against accelerometers and pedometers [48]. However, this validation study was carried out in young adults (from 24 to 39 years) and not in children and adolescents (from 3 to 18 years). From 1980 to 2012, the Finnish National Hospital Discharge Register showed that 68 (40 men and 28 women) of the 3596 participants were diagnosed with non-affective psychosis based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, and 41 (60%) cases had schizophrenia, schizophreniform disorder, or schizoaffective disorder. Lower physical activity during childhood and adolescence was related with the later development of non-affective psychosis. Specifically, after adjusting for covariates, such as sex, age, body mass index, birth weight, non-preterm birth, and mother's mental disorders, a one unit lower physical activity index, less communal activity during leisure time, and not participating in sports competitions between the ages of 9–18 were, respectively, associated with a 26%, 71%, and 158% higher risk of any non-affective psychosis. Interestingly, the findings were even stronger for schizophrenia, showing a 43%, 76%, and 388% increased risk from these physical activity measures and a 71% higher risk of schizophrenia in those with a lower intensity of physical activity/sports during childhood and adolescence. These results add to the aforementioned studies regarding the importance of considering the intensity of the physical activity as a preventive factor of future schizophrenia.

The four aforementioned prospective studies highlighted the preventive effects of physical activity during childhood, adolescence, and young adulthood on future schizophrenia. However, these findings should be considered with caution due to some issues. For example, the four studies used self-report methods for measuring physical activity, which may be prone to bias. Further, none of the physical activity questions/questionnaires were previously validated in the target population. Therefore, the use of objective and validated self-report methods for measuring physical activity may improve the current knowledge regarding the role of physical activity in schizophrenia onset. In this regard, two recent studies require discussion. In 2017, MJ Duncan, K Arbour-Nicitopoulos, M Subramaniapillai, G Remington, and G Faulkner [49] expanded the initial validation study of the Short-Form International Physical Activity Questionnaire (IPAQ) by examining the retest reliability over a 4-week period, assessing validity with a larger sample, and comparing the validity of the IPAQ to a 24-hour recall alternative among individuals with schizophrenia. They found that the test-retest reliability was low, and the correlation with an accelerometer was weak. Two years later, J Firth, B Stubbs, D Vancampfort, FB Schuch, S Rosenbaum, PB Ward, JA Firth, J Sarris, and AR Yung [50] used baseline data from the UK Biobank (2007–2010), including 1078 people with schizophrenia and 450,549 without, and

showed that the Short-Form IPAQ measures in epidemiological studies fail to capture the reduced activity levels in schizophrenia patients. Therefore, an international group is working on a worldwide project to study the validity and reliability of the Simple Physical Activity Questionnaire (SIMPAQ; for more details see [51], http://www.simpaq.org/), which is a physical questionnaire specifically designed for use in people with mental disorders such as schizophrenia. On the other hand, it seems evident that some components of physical activity should be taken into account in future studies, including (at least) the volume, frequency, and intensity of the activity. In this regard, all except one [46] of the aforementioned studies were focused on only the volume and/or frequency of moderate to vigorous physical activity. The authors of the remaining study [46] considered the frequency and intensity of physical activity but not the volume. Therefore, more research in this field is necessary before drawing firm conclusions.

21.2.2 Other Possible Predictors of Incident Schizophrenia

There is an extensive body of evidence showing that fatness/obesity (commonly assessed as body mass index) and fitness (cardiorespiratory fitness and muscular strength) levels are current and future health markers through the lifespan [52]. Regarding fitness, one study firmly established [53] that low levels of cardiorespiratory fitness (defined as the capacity of the cardiovascular and respiratory systems to supply oxygen to skeletal muscles during sustained activity [54]) are a strong predictor of all-cause and disease-specific mortality compared to traditional cardiometabolic risk factors such as age, hypertension, hypercholesterolemia, obesity, smoking, family history, elevated glucose levels, and type 2 diabetes. Given the plethora of robust evidence supporting the prognostic use of cardiorespiratory fitness, the American Heart Association recently stated that cardiorespiratory fitness must be routinely assessed in clinical practice as a vital sign [55]. A growing body of evidence [56, 57] indicates that low muscular strength (defined as the ability of a muscle to exert force [28]) is also a strong predictor of all-cause and disease-specific mortality, independently from cardiorespiratory fitness [58]. For these reasons, obesity, cardiorespiratory fitness, and muscular strength, of which the latter two are both reduced in people with schizophrenia [59, 60], should be highly considered for the evaluation and promotion of health through the lifespan.

Below, some prospective studies on the prognostic use of body mass index and fitness level for incident schizophrenia will be described and discussed.

21.2.2.1 Body Mass Index as a Predictor of Incident Schizophrenia

Regarding body mass index, the study of K Wahlbeck, T Forsen, C Osmond, DJ Barker, and JG Eriksson [61] explored the influence of maternal body size, size at birth, and childhood growth on the future risk of schizophrenia in a population-based cohort study carried out in Finland. The study used prospective data from birth records (at age 0 years) and school health records (at age 7 and 15 years) of 7086 individuals. The data included the body mass index at these ages and parental risk factors. The occurrence of schizophrenia or schizoaffective disorder, according to the *International Classification of Diseases* and *Mental Disorders* guidelines, was obtained from the Finnish Hospital Discharge Register. Of the 7086 participants, 114 (1.6%) had been diagnosed with schizophrenia or schizoaffective disorder. Although a lower late-pregnancy maternal body mass index, a low birth weight, shortness at birth, a low placental weight, and a low childhood body mass index increased the risk for schizophrenia, only a low childhood body mass index was an independent predictor of schizophrenia. Therefore, having a low body mass index during childhood seems to be an independent risk factor for future schizophrenia.

The study of HJ Sorensen, EL Mortensen, JM Reinisch, and SA Mednick [62] showed that having a lower body mass index during early adulthood also increased the risk of schizophrenia.

This study analyzed an all-male sample of 3210 individuals, with a mean age of 19 years (ranging from 16 to 24 years), who participated in the Copenhagen Perinatal Cohort developed in Denmark. These participants were born between 1959 and 1961 and were followed up with until 1999 (an approximately 21-year period). In 1999, 45 cases of schizophrenia were identified in the Danish Psychiatric Central Register according to the *International Classification of Diseases* (version 8 or 10). These schizophrenia cases had a lower young adult mean body mass index and weight compared with the cohort controls, and the results remained unchanged even when adjusting for several confounders (parental social status, birth weight, birth length, and maternal pre-pregnancy body mass index).

Two other studies [63, 64] that were based on data from the Swedish Military Service Conscription Registry found similar results in male adolescents and young adults. Specifically, the study in early adults [64] included 1,079,128 Swedish individuals aged 16 to 19 years (mean age of 18 years) who were conscripted into the Military Service Conscript Register between 1972 and 1994 and were followed up over a median of 28.3 years. In total, 4475 subjects were granted a disability pension by the Social Insurance Agency between 1972 and 2012 due to non-affective disorders (including schizophrenia). In these cases, those who were underweight during adolescence had an increased risk of non-affective disorders incident during adulthood 1.13 (1.03–1.25) compared to those of normal weight. In contrast, those who were overweight or obese (type I, II, or III) had a reduced risk of future non-affective disorders. Regarding the study carried out in young adult males, S Zammit, F Rasmussen, B Farahmand, D Gunnell, G Lewis, P Tynelius, and GP Brobert [63] examined a population-based cohort study of 1,347,520 Swedish men aged 18 to 48 years who were conscripted into the Military Service Conscript Register between 1952 and 2000 and were followed up with over a median of 30 years. These authors selected participants who were diagnosed with schizophrenia between 1970 and 2000 according to the Swedish National Hospital Discharge Register and not those who were granted a disability pension due to non-affective disorders, as in the aforementioned study. The subjects who were underweight in early adulthood had an approximately 30% increased risk of schizophrenia compared with the normal body mass index subjects. In addition, height was associated with the risk of schizophrenia. Subjects who were tall in early adulthood had an approximately 15% reduction in risk compared with the shorter subjects.

In summary, a lower body mass index during childhood, adolescence, and young adulthood was found to increase the risk of schizophrenia. However, this evidence was based on data only from men, except for the childhood data.

21.2.2.2 Fitness as Predictor of Incident Schizophrenia

The study of J Koivukangas, T Tammelin, M Kaakinen, P Maki, I Moilanen, A Taanila, and J Veijola [38], which was previously discussed (see "Physical Activity as a Predictor of Incident Schizophrenia"), showed that low levels of cardiorespiratory fitness during adolescence increased the risk of schizophrenia. Although helpful, these results should be analyzed with caution because they used the estimated peak oxygen uptake calculated on the basis of the heart rate response during submaximal cycle ergometer work stages (described by T Tammelin, J Remes, V Kujala, J Oksa, S Nayha, P Zitting, and MR Jarvelin [65]) rather than using a direct measurement of maximal oxygen uptake (the criterion measure of cardiorespiratory fitness [66]) by a pulmonary gas exchanger. Despite this limitation, this study can be considered as one of the early pieces of evidence on using fitness as a predictor of schizophrenia.

Based on data from the Swedish Military Service Conscription Registry, three studies explored the association between fitness and future schizophrenia; all were based on data from men, and two used samples of adolescent individuals to young adults (i.e., from 16 to 19 years). The study of P Henriksson, H Henriksson, P Tynelius, D Berglind, M Lof, IM Lee, EJ Shiroma, and FB Ortega [64] was previously

discussed (see "Body Mass Index as a Predictor of Incident Schizophrenia"). The author found that high levels of cardiorespiratory fitness had a protective effect against future disability pension due to non-affective disorders. As in the study of J Koivukangas, T Tammelin, M Kaakinen, P Maki, I Moilanen, A Taanila, and J Veijola [38], cardiorespiratory fitness was not measured with a reference method. In this case, the authors used the final work rate in incremental testing using an electrically braked ergometer cycle test, as explained elsewhere [67].

The study carried out by Ortega [68] analyzed whether muscular strength is prospectively related with all-cause and cause-specific premature mortality due to some causes, including psychiatric diagnoses (such as schizophrenia and mood disorders). For this, 1,142,599 Swedish male adolescents aged 16–19 years performed knee extension, handgrip, and elbow flexion strength tests and were followed up over a period of 24 years (ranging from 1 to 37 years). The adolescents with a higher level of muscular strength were 15–65% less likely to have any future psychiatric diagnosis. A major limitation of this study was that the strength tests and materials were not described in detail, and the two cited studies that theoretically explained the procedure and materials also did not include this information.

Contrary to the two aforementioned studies, the remaining study was led by J Nyberg, M Henriksson, MAI Aberg, A Rosengren, M Soderberg, ND Aberg, HG Kuhn, and M Waern [69]. It focused on only the fitness level and the later risk of serious non-affective mental disorders and showed results for those with schizophrenia and schizophrenia-like disorders, other psychotic disorders, and neurotic, stress-related, and somatoform disorders (differentiating between phobic anxiety disorders, other anxiety disorders, reaction to severe stress and adjustment disorders, somatoform and dissociative disorders, and other neurotic disorders). In total, 1,109,786 Swedish adolescent men were followed up over a period from 3 to 42 years and were included in the analyses. During the follow-up period, 4641 men were diagnosed with schizophrenia and schizophrenia-like disorders according to the *International Classification of Diseases* version 8, 9, or 10. Low levels of cardiorespiratory fitness in late adolescence were found to be associated with an increased risk of schizophrenia and other psychotic disorders. In contrast to the two studies that were based on data from the Swedish Military Service Conscription Registry and the study by J Koivukangas, T Tammelin, M Kaakinen, P Maki, I Moilanen, A Taanila, and J Veijola [38], these findings remained significant after adjusting for body mass index.

Finally, a Letter to the Editor regarding the study of SK Kunutsor, T Laukkanen, and JA Laukkanen [70] stated that cardiorespiratory fitness in middle-aged adults was linearly and inversely associated with the risk of psychosis after adjusting for established risk factors (age, smoking status, history of diabetes, history of coronary heart disease, years of education, total cholesterol, and alcohol consumption), and the association persisted even after additional adjusting for total energy intake, socioeconomic status, physical activity, and C-reactive protein levels. The authors used a large-scale population-based prospective cohort of Finnish men with a mean age of 52 years (ranging from 42 to 61 years) who were followed up with over a mean period of 18 years (ranging from 2 to 42 years) and participated in the Finnish Kuopio Ischaemic Heart Disease (KIHD; for more details see [71]) risk factor study. Cardiorespiratory fitness (peak of VO_2 max) was assessed during a submaximal exercise test using a cycle ergometer and a respiratory gas analyzer (a strength of the study) and was compared with the aforementioned studies that measured cardiorespiratory fitness using direct measures of gas exchange. These analyses and those carried out by J Koivukangas, T Tammelin, M Kaakinen, P Maki, I Moilanen, A Taanila, and J Veijola [38] were adjusted by physical activity.

In summary, five prospective studies on fitness and the incidence of schizophrenia, of which all but one used cardiorespiratory fitness and all but one used only data from men, support the hypothesis that lower fitness levels during adolescence

and young and middle adulthood are related to an increased risk of schizophrenia. The unique study that used a direct measurement of oxygen uptake when measuring cardiorespiratory fitness showed that fitness remained a strong predictor of future schizophrenia even when adjusting for body mass index, suggesting the importance of fitness as a major and independent marker of schizophrenia. Increasing the number of studies on muscular strength, performing similar studies in women, and preferentially using gold standard measurements may increase the robustness of the available evidence.

21.3 Exercise in the Treatment of Schizophrenia

21.3.1 Evidence Based on Systematic Reviews and Meta-analyses

In 2018, B Stubbs, D Vancampfort, M Hallgren, J Firth, N Veronese, M Solmi, S Brand, J Cordes, B Malchow, and M Gerber [72] published a meta-review of the evidence and Position Statement from the European Psychiatric Association (EPA), supported by the International Organization of Physical Therapists in Mental Health (IOPTMH), of exercise-based interventions and their impact on health outcomes for people with severe mental illness, including schizophrenia-spectrum disorders, major depressive disorder, and bipolar disorder. This research group searched major electronic databases up to January 2018 for systematic reviews with/without meta-analysis that investigated the effect of exercise on any severe mental illness.

In total, eight systematic reviews and meta-analyses reported the benefits of exercise for people with schizophrenia. Of these, three focused on a variety of health outcomes [73–76], three on cognitive functioning [77–79], and one on cardiorespiratory fitness [80]. Below, the main characteristics and findings of the eight studies will be discussed. All of the studies had the same quality of evidence, as assessed with the SIGN recommendations adapted from previous EPA guidelines [81, 82], which was found to be "Meta-analyses, systemic reviews of randomized controlled trials with a high risk of bias." However, the quality assessment score as determined by the authors through the AMSTAR tool [83, 84] (higher score = higher quality) varied between the studies and will be included when discussing each one.

21.3.1.1 Effects of Exercise on Various Health Outcomes

The earliest study of the four focused on the effects of exercise on various health outcomes in people with schizophrenia and was published in 2014 by A Soundy, A Muhamed, B Stubbs, M Probst, and D Vancampfort [74] (AMSTAR score 5/11). These authors investigated whether walking could reduce weight and/or have a positive influence on other health parameters (including adherence, mood, quality of life, cardiovascular risk, hypertension, cholesterol, and psychiatric symptoms) in individuals aged 16 years and over with schizophrenia. After searching in major electronic databases from inception to January 2014, 10 eligible trials (including 5 randomized controlled trials) covering 339 people with schizophrenia were identified. There was some evidence to suggest that walking interventions benefit an individual's weight, resulting in small reductions in body mass index or body fat in the short term. Evidence for other health outcomes was limited. One of the main limitations was that due to the heterogeneity of outcome measures used and the paucity of studies, the authors did not conduct a meta-analysis.

J Firth, J Cotter, R Elliott, P French, and AR Yung [73] (AMSTAR score 5/11) conducted a review and meta-analysis to establish the effectiveness of exercise for improving both physical and mental health outcomes in people with schizophrenia. The authors categorized the health outcomes into metabolic health (body composition and cardiometabolic risk factors), physical fitness (cardiorespiratory fitness and physical capacities), psychiatric symptoms (positive, negative, and general symptoms), functioning and disability (quality of life, socio-occupational functioning, and overall illness severity), comorbid disorders (specific or subscale measures of

depression/anxiety), and neurocognitive effects (brain structure and neurocognitive functioning). After searching the major electronic databases from inception to November 2013, 20 eligible studies (including 10 randomized controlled trials) covering 659 people with schizophrenia were identified. Exercise interventions included any type of exercise (aerobic, resistance, and aerobic + resistance, among others). Exercise was found to improve physical fitness, cardiometabolic risk factors, and psychiatric symptoms. Interestingly, interventions using approximately 90 min of moderate to vigorous aerobic exercise per week led to significant improvements in psychiatric symptoms, functioning, comorbid disorders, and neurocognition.

The systematic narrative review carried out by K Keller-Varady, PA Varady, A Roh, A Schmitt, P Falkai, A Hasan, and B Malchow [76] (AMSTAR score 4/11) analyzed resistance training in patients with schizophrenia. After searching the major electronic databases from inception to August 2016, 6 eligible studies (including 3 randomized controlled trials) on resistance exercise interventions involving a total of 187 people with schizophrenia were found. Out of the six studies, two examined the impact of isolated resistance exercise, and five studies examined the impact of combined (aerobic + resistance) exercise in people with schizophrenia. BA Silva, RC Cassilhas, C Attux, Q Cordeiro, AL Gadelha, BA Telles, RA Bressan, FN Ferreira, PH Rodstein, CS Daltio, et al. [85] investigated an isolated resistance training group and a combined resistance training group. Based on the two unique studies that examined the impacts of isolated resistance exercise, whole-body resistance exercise (leg press, leg curl, vertical traction, chest press, arm extension, arm curl, abdominal crunch) [85] appeared to be more beneficial than a single exercise (leg press) [86] in people with schizophrenia. Improvements of muscular strength, physical fitness, and symptom severity were found when considering all of the studies that examined the impacts of combined exercise. The limited amount, small sample sizes, and heterogeneous nature of the studies precluded a meta-analysis of the available evidence and impaired generalization of the results.

The remaining study was carried out by H Martin, S Beard, N Clissold, K Andraos, and L Currey [75] (AMSTAR score 7/11) who conducted a systematic review to identify the effects of combined aerobic and resistance training on individuals with schizophrenia. After searching in the major electronic databases from inception to September 2016, 7 eligible randomized controlled trials on combined exercise interventions and mental health variables, cardiorespiratory fitness, and strength were identified, involving 389 people with schizophrenia with a mean age of 39 years. Combined exercise was found to be effective at decreasing the symptoms of schizophrenia and increasing fitness (cardiorespiratory fitness and muscular strength, with clinically relevant improvements in the former) in people with schizophrenia. However, the authors claimed that the invention characteristics were poorly reported and that the research was scarce and, overall, was of low quality, with a high risk of bias.

21.3.1.2 Effects of Exercise on Cognitive Functioning

The 2017 study by J Firth, B Stubbs, S Rosenbaum, D Vancampfort, B Malchow, F Schuch, R Elliott, KH Nuechterlein, and AR Yung [77] (AMSTAR score 5/11) of a meta-analysis of all controlled trials investigating the cognitive outcomes of exercise interventions in schizophrenia was published in the prestigious scientific journal *Schizophrenia Bulletin.* Published studies examining the neurocognitive outcomes of exercise interventions for people with schizophrenia in comparison to a control condition were identified through a systematic search of major electronic databases from inception to April 2016. In total, 10 studies (including 7 randomized controlled trials) covering 385 participants with a mean age of 37 years (ranging from 23 to 55 years) were eligible, most of which used aerobic exercise interventions. Exercise was found to improve cognitive functioning among people with schizophrenia, particularly from interventions using higher dosages of exercise. In addition, among the different domains assessed,

including working memory (seven studies), processing speed (six studies), verbal learning and memory (six studies), reasoning and problem solving (four studies), attention/vigilance (three studies), social cognition (three studies), and visual learning and memory (three studies), social cognition showed the greatest improvements in response to exercise. However, the small number of studies limited the strength of the findings for social cognition and the other domains.

The same author conducted a systematic review of all exercise intervention studies that reported changes in brain structure or in connectivity or peripheral biomarkers, which could underlie the cognitive improvements from exercise [78] (AMSTAR score 4/11). After searching the major electronic databases from inception to September 2016, 16 eligible studies reporting data from 14 independent trials (including 9 randomized controlled trials) were identified, involving 247 people with schizophrenia with a mean age of 41 years (ranging from 20 to 59 years). Exercise appeared to improve the brain structure and connectivity in people with schizophrenia. The authors also explored peripheral biomarkers (such as brain-derived neurotrophic factor, or BDNF) that could underlie the cognitive improvements in schizophrenia from exercise; however, the accumulated evidence was too limited to draw any firm conclusions.

Regarding this last point, other researchers had previously conducted a systematic review and meta-analysis to investigate the efficacy of non-pharmacological interventions on peripheral serum and plasma BDNF levels in subjects with schizophrenia (including schizoaffective disorder) [79] (AMSTAR score 10/11). After searching the major electronic databases from inception to November 2015, six randomized controlled trials were identified. Of interest, only 3 studies used exercise interventions (1 used aerobic exercise [87], 1 used combined exercise [88], and 1 used yoga [89]), involving a total of 65 participants with schizophrenia. No beneficial effects of non-pharmacological interventions on BDNF levels were found in the exercise intervention studies. According to the aforementioned study by Firth [78], further exercise intervention trials in people with schizophrenia are needed to clarify the effect on BDNF levels.

21.3.1.3 Effects of Exercise on Cardiorespiratory Fitness

D Vancampfort, S Rosenbaum, PB Ward, and B Stubbs [80] (AMSTAR score 8/11) explored the effects of exercise-based interventions on cardiorespiratory fitness in people with schizophrenia and, when possible, performed a comparison with control interventions. All published studies were identified from a systematic search across major electronic databases from inception to May 2015. In total, 7 studies were eligible, including 3 randomized controlled trials involving 77 participants with schizophrenia with a mean age of 31 years; 48 participants with a mean age of 36 years were assigned to a control condition. Compared to the control condition, exercise was found to improve cardiorespiratory fitness in people with schizophrenia. One main limitation of this study was the small number of studies analyzed. However, given the importance of cardiorespiratory fitness as a health marker for the general population, these findings are important for this clinical population. In this sense, a meta-analysis [90] found that improvements in cardiorespiratory fitness after exercise intervention were consistently associated with reductions in negative symptoms and body mass index in people with schizophrenia. On the other hand, a recent prospective study in people with schizophrenia showed that better physical fitness was not associated with improved cognitive performance over 2 years [91]. Although these results were not contradictory, these two studies could increase the interest of researchers in exploring the impact of the cardiorespiratory condition on the future health outcomes of people with schizophrenia, as has occurred in the study of people with depression [92, 93].

21.3.1.4 Summary of Evidence and Clinical Practice Recommendations

The above discussion raises some important issues in the eight systematic reviews and meta-analyses included in the recent meta-review of

the evidence led by B Stubbs, D Vancampfort, M Hallgren, J Firth, N Veronese, M Solmi, S Brand, J Cordes, B Malchow, M Gerber, et al. [72]; the summary of the effects of exercise interventions in people with schizophrenia that were established in the Stubbs review is as follows:

- Ninety minutes of moderate to vigorous aerobic exercise per week can reduce total, negative, and positive symptoms.
- There is no evidence of strength training effects on psychological symptoms.
- There is inconsistent evidence for the effects of excise on body weight, body mass index, waist circumference, and body fat.
- Aerobic exercise increases cardiorespiratory fitness over 12 weeks.
- Aerobic exercise can improve global cognition, working memory, social cognition, and attention/vigilance. Greater effects are seen for higher doses of exercise and when interventions are delivered by exercise professionals.

All of these points were based on meta-analyses, systematic reviews, or randomized controlled trials with a high risk of bias. Therefore, more research is needed to obtain robust evidence on the effects of exercise in people with schizophrenia.

Given the amount and quality of the available systematic reviews and meta-analyses, B Stubbs, D Vancampfort, M Hallgren, J Firth, N Veronese, M Solmi, S Brand, J Cordes, B Malchow, M Gerber, et al. [72] concluded that there is good evidence (evidence type B according to SIGN recommendations adapted from SJ Schmidt, F Schultze-Lutter, BG Schimmelmann, NP Maric, RK Salokangas, A Riecher-Rossler, M van der Gaag, A Meneghelli, M Nordentoft, M Marshall, et al. [94]) showing that exercise should be utilized as an adjunctive treatment of schizophrenia to improve symptoms, cognition, and the quality of life. In this regard, the authors pointed out that the most consistent evidence is for performing at least 150 min of moderate to vigorous aerobic exercise per week. Additionally, B Stubbs, D Vancampfort, M Hallgren, J Firth, N Veronese, M Solmi, S Brand, J Cordes, B Malchow, M Gerber, et al. [72] strongly recommend that a physiotherapist or exercise physiologist should deliver, lead, and supervise any exercise-based intervention. Furthermore, systematic reviews of meta-analyses confirmed that supervised interventions and group exercise resulted in substantially better outcomes [73, 77] and reduced the dropout rate [73, 95], with further improvements seen when supervised by exercised professionals. Consistent with a major claim in a similar study of people with depression [96], D Vancampfort, S Rosenbaum, FB Schuch, PB Ward, M Probst, and B Stubbs [95] suggested that "policymakers should make the inclusion of qualified professionals such as physical therapists and exercise physiologists a priority in order to improve adherence among people with schizophrenia."

21.4 Key Points

The following key points summarize the main results discussed in this chapter regarding the research progress of using exercise to prevent and treat schizophrenia disorder:

- Schizophrenia is a global health issue associated with an increased rate of disability, morbidity, mortality, and economic impact.
- Some prospective studies show that low physical activity levels are a strong predictor of future schizophrenia.
- An increasing body of evidence demonstrates that a lower body mass index and lower fitness levels (cardiorespiratory fitness and muscular strength) could also be considered predictors of incident schizophrenia.
- Accumulated evidence has shown that exercise should be utilized as an adjunctive treatment for schizophrenia to improve symptoms, cognition, and the quality of life in people with schizophrenia.
- Most of the currently available evidence on the effects of exercise in people with schizophrenia is based on aerobic exercise, followed by combined (aerobic + resistance) exercise.

- There is weak evidence of a dose-response relationship between exercise prescription and people with schizophrenia.
- The most consistent evidence suggests performing at least 150 minutes of moderate to vigorous aerobic exercise per week.
- The evidence indicates that exercise professionals should deliver, lead, and supervise exercise interventions for schizophrenia, because this is associated with better outcomes and lower dropout rates.

Acknowledgments The work was funded by Research Group CTS-948, Universidad Pablo de Olavide, Andalusian Government; Universidad Pablo de Olavide, Spain "A2. Ayudas Puente para la Concurrencia al Plan Estatal de I+D"; European University of Madrid, Cátedra Real Madrid, Spain (funding project number P2017/RM08); Biomedical Research Networking Centre on Frailty and Healthy Aging (CIBERFES); and FEDER funds from the European Union (CB16/10/00477). JBA was supported by the Spanish Ministry of Education (grant number FPU13/05130) and by the Departamento de Innovación, Investigación y Universidad del Gobierno de Aragón y el Fondo Europeo de Desarrollo Regional—Programa Operativo FEDER Aragón 2014–2020 "Construyendo Europa desde Aragón" (reference number PUI/2018-337). The funders had no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

Competing Financial Interests The authors declare no competing financial interests.

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Exercise and Multiple Sclerosis

22

Robert W. Motl

Abstract

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system (CNS) with an estimated prevalence approaching 1 million adults in the United States. The disease pathogenesis and resulting damage express as dysfunction (e.g., walking and cognitive impairment) and symptoms (e.g., fatigue and depression) that compromise quality of life (QOL) and full participation. There has been a steadily increasing body of research on the outcomes of exercise among persons with MS, and this has accelerated sharply over the past decade. The current chapter provides a review of exercise and its outcomes, safety, and prescription in MS. This chapter initially reviews the evidence for benefits of exercise based principally on meta-analyses and literature reviews. The chapter then reviews evidence on the safety of exercise in MS and lastly provides guidelines for exercise prescription in MS. Collectively, this chapter serves as an overview and reference for researchers and clinicians interested in the benefits, safety, and prescription of exercise in MS.

Keywords

Neurological disease · Physical activity · Fitness · Exercise · Multiple sclerosis

22.1 Overview of Multiple Sclerosis

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system (CNS) with secondary neurodegenerative processes in its pathogenesis [1]. This disease has an estimated prevalence approaching 1 million adults in the United States and occurs nearly three times more often among women than men [2]. There is a shifting age demography of MS such that it is most common among adults between the ages of 55 and 64 years in the United States [2]. MS is clinically characterized by relapses, lesions in the CNS, and progression of neurological disability. Those clinical expressions are brought about by periods of inflammatory demyelination and transection of axons as well as neurodegeneration involving loss of trophic support of neurons. The disease pathogenesis and resulting damage express as dysfunction (e.g., walking and cognitive impairment) and symptoms (e.g., fatigue and depression) that compromise quality of life (QOL) and full participation.

MS itself is typically treated through disease-modifying therapies (DMTs) that target immunological signaling proteins (e.g., interferons,

R. W. Motl (✉)
Department of Physical Therapy, School of Health Professions,University of Alabama at Birmingham, Birmingham, AL, USA
e-mail: robmotl@uab.edu

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_22

cytokines) and/or populations of immune cells (e.g., lymphocytes). Such DMTs reduce relapse rates and slow progression of disability by controlling inflammatory activity. The DMTs do not control neurodegenerative processes nor cure the disease and further do not target dysfunction nor the symptoms of MS. Accordingly, persons with MS still experience residual symptoms and dysfunction and worsening of QOL, and this highlights the importance of identifying other approaches that can improve function, manage symptoms, and optimize QOL and participation in activities of daily living.

There has been a steadily increasing body of research on the outcomes of exercise among persons with MS, and this has accelerated sharply in the past decade [3]. The current chapter provides a review of exercise and its outcomes, safety, and prescription in MS. This chapter initially reviews the evidence for benefits of exercise based largely on meta-analyses and literature reviews. Such an approach is necessary, as over 54 clinical trials have been undertaken on exercise in MS over the past decade alone [3] and a selective review of papers would be arbitrary and extend beyond the word limits of this chapter. The chapter further reviews evidence on the safety of exercise in MS and lastly provides guidelines for exercise prescription in MS. Collectively, this chapter serves as an overview and reference for researchers and clinicians interested in the benefits, safety, and prescription of exercise in MS.

22.2 Scope of Exercise Benefits in MS

One recent review provided a general picture regarding the range of exercise benefits for people with MS based on 54 clinical trials performed between 2006 and 2016 [3]. The papers generally reported that exercise was associated with positive effects on walking/mobility, neurological disability, pain, cardiorespiratory fitness, muscular strength and endurance, body weight, balance, mental health (i.e., depression, anxiety, cognitive function, fatigue), and QOL [3]. Other reviews have focused on the benefits of exercise for disease modification in MS [4, 5]. This section of the chapter presents data on the benefits of exercise in MS, and it is organized based on the International Classification of Functioning, Disability and Health (ICF) model. Such an organization scheme is consistent with a previous review paper [6] and includes sections on MS pathogenesis, body functions, activities, and participation outcomes. The application of the ICF model essentially facilitates the classification of existing evidence on benefits of exercise into focal categories along the MS-disease process.

22.2.1 Effect of Exercise on MS Pathogenesis

Researchers have recently developed arguments that exercise may represent a disease-modifying behavior by impacting the latent MS pathogenesis [4, 5]. One group of researchers provided a literature review on the topic of exercise as a DMT [5] by first identifying metrics for evaluating disease modification and progression in MS (i.e., relapse rate, neurological disability and its progression, brain lesion volume, and neuro-performance outcomes of walking and cognition) and then reviewing evidence for exercise as a DMT. The evidence indicated that exercise was associated with reduced relapse rate, neurological disability and progression, and lesion volume and further yielded improved neuro-performance, particularly walking outcomes. Of note, one review of 26 randomized controlled trials (RCTs) that included 1295 participants with MS reported relapse rates of 4.6% and 6.3% for exercise and control conditions, respectively; those rates yielded a relative risk of relapse for exercise training of 0.73 compared with control conditions (i.e., 27% reduction in relapse rate for exercise training) [7].

There is a noteworthy limitation of the existing body of research that must be considered when making the case for exercise as a potential DMT. This limitation involves the quality and quantity of evidence regarding exercise effects on immunological and neurotrophic factors that underpin the pathophysiology of MS based on

clinical and basic science [8]. That research indicates the lack of a clear picture regarding exercise effects on the basic pathophysiology of MS [9]. Collectively, the existing evidence provides a positive, yet preliminary, picture for exercise as a DMT in MS, but requires additional research regarding exercise effects on cellular biomarkers of MS pathogenesis [10].

22.2.2 Effect of Exercise on Mental Body Functions

Fatigue Fatigue represents one of the most common, debilitating, and poorly managed symptoms of MS. An estimated 80% of persons with MS report severe or debilitating symptomatic fatigue [11], and research has demonstrated no significant or systematic benefit of pharmacological management for fatigue in MS [12]. This supports consideration of other approaches for managing fatigue in MS, and exercise training has emerged as a leading strategy that might yield clinically meaningful improvements in fatigue.

One meta-analysis undertook a quantitative synthesis of RCTs examining exercise training effects on symptomatic fatigue in persons with MS [13]. The meta-analysis included 17 RCTs involving 568 persons with MS and reported an overall, weighted mean effect size (ES) of 0.45. The weighted mean ES was slightly heterogeneous, but no moderators were identified for explaining variance in the mean ES. Importantly, the mean ES of 0.45 approached the widely accepted value of 0.5 that has been deemed clinically meaningful in QOL research [14]. Overall, the meta-analysis indicated that exercise training was seemingly efficacious for reducing fatigue in persons with MS and further highlighted two noteworthy limitations regarding the lack of (a) comparative effectiveness research and (b) samples with severe or debilitating fatigue.

Another recent meta-analysis summarized the available research comparing three different approaches, namely, exercise, education, and medication, for reducing fatigue in MS [12]. The meta-analysis included 18 rehabilitation and 7 pharmacological trials targeting fatigue in MS. The average ESs for exercise and education were 0.57 and 0.54, respectively, whereas the ES for medication was 0.07—exercise was as efficacious as education programs for reducing fatigue, and both approaches were seemingly better than common medication approaches for managing fatigue in MS. The authors did highlight the continuing limitation of severe or debilitating fatigue not being an inclusion criterion in RCTs of exercise. This important limitation precludes the classification of exercise as a "treatment" for MS-related fatigue, and the available evidence suggests that exercise can help manage this symptom in MS.

Depression Depression represents another hallmark symptom of MS. An estimated 50% of persons with MS will present with major depressive disorder over the lifetime of this disease [15]. Persons with MS have further reported depressive symptom scores that were nearly 1 SD higher than those of the general population [16]. The existing research does not support conventional pharmacological management of depression in MS and suggests that cognitive behavior therapy is possibly efficacious and may be considered in the treatment of depressive symptoms [17]. There is emerging evidence that exercise might be an additional approach for managing depressive symptoms in MS.

One meta-analysis has examined the overall effects of exercise training on depressive symptoms in RCTs of MS [18]. Exercise demonstrated a small, but statistically significant, overall ES of 0.36, and this indicated an improvement in depressive symptoms compared with control conditions. The overall effect was not heterogeneous and did not support a search for moderator variables. One limitation of the meta-analysis included a lack of focal examination of the effects of specific exercise modalities on depressive symptoms—this hampers recommendations for clinical practice on the efficacy of a specific exercise program. As with meta-analyses regarding exercise effects on fatigue [12, 13], another primary limitation of exercise studies on depressive

symptoms involved the lack of persons with MS who had major depressive disorder or elevated depressive symptomology.

Another recent meta-analysis examined the effects of exercise on depressive symptoms in adults with neurological disorders (including MS) and highlighted the possible importance of meeting public health guidelines for physical activity within the context of a given exercise intervention [19]. That meta-analysis included 26 RCTs of exercise involving 1324 participants with 7 different neurological disorders, including Alzheimer's disease (n = 4 trials), migraine (n = 1), MS (n = 13), Parkinson's disease (n = 2), spinal cord injury (n = 1), stroke (n = 2), and traumatic brain injury (n = 3). The meta-analysis yielded an overall ES of 0.28; this favored a reduction in depressive symptom outcomes after exercise compared with a control condition. Of note, exercise programs that met physical activity guidelines yielded an overall ES of 0.38 compared with an ES of 0.19 for studies of exercise that did not meet physical activity guidelines. This meta-analysis provides initial evidence that exercise, particularly when meeting physical activity guidelines, can improve depressive symptoms in adults with neurological disorders.

One recent meta-analysis examined moderators of exercise training effects on depressive symptoms among people with MS [20]. The meta-analysis included 24 ESs derived from 14 RCTs that included a total of 624 people with MS. Overall, exercise training significantly reduced depressive symptoms by a heterogeneous mean ES of 0.55, and the overall ES exceeded the 0.5 guideline for clinical meaningfulness [14]. Interestingly, improvement in fatigue moderated the overall effect of exercise on depressive symptoms such that there were significantly larger antidepressant effects in trials where exercise significantly improved fatigue (ES = 1.04) compared with trials where there was no significant improvement in fatigue (ES = 0.41). These data suggest that exercise-induced improvements in fatigue significantly moderated exercise training effects on depressive symptoms in MS. Nevertheless, one continuing limitation of the research is the lack of persons with MS who have major depressive disorder or elevated depressive symptomology. This limits our understanding of exercise as a "treatment" of depression in MS.

Cognition Cognitive dysfunction is another common and burdensome consequence of MS. An estimated 65% of persons with MS demonstrate impaired cognitive performance based on objective neuropsychological testing, and cognitive dysfunction is a primary determinant of employment status, instrumental activities of daily living, and QOL [21]. Of note, pharmacological approaches have been ineffective for managing cognitive problems in MS, and the efficacy of cognitive rehabilitation has only recently been established in clinical trials [22], but this approach alone is not completely beneficial for restoring cognitive function [23]. There is an abundance of evidence from the general population indicating that exercise training may improve cognitive function across the lifespan [24]. This has prompted considerable interest in the possibility that exercise might yield similar effects in MS [25].

Researchers recently conducted a systematic review of exercise training as well as physical activity and physical fitness effects on cognition in MS [26]. The review identified 26 usable papers regarding exercise, physical activity, and physical fitness effects on cognition in persons with MS. There were conflicting evidence for the effects of exercise training on cognition in MS and overall positive, but not necessarily definitive, evidence for the effects of physical activity and physical fitness on cognition. The lack of definitive evidence supporting physical activity and physical fitness benefits on cognitive performance was largely based on Class III and Class IV evidence (i.e., cross-sectional, within-subjects designs). Overall, the primary conclusions were that there is insufficient research from well-designed studies to definitively conclude that exercise, physical activity, and/or physical fitness can improve cognition in MS. This was based, in part, on methodological issues of Class I and II (i.e., randomized controlled trials) studies, namely, inclusion of cognition as a secondary

outcome, poorly developed exercise interventions, and paucity of research on cognitively impaired persons with MS. The promising evidence from Class III and Class IV studies may be useful for informing the development of high-quality interventional research for clarifying the possibility that exercise, physical activity, and fitness may be useful for managing and treating cognitive impairment in MS.

22.2.3 Effect of Exercise on Cardiovascular and Neuromuscular Body Functions

There is substantial evidence for physiological deconditioning involving the cardiovascular and neuromuscular systems of persons with MS. Persons with MS demonstrate reduced aerobic capacity and muscle strength compared with healthy adults who do not have MS [27], and these differences are larger as a function of disability status [28]. The declines in cardiovascular and neuromuscular capacity might be associated with reduced walking performance [29] and fatigue [30]. The ideal approach for improving cardiovascular and neuromuscular functioning in persons with MS involves exercise training.

One recent review provided a quantitative synthesis of 20 RCTs that examined the effect of exercise training on muscular and cardiorespiratory fitness in persons with MS [31]. The mean overall ES was 0.27 for muscular fitness outcomes and 0.47 for cardiorespiratory fitness outcomes. The weighted mean ES was not heterogeneous for either muscular or cardiorespiratory fitness outcomes. Such evidence supports that exercise training is associated with small improvements in muscular fitness and moderate improvements in cardiorespiratory fitness outcomes in persons with MS.

22.2.4 Effect of Exercise on Sensory Body Functions

Balance dysfunction is a common sensory abnormality in MS that can influence walking, falls and falls risk, and activities of daily living in MS [32]. One meta-analysis has examined the effects of 11 physiotherapy interventions on balance in people with MS [33]. Overall, the methodological quality of the studies ranged between poor and moderate. The mean ES for resistance and aerobic training on balance was non-significant and small in magnitude with a mean ES of 0.22. There was a small and non-significant effect of resistance and aerobic exercise training on balance outcomes in people with MS who had mild or moderate disability. That meta-analysis further noted substantial limitations associated with the small quantity and poor quality of the available research on the effects of exercise training on balance outcomes.

Another common sensory abnormality of MS is pain, and this symptom of MS has profound effects on QOL and other outcomes (e.g., fatigue), but is poorly managed. One recent meta-analysis has provided evidence supporting the effect of exercise for managing pain in people with MS [34]. The meta-analysis included RCTs that recruited people with MS where exercise was the intervention and pain was an outcome identified through five electronic databases. There were 10 studies that met the inclusion criteria with a total sample size of 389 persons with MS. The exercise interventions were associated with less pain compared with passive control groups with mean ES of 0.46. There was between-study heterogeneity, but there were no moderators that explained variance in the mean ES. Overall, this meta-analysis provided some evidence that exercise alleviates pain in MS, but there were limitations in study quality associated with a high risk of bias across studies.

22.2.5 Effect of Exercise on Activities

The effect of exercise on activities has typically focused on the outcome of walking. This is logical as walking represents a major activity limitation in MS and greatly impacts participation and QOL outcomes [35]. Walking further represents one of the most valued activities by people with MS [36] and is one of the most visible outcomes of the disease. One meta-analysis examined the overall effects of exercise training on walking mobility in MS [37]. The meta-analysis included 22 papers that involved 66 ESs and 600 persons with MS and yielded a weighted mean ES of 0.19. Of note, there were larger effects for supervised exercise training (ES = 0.32), exercise programs that were less than 3 months in duration (ES = 0.28), and mixed samples of relapsing-remitting and progressive MS (ES = 0.52). Such data collectively support that exercise training is associated with a small improvement in walking mobility in MS, and this may be optimized under conditions of supervised exercise training.

One recent and updated meta-analysis has quantified the benefits of exercise on walking ability in MS [38]. That study focused on average improvements in walking ability based on the 10-m walk test (10mWT), timed 25-foot walk test (T25FW), 2-min walk test (2MWT), 6-min walk test (6MWT), and timed up-and-go (TUG) from 13 RCTs. Exercise yielded a significant, clinically meaningful improvement in walking speed, measured by the 10mWT (mean difference [MD] reduction in walking time of −1.8 s), but a non-significant change in the T25FW (MD = −0.6 s). Exercise further yielded significant improvements in walking endurance as measured by the 6MWT and 2MWT, with increased walking distances of 36.5 m and 12.5 m, respectively. The exercise-related improvement on 2MWT performance was clinically meaningful. By comparison, there was minimal exercise-related improvement for the TUG (MD = −1.1 s). This meta-analysis further supports improvement in speed- and endurance-related walking outcomes with exercise training in persons with MS and that improvements on select outcomes can be considered clinically meaningful.

22.2.6 Effect of Exercise on Participation Outcomes

The ICF category of participation includes health-related quality of life (HRQOL) and overall QOL. HRQOL reflects an individual's perception of physical and mental health status, whereas overall QOL reflects a person's judgment of satisfaction with life based on an evaluation of important life domains. Importantly, both HRQOL and overall QOL are compromised in MS when compared with healthy controls and even persons with other chronic diseases and conditions [39].

One systematic review included evidence from 54 studies regarding the effects of exercise training on multiple outcomes including HRQOL in adults with MS [40]. Overall, there was inconsistent evidence regarding the effects of exercise training on HRQOL, although exercise was associated with improvements in other outcomes (e.g., cardiorespiratory and muscular fitness) that were included in the systematic review. Overall, the evidence suggested that exercise may improve HRQOL among those with MS, but required further, focal examination.

An older meta-analysis has examined the effect of exercise training interventions on QOL outcomes among persons with MS [41]. Thirteen studies were included in the meta-analysis that involved a total of 484 MS patients. The weighted mean ES was 0.23 and favored an improvement in QOL with exercise training. There were larger effects associated with MS-specific measures of QOL. The evidence from this meta-analysis supports a small, but statistically significant, improvement in overall QOL with exercise training among persons with MS.

22.2.7 Summary of Exercise Effects in MS

This section of the chapter was guided by the ICF model for classifying the evidence regarding exercise training effects on outcomes in MS. The existing evidence demonstrated a pattern of smaller effects of exercise on outcomes when moving from body structure and function through

activity performance. This is logical as body structure and function represent more proximal outcomes associated with adaptations as a result of exercise itself, whereas activity performances (i.e., participation) are more distal outcomes that are likely not the direct result of exercise training. This is consistent with models of exercise and physical activity effects on QOL in aging [42, 43]. There is obviously a need for considerable work in the areas of disease pathogenesis, activities, and participation within the ICF framework for providing a complete picture of exercise in MS.

22.3 Safety of Exercise in MS

The safety profile of exercise has been described in a recent review of exercise in persons with MS [7], and this is critical for informing decisions and recommendations regarding its safety. To that end, the systematic review focused on adverse events (AEs) reported in RCTs of exercise training in MS. We searched electronic databases for RCTs of exercise training in MS. We calculated the rate of AEs and the relative risk of AEs for exercise training versus control. Twenty-six studies were reviewed that included 1295 participants. We determined that the rate of AEs was 1.2% and 2.0% for control and exercise, respectively. The relative risk of AEs for exercise training was 1.67, and the risk of AEs was no different when compared with evidence from the general population of adults who participate in exercise. The most common AEs involved musculoskeletal issues (e.g., low back and joint pain) associated with resistance exercise training. This evidence should reduce uncertainty regarding the safety profile of exercise training in MS.

22.4 Prescription of Exercise in MS

There are two primary resources on the prescription of exercise in people with MS [44, 45]. One set of guidelines [45] were developed based on a systematic literature review of exercise training interventions in MS [40]. The resulting guidelines suggest that persons with MS who have mild or moderate disability should engage in at least 30 min of moderate-intensity aerobic activity two times per week and strength training exercises for major muscle groups two times per week. The aerobic and resistance exercise training can be performed on the same day, but should be separated by 24 hours (i.e., not performed on consecutive days). This prescription should yield fitness benefits and possibly reduce fatigue, improve mobility, and improve components of HRQOL. Importantly, these guidelines have not been formally tested and require evaluation before broad application, particularly among those with advanced disability with MS.

Another set of guidelines was developed through a scoping review of existing resources on exercise prescriptions in persons with MS, stroke, and Parkinson's disease for the provision of resources that are uniformly recognizable by healthcare practitioners and patients/clients with these diseases [44]. This paper, in particular, synthesized resources that reported aerobic and resistance training guidelines for people with MS, stroke, and PD. Regarding MS, the systematic search yielded ten eligible resources from electronic databases and textbooks or websites of major organizations. Data were extracted (exercise frequency, intensity, time, and type) and synthesized into recommendations per disease. Exercise guidelines for MS consistently recommended 2–3 days/week of aerobic training (10–30 min at moderate intensity per session) and 2–3 days/week of resistance training (1–3 sets between 8–15 repetitions maximum per session). The frequency ranges between 2 and 3 days per week and should generally start with 2 days per week and progress toward 3 days per week over time. The duration of the exercise bouts ranges between 10 and 30 min and should gradually progress from 10 to 30 min over time. The intensity should be moderate and range between 11 and 13 on the 20-point rating of perceived exertion scale, or between 40 and 60% peak oxygen consumption or peak heart rate. The overall progression should start with increases in either duration or frequency. Progressions in intensity

should be based on the tolerability of the individual with MS, only after duration and frequency are well tolerated. This harmonizing of exercise guidelines provides a prescriptive basis for healthcare providers, exercise professionals, and people living with MS regarding disease-specific exercise programming. Importantly, these guidelines still require verification for benefits and safety before broad application, particularly among those with advanced MS disability.

22.5 Next Steps Regarding Exercise in MS

There is an abundance of evidence supporting the benefits of exercise in MS. Nevertheless, we still observe low rates of participation in physical activity among persons with MS, particularly when compared with the general population [46]. This is, in part, associated with major gaps in research that require remediation [9]. Some of the necessary steps for guiding future research include identifying a minimally effective dose of exercise for benefits, focusing on exercise and neuroplasticity, and understanding exercise benefits, safety, and prescription in advanced stages of MS.

22.5.1 Minimal Dose of Exercise

The promotion of exercise in MS requires identifying the "minimally" effective dose of exercise for benefits; this has not been uniformly established for any of the outcomes identified in this chapter. Such research could be guided by recent guidelines for the prescription of exercise in MS [44, 45]. Importantly, these guidelines have not been formally tested and require evaluation before broad application, particularly among those with advanced MS disability. There further is a need for focal research on the dose-response association between exercise parameters and outcomes of MS. Such studies might focus on the dose of exercise based on manipulations of the intensity, frequency, and duration of exercise bouts and the associated outcomes for persons with MS. This will assist in the promotion of exercise by clearly identifying the dose of exercise necessary for benefits as a target for persons with MS.

22.5.2 Exercise and Neuroplasticity

Exercise can improve the structure of the CNS [47]—this is based on a wealth of evidence from animal studies and human research involving older adults. For example, RCTs of exercise training in older adults consistently demonstrate improvements in the volume of the hippocampus based on magnetic resonance imaging, and this translates into better learning and memory [48]. There is a growing body of research indicating that physical fitness and physical activity are associated with volumes of the basal ganglia, hippocampus, and thalamus in persons with MS [49–51]. Such cross-sectional research has informed the design of a recent pilot RCT wherein aerobic exercise training yielded improvements in the viscoelastic properties of the hippocampus that were associated with changes in learning and memory in persons with MS [52]. This research is exciting, as it provides a possible basis for exercise as a countermeasure for CNS decline in MS, yet the evidence derives from a small number of cross-sectional studies and only one RCT. This is an obvious area of future research for extending our knowledge of the pleotropic benefits of exercise in MS.

22.5.3 Exercise in More Advanced Stages of MS

The evidence for the benefits of exercise in persons with MS primarily has been established in those with mild-to-moderate disability. Nevertheless, mobility impairment (e.g., use of assistive device for ambulation) is common in MS, and those with more severe disability have greater detriments in aerobic fitness, muscular function, and balance than those with lower disability. Those persons with MS who have more severe disability may in fact represent the people

who are most in need of exercise programs. To that end, a recent systematic review was conducted of the current literature regarding exercise training in those with severe MS mobility disability (i.e., Expanded Disability Status Scale (EDSS) ≥ 6.0) [53]. This systematic review identified 19 relevant papers from 18 studies overall; 5 studies involved aerobic and/or resistance exercise training and 13 studies involved adapted exercise methods (i.e., body-weight support treadmill training, total-body recumbent stepper training, and electrical stimulation cycling). Of the five studies that examined exercise, two reported that resistance exercise training yielded significant improvements in muscle endurance; there were no significant improvements in any outcomes from the three studies of aerobic exercise training. Of the 13 studies that examined adapted exercise training, 9 reported significant improvements in disability, physical fitness, physical function, and/or symptomatic and participation outcomes. Collectively, the evidence is promising for beneficial effects of exercise in persons with severe MS disability, yet there is a lack of high-quality evidence regarding exercise for managing disability accumulation and associated outcomes in persons with severe MS disability. There further is limited research on the safety and prescription of exercise in this segment of MS. This highlights the importance of future research for optimizing the safety, prescription, and efficacy of exercise training in persons with MS who have severe disability.

22.6 Summary

Overall, there is increasing evidence for the role of exercise in managing the MS-disease pathophysiology, functions, and symptoms and optimizing QOL and participation outcomes. There further is evidence for the safety and prescription of exercise in MS. Nevertheless, there are exciting opportunities for research on exercise and neuroplasticity in MS and a need for developing a strong knowledge base regarding exercise in persons with advanced stages of MS. Such research will provide a comprehensive knowledge base for the promotion of exercise by healthcare providers as an approach for managing MS itself and the many consequences of this disease [54].

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Exercise and Anxiety

23

Aaron Kandola and Brendon Stubbs

Abstract

Anxiety disorders are a group of highly prevalent mental health conditions that can have a debilitating impact on daily functioning and well-being. They can co-occur with other mental health disorders, such as depression. People with anxiety disorders are also at an elevated risk of cardiovascular disease and premature mortality. Physical activity appears to be protective against anxiety disorders in clinical and nonclinical populations. Exercise, a subset of physical activity, has been shown to significantly reduce the symptoms of anxiety. The mechanisms through which exercise produces these effects are likely to involve a combination of biological and psychological factors. Physical activity may also be useful in reducing the symptoms of comorbid mental health conditions and the risk of physical health complications over time. Promoting physical activity could be a method of preventing or treating anxiety disorders with a wide range of benefits. However, further research will be necessary to address important gaps in the literature before these approaches can be fully implemented in mental health services.

Keywords

Physical activity · Exercise · Anxiety · Stress · Depression

23.1 Anxiety Disorders

Anxiety disorders are among the most prevalent and debilitating mental health conditions worldwide. The global prevalence of anxiety disorders ranges between 3.8% and 25% [1]. One major population-based survey in the USA found that anxiety disorders had a lifetime prevalence of 31.9% in adolescents aged between 13 and 19, making them twice as common as mood disorders in this sample [2].

Anxiety is an aversive state of worry that becomes persistent and severe in anxiety disorders [3]. Several subtypes of anxiety disorders exist, including phobias, social anxiety disorder, agoraphobia, generalized anxiety disorder, and separation anxiety disorder. While anxiety is a central feature of all subtypes, each occurs with a range of other symptoms that can have a serious impact on the well-being and daily functioning.

A. Kandola (✉)
Division of Psychiatry, University College London, London, UK
e-mail: a.kandola.18@ucl.ac.uk

B. Stubbs
Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London, UK

Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_23

Data from the Global Burden of Disease Study suggest that anxiety disorders are the sixth leading cause of disability worldwide [4].

People with anxiety disorders are at a greater risk of other mental health conditions, such as depression [5]. They also appear to co-occur with several chronic physical health conditions. For example, people with anxiety disorders have a 26% to 52% increased risk of cardiovascular disease [6, 7].

23.2 Exercise and Anxiety: Epidemiological and Clinical Evidence

Several epidemiological studies report a link between physical activity engagement and the incidence of common mental health disorders. In the general population, physical activity is inversely correlated with the incidence or symptoms of anxiety disorders [8–13]. Data from the World Health Survey spanning 47 countries suggests that not meeting guidelines of 150 minutes of moderate-to-vigorous physical activity increases the odds of an anxiety disorder by 32%, compared to those who did reach this guideline [14].

This evidence suggests that high levels of physical activity could be protective against anxiety disorders, whereas low levels of physical activity appear to be a risk factor for anxiety disorders. It stands to reason that increasing physical activity could help to reduce the symptoms of anxiety in people with anxiety disorders.

A growing number of studies have sought to investigate whether exercise-based interventions are effective forms of treatment for anxiety symptoms. Several recent meta-analyses have found that trials of exercise-based interventions have a small or moderate effect on reducing the anxiety symptoms in people with anxiety disorders [15–18]. This anxiolytic effect has also been found in people without a diagnosed anxiety disorder [19–21, 17]. There appears to be a reasonable evidence base to suggest that exercise-based interventions can reduce the symptoms of anxiety in people with anxiety disorders and nonclinical populations.

23.3 Exercise Treatment

The utility of exercise as a treatment for anxiety disorders spans further than its capacity to reduce anxiety symptoms. Increasing physical activity levels through exercise-based interventions could have a broader range of benefits for people with anxiety disorders.

Among the most important additional benefits of exercise in people with anxiety disorders relate to its impact on physical health. People with anxiety disorders are at an elevated risk of physical health complications and premature mortality [22, 7]. These physical health complications primarily relate to cardiovascular disease [6, 22–24]. There is a clear need to prevent the development of these physical health comorbidities that occur with anxiety. But current treatment approaches are not suitable for reducing cardiovascular risk, such as the use of SSRIs or talking therapies [25].

Physical inactivity is a modifiable cardiovascular risk factor and is high in people with anxiety disorders [14]. Exercise interventions represent a useful method of promoting physical activity and thereby reducing cardiovascular risk. Research has demonstrated that exercise-based interventions can improve cardiorespiratory fitness and physical health in people with schizophrenia [26, 27] and depression [28]. It stands to reason that these effects would also hold true for people with anxiety disorders, but research is lacking in this area [27].

It is possible that exercise could also be useful in preventing or treating other mental health conditions that often occur with anxiety disorders, such as depression [5] and substance use disorders [29]. A recent meta-analysis of 49 prospective studies found high levels of physical activity to be protective against depression in all age groups [30]. Trails of exercise-based interventions demonstrate that exercise can also significantly reduce depressive symptoms in people with [31] and without [21] depression. Physical

activity and exercise may also be useful in treating substance use disorders [32] and related stress disorders [33].

The utility of exercise-based interventions in the treatment of anxiety disorders is clear. Physical activity and exercise appear to be protective against the symptoms of anxiety and can reduce anxiety symptoms in people with and without anxiety disorders. Unlike other forms of treatment, they can simultaneously address the serious physical health risks of cardiovascular disease and premature mortality that occur with anxiety disorders. The transdiagnostic utility of exercise interventions may also extend to other mental health conditions that can co-occur with anxiety, such as depression and substance use disorders.

23.4 How Might Exercise Produce Anxiolytic Effects?

Despite the links between exercise and anxiety, little is known about the mechanisms that underlie their interactions. Exercise elicits a plethora of adaptive changes throughout the body and brain. This creates a challenge for elucidating which are the primary mechanisms that have anxiolytic effects.

Physiological stress, modulated in part by the hypothalamic pituitary adrenal (HPA) axis, appears to play a central role in a range of psychiatric conditions including anxiety and stress-related disorders [34–36]. Exercise exerts an influence on stress and the HPA axis, which could contribute toward its anxiolytic effects.

In 1996, Sothmann et al. [37] proposed a cross-stressor adaptation hypothesis for exercise training. They suggest that acute bouts of exercise elicit a physiological stress response that promotes adaptation over time, such as in the HPA axis. These biological adaptations may then protect against other stressors more broadly, such as psychosocial stress or other stressors related to anxiety disorders.

There is some evidence to support this conceptual framework. Both exercise and other acute stressors have a dose-dependent effect on HPA and the sympathetic nervous system (SNS) activation [38, 39]. For example, lower-intensity exercise promotes a cortisol response in the HPA axis, which is greater with higher-intensity form of exercise [39].

Exercise may have an acute and long-term effect on dampening the stress response. A systematic review found that acute bouts of aerobic exercise prior to a psychosocial stress task significantly reduced systolic and diastolic blood pressure in ten RCTs [40]. This effect was found to be dose dependent, in that greater amounts of exercise had a larger impact on reducing blood pressure. Acute bouts of exercise are also associated with a significant reduction in state anxiety in subsequent emotional exposure tasks [41].

It is possible that long-term exercise training will lead to changes in physical fitness that are protective against stress. An early systematic review found the evidence to be inconsistent as to whether these acute effects translate into long-term physiological adaptations to stress [42]. They found that cardiorespiratory fitness changes could elevate physiological responses to stress, but it may promote a greater recovery from stress. The authors noted a high level of heterogeneity between studies and key gaps in the literature at the time.

More recent work has been promising. One study found that a 12-week exercise training program led to improvements in fitness and reduced stress reactivity in cortisol, heart rate, and heart rate variability compared to a relaxation program [43]. Another study found that elite sportsmen had significantly lower cortisol, heart rate, and state anxiety in response to stressors compared to untrained participants [44]. Similar findings have been demonstrated in real-world settings. A 20-week exercise training program in students significantly reduced heart rate variability during a stressful exam period compared to sedentary students [45]. Other studies have demonstrated a negative relationship between objectively measured physical activity levels and HPA activation in response to stress [46].

There is a growing cohort of evidence to suggest that acute and long-term exercise is protective against environmental stressors, such as

psychosocial stress. Exercise appears to produce these effects by modulating physiological responses, primarily in the HPA axis. It is possible that exercise elicits this HPA adaptation through its vast neurogenic effects on the brain [47, 48].

For example, exercise has a particularly potent effect on the hippocampus [49]. It stimulates several hippocampal processes ranging from the upregulation of neurotrophic factors to changes in vasculature and the rate of neurogenesis [48]. Through these processes, exercise can promote hippocampal functioning in a way that contributes toward mental health [49].

The hippocampus contributes toward stress regulation [50]. Neuroimaging studies have shown the hippocampus to be directly involved in feedback loops with the HPA axis [51]. In a study by Zschucke et al. [52], participants with high cardiorespiratory fitness and sedentary participants underwent an acute exercise session or a placebo before engaging in an fMRI-based stress task. Compared to controls, participants in the exercise group expressed a lower cortisol response to the stress task, which was correlated with higher levels of activation in the hippocampus and lower activation in the prefrontal cortex. Participants with high levels of physical fitness had lower cortisol responses to the stress task than sedentary participants. These findings suggest that along with the prefrontal cortex, the hippocampus regulates HPA activity. The authors propose that exercise contributes toward a negative feedback loop involving these regions and the HPA axis to reduce stress.

More research would be beneficial in this area to elucidate the exact mechanisms through which exercise appears to interact with the HPA axis and modulate the stress response. These mechanisms are likely to play a causal role in the anxiolytic effects of exercise. A range of other mechanisms also exist through which exercise may exert an anxiolytic effect.

For example, inflammation and oxidative stress may contribute toward the etiology of anxiety disorders [53, 54]. A large cohort study found that people with anxiety disorders had elevated levels of the pro-inflammatory cytokine C-reactive protein (CRP), particularly in those with a late-onset anxiety disorder [55]. Contrastingly, exercise is associated with anti-inflammatory pathways that may be relevant for a range of conditions [56]. Through modulating inflammatory and oxidative stress pathways, exercise could prevent or reduce the severity of anxiety symptoms [54].

There is also a significant psychological impact of exercise that likely works in tandem with the biological mechanisms to reduce symptoms of anxiety [25]. For example, exercise reproduces many of the physiological responses associated with anxiety [38, 39] but without the same aversive experiences. Contrastingly, exercise is associated with mood-enhancing, anxiolytic effects [57]. It is possible that repeated bouts of exercise reproducing the physiological impact of anxiety through a less aversive state could reduce anxiety sensitivity over time [58, 59]. The premise of this concept is similar to the cross-stressor adaptation hypothesis [37] in that exercising may have broader implications outside of the acute experience itself, for overall functioning and well-being.

Exercise is likely to exert its anxiolytic effect through a combination of biological and psychological mechanisms. Future research should focus on elucidating these pathways, to better understand how both exercise and anxiety work on a mechanistic level. This understanding can be used to further optimize the treatment of anxiety disorders.

23.5 Future Directions

While a reasonable amount of evidence exists for the anxiolytic effects of anxiety, further research will be necessary to establish exercise-based interventions as a major treatment for anxiety disorders. Three priorities for future research should include the following: establishing the importance of physical fitness in treating anxiety, the optimal frequency, intensity, type, and duration of exercise interventions; and methods of promoting adherence to exercise-based therapy [25].

The distinction between physical activity and exercise is often overlooked in the literature and has led to a lack of clarity over the role of physical fitness in treating anxiety. Physical activity refers to any bodily movement that increases energy expenditure, but exercise refers to structured, repetitive movement with the purpose of improving physical fitness [60]. Cardiorespiratory fitness is a major component of overall physical fitness. It is possible to objectively measure cardiorespiratory fitness through graded exercise tests. But objective measures of fitness are rare in studies of physical activity or exercise and anxiety [17, 18]. As a result, little is known as to whether changes in physical fitness are necessary for these interventions to reduce anxiety symptoms.

It is also possible that baseline levels of physical fitness could influence the extent to which participants may benefit from the intervention [25]. For example, some studies have found that people with lower levels of cardiorespiratory fitness at baseline show the greatest reductions in anxiety symptoms following an exercise intervention [60, 61]. Such studies suggest that the magnitude of change in physical fitness could influence treatment response. It is possible that people with moderate or high levels of physical fitness may not respond as well to exercise-based therapy. This would mean that exercise-based interventions would be most appropriate for people with anxiety disorders who have low levels of cardiorespiratory fitness. However, given the wider benefits of exercise to other physical and mental health conditions, it is likely that exercise-based interventions would augment the treatment of most people with anxiety disorders.

A greater understanding of the role of physical fitness in anxiety disorders would also be beneficial for preventing the condition. Several prospective studies have found that higher levels of cardiorespiratory fitness are protective against incidences of depression [62–64]. There is evidence to suggest that cardiorespiratory fitness could also be protective against other mental health conditions, such as schizophrenia or stress-related disorders [65]. While there is some indication that this may also be true for anxiety disorders [66], there is comparatively little work in this area.

Future research should focus on establishing the role of physical fitness in the treatment and prevention of anxiety. This should involve the incorporation of graded exercise tests in trials or epidemiological studies. These tests can provide important metrics such as VO2 max, an objective measure of cardiorespiratory fitness. The use of objective measures is particularly important in epidemiological studies, which predominantly rely on self-reported measures of physical activity.

Establishing the optimal structure of exercise-based intervention will also help to ensure their effectiveness in reducing anxiety symptoms. There is currently no consensus over the ideal frequency, intensity, type, and duration of exercise for treating anxiety symptoms [18, 25]. Many exercise trials inadequately report relevant details on the structure and administration of exercise interventions [17, 67]. There is also an insufficient amount of variation of exercise protocols used by trials to establish any discernible differences in their effect on symptoms [18]. Future research should address these shortcomings by directly assessing the impact of different types of exercise protocols on the symptoms of anxiety. It would also be beneficial for authors to provide clearer details on the exercise protocols used in each study. This would facilitate the comparison of exercise protocols across multiple studies in systematic reviews and meta-analyses.

Finally, adherence to exercise therapy is likely to be a major barrier to the success of these interventions in the treatment of anxiety disorders [25]. Increasing physical activity and exercise levels in any population can be challenging as it requires a degree of self-motivation, perseverance, and a tolerance of discomfort. The challenge is even greater in people with mental health problems, who may be experiencing symptoms that counteract the motivation to exercise. Developing effective methods for promoting motivation among people with anxiety disorders to regularly engage in exercise will be foundational to their success as a treatment.

Competing Financial Interests The authors have no competing financial interests to declare.

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Part VII

Exercise and Respiration System

Exercise and Chronic Obstructive Pulmonary Disease (COPD)

24

Giuseppe Fiorentino, Antonio M. Esquinas, and Anna Annunziata

Abstract

Systemic effects of COPD lead to cardiovascular co-morbidities, muscle wasting and osteoporosis that, in turn, lead to inactivity and physical deconditioning. This evolution has a direct influence on the health-related quality of life (HRQoL) of patients suffering from this respiratory disease. Pharmacological therapy leads to improvement in shortness of breath, but it has a limited effect on the physical deconditioning. Pulmonary rehabilitation relieves dyspnoea and fatigue, improves emotional function and enhances the sense of control that individuals have over their condition. These improvements are moderately substantial and clinically significant. Rehabilitation serves as an essential component of the management of COPD and is beneficial in improving health-related quality of life and exercise capacity.

Keywords

Chronic obstructive pulmonary disease, COPD · Pulmonary rehabilitation, PR · Training · Whole-body vibration training · Neuromuscular electrical stimulation, NMES

List of Abbreviations

6-MWD	6 minute walking test
AECOPD	Acute exacerbations of chronic obstructive pulmonary disease
COPD	Chronic obstructive pulmonary disease,
CPAP	Continuous positive airway pressure
DW	Downhill walking
HRQOL	Health-related quality of life
HX	Heliox
IMT	Inspiratory muscle training
LFF	Low-frequency fatigue
MTL	Mechanical threshold loading
NIV	Non-invasive ventilation
NMES	Neuromuscular electrical stimulation
PImax	Maximal inspiratory pressure
PR	Pulmonary rehabilitation
QoL	Quality of life

G. Fiorentino (✉)
Division of Respiratory Physiopathology and Rehabilitation, A.O.R.N. "Dei Colli" - Monaldi Hospital, Naples, Italy

Salerno, Italy

A. M. Esquinas
Intensive Care Unit, Hospital Morales Meseguer, Murcia, Spain

Non Invasive Ventilatory Unit, Hospital Morales Meseguer, Murcia, Spain

A. Annunziata
Division of Respiratory Physiopathology and Rehabilitation, A.O.R.N. "Dei Colli" - Monaldi Hospital, Naples, Italy

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_24

RT	Resistance training
TFRL-IMT	Dynamically controlled tapered flow resistive load
WBVT	Whole-body vibration training

24.1 Introduction

Chronic obstructive pulmonary disease (COPD) will be a growing and significant cause of chronic morbidity and death worldwide in the next decade [1].

In this disease, airflow limitation increases the work of breathing and produces modifications in ventilatory mechanics and static and dynamic pulmonary hyperinflation. The related modifies of thorax geometry and diaphragm length, displace the muscle away from its optimal range to generate the required forces. A concomitant reduction in muscle mass is due to the interaction of several molecular mediators such as inflammation, hypoxia-inducible factor-1 signalling pathway, oxidative stress and reduced oxidative enzyme capacity and capillary numbers [2].

Moreover, genetics, cigarette smoke, hypercapnia, acidosis and metabolic disorders containing testosterone and vitamin D deficiencies, nutritional abnormalities, drugs, co-morbidities, exacerbations, systemic inflammatory response, reduced physical exercise and ageing are all pathological factors that mediate muscle disorder of the lower limbs [3].

Matched with healthy persons of the same age, COPD patients typically have a higher metabolic cost of performance with early-onset lactic acidosis and reduced maximal work rate and oxygen consumption [4]. The progressive inactivity leads to deconditioning that further increases the sense of respiratory effort. Patients often become progressively housebound and isolated from their family, friends and colleagues, with related worsening depression and anxiety that frequently impair the patient's quality of life (QOL) [5].

24.2 Muscle Modification in COPD

The speed of fibre contraction and primary type of metabolism inversely determine their resistance to fatigue and are the main physiologic features. Type I fibres, which belong to slow-twitch fibres and highly resistant to fatigue. Type IIx is fast-twitch fibres and unresistant to fatigue. Respiratory muscle disorder is quite common in persons with COPD and can contribute to impaired muscle function, reduced exercise capacity and activity [6]. The respiratory muscles undergo a progressive adaptation that makes them more fatigue-resistant, but there is a decline in both strength and endurance [6]. Muscle fibre atrophy is a significant systemic impairment in COPD. The number of types I fibre is less than in healthy person with an increase in type IIb fibre, which might lead to increased leg muscle fatigability and reduced endurance [2]. Skeletal muscle dysfunction is another critical factor that can contribute to exercise intolerance in patients with COPD [7]. This skeletal muscle dysfunction is characterised by a reduction in muscle mass and strength, atrophy of type I, and type II muscle fibres, reduction in fibre capillarization [3].

The decrease in muscle fibre cross-sectional area (CSA) is a marker of muscle atrophy and a predictor of mortality in COPD [8]. There is a reduced regenerative repair with an unbalance between protein degradation and synthesis, which is intensified by reduced regeneration [9].

Muscle fatigue is a symptom that the muscle temporarily lost the ability to execute a task, which can be associated with the incapacity of metabolism and contraction to supply the same work output continuously. What is more, endurance decrease was related to early muscular fatigue and was impossible to be predicted from their airflow limitation or quadriceps muscle weakness.

In European research, it was estimated that in the 30% of the COPD patients, at the initial stages of the disease, quadriceps muscle disorder was a prominent manifestation. In another investigation about COPD patients (GOLD I–IV), quadriceps strength and rectus femoris cross-sectional area were also significantly reduced

(19–25%) [10]. Importantly, acute exacerbations influence negatively muscle mass and function in COPD [11]. Apparent dyspnoea in response to a demand for high-intensity, repetitive muscle contractions is the main characteristic of the exercise intolerance most frequent observation in patients with COPD. Oxygen delivery and consumption by the legs is unaffected at submaximal exercise but maybe severely impaired at peak exercise because of complex interactions involving central and peripheral factors [12]. Other factors as insulin-like growth factor-1 can contribute to skeletal muscle hypertrophy, whereas it is decreased during the acute exacerbation of COPD [13].

In COPD patients there is a constant low-grade systemic inflammation with higher levels of pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-alpha); interleukin (IL)-6, 8, 18; and acute-phase proteins. Elevated IL-6 levels and TNF-alpha are also associated with radiological evidence of quadriceps wasting in COPD and reduced lean body mass [14].

Exercise limitation can worsen with pathologies evolution. In contrast to no modifications observed in respiratory function, exercise training, generally, can improve the exercise tolerance in COPD people. The eccentric training with moderate intensity can help to avoid sarcopenia, commonly developed in COPD patients [15].

24.3 Patient Candidacy for Exercise Training

The 2018 GOLD document concludes that pulmonary rehabilitation is the most effective therapeutic strategy for improving dyspnoea, performance and exercise tolerance [1].

No regular exercise can be adapted for all patients. Perhaps resistance and endurance training are frequently used in exercise programs. Exercise training modalities that utilize the features of eccentric training to achieve rehabilitation objectives are more and more common in COPD. In addition to this, elderly patients with COPD and sarcopenia also benefit from pulmonary rehabilitation to the extent that frailty indices ameliorate mostly [16].

Common strategies for exercise training in COPD are exercise with progressive augmentation in load over time. A walk, run, stair climb or swim is an example of endurance training exercises. In opposite, strength training involves bursts of work over a shorter period, such as occur with a weight lift.

Commonly there are possible two ways to train, either aerobic capacity (endurance training) or the force of muscles (strength training). Endurance training has as objective improvement of the power of the organism to perform aerobic work by activities such as racing and bicycling, in which a significant muscle mass is involved. Effective exercise intensities are characterised by individual target heart rates to be achieved in training sessions, continuing typically 30 min or longer for 5 days/week [17]. Strength training targets single muscles or muscle groups how great protocols apply 1–3 sets of 8–12 near maximal contractions for an individual muscle of muscle groups in 2–3 exercise sessions per week [18]. Resistance and strength training are thus opposite terminals of a range of training protocols with the importance either on the metabolic activity of the entire organism (endurance) or the maximal performance capacity of singular muscles. Endurance training can be structured as a low load but high repeated training with a weekly performance of thousands of muscle contractions while high load but low repetitive strength training protocols are done with only a few hundred tough contractions per week [19].

24.4 Training Modalities

When the high external resistivity induces eccentric contractions during slow deceleration manoeuvres (negative work), the myofilament is lengthened. Contemporary muscle contraction during sarcomere lengthening is considered to recruit energy and reduce metabolic needs through reduction of the rate of detachment between bridges and maintain a relatively higher proportion of bridging between bridges. The

reduction of metabolic demand could derive from various ways such as the reduction of oxygen absorption, heart rate, blood pressure and ventilation.

In addition to lower energy demands for muscle contraction, eccentric manoeuvres can also improve the generation of higher muscle strength. Eccentric training (negative work) is an exercise in which muscles stretch during contraction and provides braking and control mechanisms for limb movement. Eccentric training, which requires minimal energy, can be ideal for pulmonary rehabilitation and to increase both strength and muscle strength [20, 21]. The characteristics of eccentric contractions are strongly associated with COPD as they make a perfect physiological basis and mechanisms to understand exercise intolerance associated with dyspnoea and/or fatigue. The idea of the most suitable training association within a PR program should be based on the characters that appear in the detailed basic assessments of individuals with COPD [22].

The exercise program must be individually tailored to meet the needs and goals of the patient, using resources available. The components of exercise prescription contain "FITT principles": frequency, intensity, type and timing. Usually, more than twice sessions of 20–30 min/week over a prolonged period (8 weeks or more) are recommended for COPD patients [23].

The intensity and duration of the exercise training are the most critical factors of predicting outcomes, including the oxidative adaptability of muscles and the resistibility to oxidative damage. It has been proved that the exercise training intensity can change the structure of muscle fibres, while the duration can improve the capillary growth and the oxidative adaptability of muscles [24]. Low-intensity training is well tolerated by COPD patients and is particularly suited to those with the severe form of the disease.

Low-intensity or intermittent training modalities can be perfect choices when the COPD individuals have difficulty in achieving the anticipative intensity or duration. High-intensity and enduring exercise training modalities are frequently applied in pulmonary rehabilitation. High-intensity rehabilitation exercise is known to increase the muscular aerobic metabolism that allows tolerating a higher magnitude of activity without limiting dyspnoea [25]. Interval or intermittent training might be the right choice for those with a more serious disease and higher symptom burden of illness. It is recommended that the resistance goal is set to the level of equal to 60–70% of the maximal duplication manoeuvre and executed 8 ~ 12 duplications in 1–3 sets per session [26].

The variation or modification of the times necessary to complete the exercise necessary for that type of training, allows you to manipulate the variables for maximizing efforts and to reach the appropriate preparation with the expected results [27].

Compared with the regular method, intensive interval training leads to a minor level of dynamic pulmonary hyperinflation and a notably longer tolerated training period and, concurrently, a lower degree of exertional dyspnoea. The suggested periodization for enhancing the adaptations of skeletal muscle and realising advantages is no less than 3 intervals once a week, with a combination of superintended and self-monitoring sessions for 8 weeks. High-intensity exercise, characterised as more than 60% of work rate maximum for a 20–60 min duration is associated with greater advantage than low-intensity training. Choosing an exercise intensity needs to be based on the skeletal muscle weakness and an aim of making an effective anabolic stimulus to improve the oxidative ability of skeletal muscle [28].

Intermittent training is a candidate to perform endurance training in COPD individuals who have symptoms as expiratory dyspnoea, fatigue or incompleteness of the target intensity and/or duration. In intermittent training, high-intensity training is combined with others of low-intensity training. Resistance or strength exercise training composed of heavy loads lifting by regional muscle groups can increase muscle mass and improve the forces of peripheral muscles in COPD individuals [29].

Increase in muscle mass and power is obtained more mainly in response to resistance training than to endurance exercise training. Additionally, patients experience less dyspnoea during the resistance exercise process than in programs of endurance exercise training. Furthermore, endurance exercise training also induced a fibre-type shift to a more fatigue-resistant phenotype (increased slow-twitch fibres) and an amelioration in the oxidative ability of the limb muscles in patients undergoing training. Increase in mass and strength of the quadriceps muscle were also observed in response to resistance training in patients with COPD [30].

24.5 Principal Pulmonary Rehabilitation Strategies

24.5.1 Inspiratory Muscle Training (IMT)

In the last decades, inspiratory muscle training (IMT) has been attracting an increasing study in individuals with COPD [31]. IMT working with a threshold or resistive load becomes the most popular method, with the indication usually based on the maximal inspiratory pressure (PImax) is generally applied to improve inspiratory muscle strength. The top three types used in training are flow-resistive loading, mechanical threshold loading (MTL) and normocapnic hyperpnoea (low pressure-high flow loading). Recent literature shows that an electronic flow resistive breathing device was developed with a dynamically controlled tapered flow resistive load (TFRL-IMT). This loading combines the speciality of threshold loading and flow-resistive loading [32].

A meta-analysis of 32 studies revealed that the additive effect of respiratory muscle training beside multimodal PR, including general exercise training is comparatively small [33]. The best intensity of exercise training is not comprehended and varies from 15 to 80% of PImax. An original resistance more significant than 30% of PImax is recommended and increases as a step-by-step style [34]. Also, the alternative duration was unknown, the preponderance of literature presented a complete training period of 30 min to 1 h daytime, with sessions usually divided into two or three sittings, 3–7 days/week. Most IMT interventions in COPD patients have been performed as wholly or partially supervised daily training for 30 min with controlled training loads using MTL-IMT [35].

24.5.2 Downhill Walking (DW)

Downhill walking (DW) is an exercise modality with a high eccentric component embedded in a common exercise that combines endurance exercise of the quadriceps femoris muscles with aerobic training. The greatly fatiguing potential of downhill walking in combination with low metabolic demand of the eccentric component makes downhill walking a potentially well-suited training modality for COPD individuals. It gives a unique chance to efficiently induce skeletal muscle stress while simultaneously minimising ventilatory demand during exercise [36]. In a study of COPD patients, 90% of participants experience contractile muscle fatigue after a 20-min bout of downhill walking compared to 60% of patients who executed the training on a level treadmill. In addition, patients exercised with 17% less oxygen consumption and 9% less ventilation during downhill walking than treadmill walking. Although the training session progression rate was demonstrated to be increased in the downhill walking group, further studies need to perform to answer these reactions in detail [37].

The improvement of low-frequency fatigue (LFF) may be an essential determinant of an optimal answer to exercise. LFF occurs when the muscle force response to low-frequency stimulation decreases in association with a slow (hours or days) recovery [38]. It is characterised by decreased intracellular calcium ion concentration and muscle damage. LFF can be efficiently stimulated via eccentric muscle training due to its capacity to induce skeletal muscle damage. The benefits of producing LFF in people with COPD

have been recently demonstrated in a study of exercise training [39]. In this study, the development of quadriceps LFF following a single exercise session (in approximately 30% of participants) was associated with superior improvements in functional exercise capacity and symptoms related to the quality of life at the conclusion of the 12-week high-intensity rehabilitation programme. This highlights the possible importance of recognising treatment modalities capable of eliciting LFF.

Therefore, the downhill walking does not appear to have a notable role in the advancement of COPD symptoms in this situation, but leads to a better quality of life QoL of the patient, by increasing her ability to perform ADL and decreasing her muscle weakness and general tiredness. In our case, 3 months after the initiation of exercise therapy, the patient was, and her improvement was sustained [40].

24.5.3 Eccentric Resistance Training (RT)

An essential aspect of eccentric muscle work is its reduced energetic requirement. Typically, there is an approximately fourfold lower energy requirement when walking downhill than when walking uphill over the same gradient [41]. Eccentric exercise thus presents a modality by which high loads on muscle tissue can be combined with small energy requirements for muscle contraction. It is commonly accepted that (high) mechanical load is of predominant importance for muscle maintenance and adaptation [42]. When RT (incongruous upper and lower limb activities) is compared with endurance exercise alone or to a mixture of both, the amelioration in maximal exercise capacity during an incremental cycle test and HRQOL was similar among all exercise modalities. The less oxygen consumption and dyspnoea scores during resistance training may be effective and better tolerated in COPD patients. The prescription for RT should follow the rules of one maximal repetition. The protocol is described as the maximal load, which could be moved once only over the full range of motion without compensatory movements. The appropriate prescription for COPD individuals is 1–3 sets of 8–12 repetitions at a frequency of 2 or 3 days/week, with loads reaching from 60 to 70% of the one-repetition maximum or one load that produces fatigue following 8–12 repetitions [43].

To improve the dyspnoea levels, higher duration of preparation (higher than 8 weeks) may be required. The rules of overload are critical, and an increase in loads requires to maximise training gains over time. The increasing strength of muscle is shown by the improved performance of practical actions, notably when exercises closely replicate daily activities. To obtain a decrease in breathless during the upper limb exercise, a specific ventilation mode may be helpful for these tasks. Recently, it was reported that severe COPD patients had tried a regular load arm lifting distribution to symptom resistance and were randomly attributed to either inhale or exhale during the lift or unconstrained breathing. The breathing modality of exhaling during the lift was correlated with obviously higher muscle endurance. This strategy can be quickly adopted for the endurance training of the upper limb to maximise performance, which may translate into reduced symptoms over a more extended training duration [44].

The result of upper limb training on dyspnoea levels, during home activities and upon HRQOL, is less reassuring. There is an obvious reduction in breathlessness in neither supported nor unsupported training.

Single limb exercise training (one limb at one time) could be regarded as an alternative exercise training strategy for people with severe respiratory disease. Richardson et al. reported that single-legged dynamic knee extension exercises exhibited more magnificent work than the regular two-legged cycling, with lower minute ventilation, peak heart rate and dyspnoea in COPD patients [45].

Low-load/high-repetition single limb exercise training, including exercising one of the upper/lower limbs at a time; interchange left to the right side in each exercise set. To reduce the ventilatory demand and oxygen consumption under a higher training intensity, this strategy utilizes a small volume of muscle mass, which is

recruited at a single given time. For individuals with severe COPD, low-load/high-repetition of single limb training with elastic bands can improve not only the strength of peripheral muscle but also the work capacity of the extremities. However, this training strategy had no benefits on cycling endurance capacity and did not influence the life quality [46].

Eccentric cycling is an improvement of popular cycling on a stationary cycle ergometer. The workload used during eccentric cycling depends on the force people use to break the system. The rationale for use is elicited exercise has a less metabolic requirement but a higher power output [47]. During regular cycling, people impulse the cadence by pushing the pedals against the resistance offered from the ergometer. In addition, Rocha Vieira et al. reported that eccentric cycling caused minimal muscle soreness and symptoms of dyspnoea and muscle fatigue, reinforcing its potential in this population [47].

Single-legged cycling is an alternative strategy to build up the positive benefits from endurance training while minimising the ventilatory load could be obtained by partitioning training to a smaller muscle group and supporting the same muscle load adaptation of popular seated cycling that requires unilateral pedal propulsion in the forward direction [48]. During a fixed power exercise testing, compared on two-legged cycling (70% of peak power), one-legged cycling (intensity of 35% of two-legged peak power) produced a similar metabolic requirement, at lower minute ventilation and less dyspnoea. This new strategy can increase the efficacy of endurance exercise in COPD patients, with them being able to improve their work capacity [49].

After practised three times weekly for 7 weeks, VO2 peak was obtained a more obvious improvement in one-legged cycling group (15 min per leg) than in the two-legged cycling (30 min in total) group. Besides its safety and rational completion rate, single-legged cycling has been proved to improve peak cycling power, VO2 peak and peak minute ventilation over and above changes seen with two-legged cycling. Single-legged cycling has also been reported that it can improve the 6-min walk distance and the quality of health-related life. The training requires an appropriate cycle ergometer, with patients having their inactive footrest on the crossbar located centrally on the head of the ergometer cycle during the exercise [50].

While these cycle ergometers within PR programs were considered to be satisfactory and received no position correction by the patients, they may change the choice of patients in which this kind of training is possible.

24.5.4 Neuromuscular Electrical Stimulation (NMES)

NMES uses a battery-powered stimulator unit to produce a controlled contraction of the muscles via skin electrodes. Transcutaneous electrical stimulation of skeletal muscles seems to be an alternative rehabilitation form in which muscles are trained without any exercise. The muscle group most commonly targeted by NMES is the quadriceps. In patients who are powerless or reluctant to adhere to existing forms of exercise, NMES may propose an alternative way of enhancing leg muscle strength [51]. To achieve the expected muscle contraction, the electrical stimulation is used, and its intensity, duration and frequency of the stimulus are given. A standard program consists of 30–60 min of quadriceps stimulation, 3–5 times weekly for 4–6 weeks [52]. A relatively long contraction period followed by an even more extended rest period may be advantageous. These protocols, which commonly feature in studies undertaken in people with COPD, aim to create the most significant force during each and every contraction because the mechanical stress is likely to stimulate the synthesis of the contractile proteins [53]. As the metabolic response during an NMES session is significantly lower compared to a resistance exercise training session in patients with COPD, this technique may be particularly relevant to severely deconditioned or bed-bound patients [54]. Many of the most obvious drawbacks associated with training (dyspnoea, minimum cardiocirculatory demands, and psychosocial aspects) exist in electrical stimulation. NMES can lead to

improvements in muscle strength and exercise performance, with pooled data revealing mean between-group differences in peak quadriceps torque and 6-min walking distance of 9.7 nm (95% CI 1.2, 18.1) and 48 m (95% CI 9, 86), respectively [55]. Recent studies have also demonstrated favourable changes in markers of anabolism/catabolism and the quadriceps fibre type profile following NMES.

PR programmes, especially during AECOPD, are challenging to implement because of patients' clinical condition, and strategies that avoid respiratory system stress are needed. In answer to that need, high-frequency NMES has been successfully used as a localised training modality in severely impaired patients who are incapable of following formal PR or tolerating higher training intensities. This treatment has several limitations as skin pain and reproducibility [56].

However, studies remain small, follow-up data are lacking, and the patient phenotypes most likely to benefit have yet to be identified.

24.5.5 Whole-Body Vibration Training (WBVT)

Vibration training is defined as voluntarily exposed to the dynamic frequencies body via specific joint angles for any restricted time.

Vibration training is a novel technology in sports science [57]. Professionals, fitness and centres of rehabilitation are extensively using vibration training in the applications. WBVT is a new therapeutic modality of lung rehabilitation targeting to improve the neuromuscular performance of persons with a neuromuscular disorder, which is used via a vibration surface generating sinusoidal vibrations [58]. WBVT induced advancements in the activation of neuromuscular. The simplest mechanism to define WBVT-induced reflex muscular movement is the tonic vibration reflex. In past resistance exercise training from voluntary muscle control, the muscle contractions during WBVT are provoked by stretch reflexes. The specific mechanisms of the muscle function improved by WBVT still need to further defined. Muscle contraction is obtained during WBVT, and chosen muscles could be stimulated and enhanced. Many amplitudes and frequencies series with popular technology get it accessible to an extensive mixture of WBVT methods to be used on humans [59]. In COPD patients) WBVT increases blood circulation nearly 14%, the level of vascular endothelial growth factor and endothelial, thereby promoting blood vessel formation [60]. In addition, WBVT can effectively improve the muscle elasticity and coordination and further decrease threshold of the muscle spindle excitability with improved exercise capacity in COPD. Furthermore, stable COPD patients benefited stronger than severe COPD persons [61]. WBVT had advantageous results on the capacity of functional training, which was principally measured by and change of 6-MWD [62].

Nevertheless, few pieces of evidence advised that WBVT may enhance lung function and the life quality in COPD individuals concerning a shift of FEV1 (% predicted) and SGRQ score. WBVT has an effective role in improving the clinical symptoms of COPD, which is principally correlated to the increased the respiratory muscles contraction forces, which further stimulates the respiratory function, improves the ratio of ventilation, blood flow, and the breathing capacity [63, 64]. The whole-body vibration training (WBVT) has been identified as an alternative intervention to improve exercise capacity and quality of life of COPD patients. Two available kinds of literature did not observe an obvious improvement in force of quadriceps muscle after either the 6 or 12-week outpatient WBVT programs [64].

Cristi et al. have shown that 9 weeks of WBVT in low-intensity do not modify inflammatory markers (C-reactive protein, IL-6, IL-1β, IL-10 and TNF-α) in older adults [65]. On the other hand, Rodriguez-Miguelez et al. showed that 8 weeks of WBVT in moderate intensity (platform amplitude: 4 mm) induced anti-inflammatory adaptations, by increasing IL-10 and decreasing pro-inflammatory markers, such as C-reactive protein and TNF-α, in elderly subjects [66].

24.6 Contractile Fatigue After Exercise

In patients with moderate-to-severe COPD, the quadriceps muscle is more susceptible to develop early contractile fatigue. The majority of COPD patients develop quadriceps contractile fatigue during an endurance cycle test performed until symptom limitation or several episodes of maximal single muscle exercise. Some patients do not manifest contractile fatigue during training because they do not produce adequate training intensity due to ventilatory limitations [67]. The sensation of breathlessness during exercise was not related to the development of contractile fatigue during training. The sensitivity to developing contractile fatigue during exercise is seen more often in patients with higher glycolytic enzyme activity in the muscle cytoplasm, lower muscle capillarization and earlier blood lactate accumulation during exercise. In these patients, fundamental muscle changes associated with early metabolite accumulation during exercise training may lead to early contractile failure of the working muscles, despite the low absolute exercise intensities. Ventilatory limitations might prevent patients with better preserved oxidative metabolism from reaching a sufficient training intensity to induce a similar overload [68, 69].

24.7 Nutritional Support and Anabolic Stimulation

It is necessary to support adequate nutritional for COPD patients. In addition, COPD patients have observed an increasing in body weight, muscle mass, respiratory and limb muscle strength, exercise capacity, and quality of life, with body composition alteration adaption to three oral liquid nutrients administered together with an 8-week pulmonary rehabilitation program [70]. Dietary supplementation appears to be useful, especially in combination with an anabolic stimulus like exercise training in patients with advanced COPD and poor body composition. Multi-anabolic drugs and bioactive nutrients like testosterone, growth hormone and its analogues, megoestrol acetate, L-carnitine, creatine, antioxidants, and vitamin D supplements could benefit to mass muscle reduction and dysfunction of limb muscles in persons with COPD [71]. More evidence from extensive clinical trials is needed to illustrate the safety and possible side effect before any of these drugs can be implemented in clinical settings.

24.8 Oxygen Supplementation During Exercise

More recently, the use of oxygen therapy in improving outcomes from pulmonary rehabilitation in patients with COPD has been evaluated in several studies. Desaturation estimation during exercise tolerance testing on room air at baseline, along with the individual response to supplemental oxygen, guides to which single patient benefits from oxygen supplementation during training [72].

In general, a difference must be made between the immediate effect of oxygen on exercise performance and its value in the exercise-training component of pulmonary rehabilitation. The rationale is that supplemental oxygen therapy improves peripheral muscle oxygenation, dyspnoea and exercise capacity in COPD patients with hypoxaemia, probably permitting them to train at higher intensities.

The use of oxygen increases maximal exercise performance immediately in the laboratory, but examinations its effect in improving the exercise-training effects have produced inconsistent results. The long-term outcomes when supplemental oxygen is discontinued and the impact on other outcomes remain to be defined [73, 74].

24.9 Non-invasive Ventilation (NIV)

In COPD individuals, limited expiratory flow and dynamic hyperinflation during exercise may enhance the respiratory function and has been correlated with the initial termination of training. To discharge the respiratory muscles and

overcome the work of breathing, NIV has been used as an aid to exercise [75]. In response to NIV during exercise, the improvement in breathing is mainly associated with the adaptions in the load/capacity balance of the respiratory muscles. Several small RCTs have indicated that the NIV addition to a training program in patients induced a higher training intensity being tolerated and more significant improvements in exercise capacity. Using a continuous positive airway pressure (CPAP) during training in COPD individuals caused reduced tidal excursions of oesophagal pressure. It inhibited inspiratory effort during CPAP was obviously associated with reductions in perceived dyspnoea intensity. In addition, it was found that pressure support ventilation can be able to reduce inspiratory effort and dyspnoea during exercise in COPD [76]. The application of NIV requires additional equipment, experience, especially in the early setting. The real difficulty is the choice of optimal pressures and the different assistance for a single patient to accommodate to the interventions during exercise training. Based on these reasons, its practical usage might be preserved for COPD patients who are obviously restricted in their ability to achieve a low intensity of exercise training during endurance or resistance exercise due to significantly dynamic hyperinflation and intolerable dyspnoea.

24.10 Heliox Supplementation

Heliox (HX) is defined as a low-density gas combination (79% helium, 21% oxygen) that has been used in COPD patients to reduce airflow resistance during the increasing ventilatory needs of exercise. HX-induced decrease of dynamic lung hyperinflation is correlated with consistent change in indices of cardio-circulatory function such as HR kinetics in the rest-to-exercise transition in COPD patients [77]. Heliox breathing improves the maximal resting size of the flow-volume loop and appears to slow down the increase in EELV during training. It will simultaneously prevent functional weakening and load on the respiratory muscles during use [78, 79].

24.11 Conclusion

COPD patients have various degrees of activity limitation because of skeletal muscle disorder. Physical activity is essential for all patients with COPD. While this is probably especially the case for patients referred to pulmonary rehabilitation, evidence on physical activity in the context of pulmonary rehabilitation is limited. Both exercise training and physical activity interventions should be an integral and complementary part of pulmonary rehabilitation and are essential assets to the management of patients with COPD. Both have distinct goals; exercise training aims to enhance fitness, physical activity programs aimed at behaviour change towards a more active lifestyle. We suggest that exercise training is needed in the first phase of a pulmonary rehabilitation program to increase exercise tolerance and general physical fitness. Due to the type of intervention, not much change in physical activity is expected when an exercise training program is offered alone. When the functional reserve is sufficiently large, behavioural responses can be introduced to translate the physiological gains into daily-life activities. Further research is needed to answer the remaining questions concerning optimal timing, duration, intensity, patients' preferences and patient selection when combining both interventions to achieve the long-term health-enhancing behaviour in these patients.

Competing Financial Interests The authors declare no competing financial interests.

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Exercise and Asthma

25

Shengguang Ding and Chongjun Zhong

Abstract

Asthma is a chronic lower respiratory disease that is very common worldwide, and its incidence is increasing year by year. Since the 1970s, asthma has become widespread, with approximately 300 million people affected worldwide and about 250,000 people have lost their lives. Asthma seriously affects people's physical and mental health, resulting in reduced learning efficiency, limited physical activities, and decreased quality of life. Therefore, raising awareness of the risk of asthma and how to effectively treat asthma have become important targets for the prevention and management of asthma in recent years. For patients with asthma, exercise training is a widely accepted adjunct to drug-based and non-pharmacological treatment. It has been recommended abroad that exercise prescriptions are an important part of asthma management.

Keywords

Asthma · Respiratory disease · Exercise

25.1 Background

Asthma is a common disease, mostly in the elderly and children, and the patients are likely to lose their life during the onset in case of lacking timely treatment [1]. The main features of asthma are symptoms of variability and recurrence, reversible airflow obstruction, and bronchospasm. Common symptoms are wheezing, coughing, chest tightness, and difficulty breathing [2]. Asthma is caused by a complex interaction between genetic and environmental factors, which typically include: exposure of pollutants and allergens in the air; and drugs such as aspirin and β-receptor blocker. In terms of genes, asthma is heritable, and many susceptible variants have been discovered in genome-wide association studies [3]. The diagnosis of asthma is usually based on several types of symptoms, the response to treatment at different times, and the measurement of spirometry. Medical classification of asthma is based on the frequency of onset, forced respiration (FEV1) within 1 s, and peak expiratory flow to classify [4]. Asthma can be divided from mild to severe: asthmatoid bronchitis, bronchial asthma, and cardiac asthma [5]. Patients with asthmatic bronchitis usually cough for a long time with a noticeable wheezing [6]. Most bronchial asthma occurs in children or young people, and it usually occurs in the spring and autumn or in the cold. The asthma attacks come faster and are characterized by difficulty breathing

S. Ding · C. Zhong (✉)
Department of Thoracic and Cardiovascular Surgery, The Second Affiliated Hospital of Nantong University, Nantong, China

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_25

[7]. Patients with cardiac asthma may usually develop to coronary heart disease, rheumatic heart disease, cardiomyopathy or hypertension, and left ventricular heart failure, causing blood stasis in the lungs, gas exchange disorders, and asthma [8].

The current phenotype of asthma can be divided into two broad categories, namely Th2-associated asthma and non-Th2 asthma [9]. Th2-associated asthma is characterized by allergic, airway hyperresponsiveness, eosinophilic inflammation, and available hormone therapy. This asthma mainly includes early-onset asthma (mainly allergic asthma, prepubertal onset); late subgroup of eosinophilic asthma (onset after 20 years of age); and exercise asthma [10]. Non-Th2 asthma may account for a large proportion of the overall asthma population, but compared to Th2 asthma, we know little about the molecular mechanisms of this type of asthma and some of the asthma phenotypes it may include. There is no Th2 type inflammatory response, and such asthma is not suitable for the treatment with hormones [11]. From the current research results, obesity-associated asthma, neutrophilic asthma, and some mild-to-moderate late-onset asthma can be classified as non-Th2 asthma [12]. Asthma is also associated with a variety of complications, including rhinitis, sinusitis, gastroesophageal reflux disease, obstructive sleep apnea, hormonal disorders, and psychopathology [13]. If you have asthma without healing for a long-term treatment, in addition to pulmonary emphysema and pulmonary heart disease, patients may be prone to development pneumothorax and mediastinal emphysema [14]. The reason is that the gas stays in the alveoli during the asthma attack, causing excessive alveolar gas and a significant increase in intrapulmonary pressure [15]. All of these symptoms exacerbate the quality of life and mental health of people with asthma and limit activities of daily living. Due to the fear of asthma, asthma patients are unable to participate in physical exercise, physical strength is reduced, and the symptoms are worsened [16]. In addition, the degree of anxiety and depression in asthma patients is positively correlated with the number and severity of asthma attacks, and this psychological disorder can change the breathing pattern of the person, resulting in irregular breathing, often sighing, and chest breathing is dominant [17].

Asthma attacks are the activation of many immune or non-immune cells through a series of interlocking immune responses, which then produce large numbers of cytokines involved in the pathological process of asthma [18]. Cytokines are activated by immune cells or non-immune cells to synthesize and secrete a group of small molecular peptides and glycoproteins that regulate and mediate immune responses and inflammatory responses. They play a very important regulatory role in the pathogenesis of asthma [19]. Cytokines regulate airway inflammation in asthma by affecting antigen presentation, information transmission, gene transcription, synthesis and inactivation of IgE, expression of adhesion molecules, differentiation of inflammatory cells, airway smooth muscle spasm and airway reconstruction [20]. The cytokines that have a positive regulatory effect on asthma include IL-1~9, IL-11, IL-13~16, GM-CSF, G-CSF, TNF, and PDGF. The main regulators of asthma are IFN-r, IL-1, IL-10, IL-12, IL-18, TGF-β, and so on [21]. Cytokines are mainly derived from the following cells: airway epithelial cells, mast cells, eosinophils, macrophages, lymphocytes, pulmonary vascular endothelial cells, lung fibroblasts, and other cells [22]. The role of cytokines does not act independently. They form a cytokine network to play a biological role through the mutual regulation of synthetic secretion, the mutual regulation of receptor expression, and the interaction of biological effects. Although research on the role of cytokines in asthmatic inflammation has made some progress, many mechanisms remain unclear. As cytokine research progresses further, the pathogenesis and control of asthma are eager to update and break through.

At present, asthma cannot be cured, but it can be effectively controlled. Keep away from asthma-inducing factors such as allergens and irritants, in addition to regular inhaled corticosteroids can be very helpful in controlling the condition [23]. The benefits of exercise have long been recognized, which can improve cardiopulmonary

function and metabolism of other organs, help to enhance the body's immunity, reduce the risk of heart and lung disease, and delay aging [23]. Many studies have shown that exercise has many benefits for various organ systems in the human body, especially in clinical exercise rehabilitation therapy [24]. Its quantitative and individualized exercise programs can have a direct impact on patients with different rehabilitation needs [25]. For patients with asthma, exercise training is a widely accepted as an adjunct to drug-based and non-pharmacological treatment. Because exercise may lead to worse asthma symptom, many asthma patients avoid exercise because of afraid of exacerbation [26]. Therefore, scientists hold different opinions on whether asthma patients should do exercise and what sports to choose [27]. In particular, whether children with asthma can do exercise in the same way as normal children is an important part of non-pharmacological treatment of asthma in children [28]. A large number of research data have shown that children with asthma are safe and beneficial with regular exercise [29]. Exercise can improve lung ventilation and increase lung capacity, which effectively alleviates symptoms of asthma attacks, reduces the number of episodes of disease, and reduces the amount of antibiotics used and the financial cost of treatment [30]. What is more, it also prevents the development of emphysema [31]. Exercise therapy is a kind of rehabilitation therapy that is both economical and effective [32]. It is convenient and feasible. Asthma patients should be encouraged to participate in appropriate sports activities such as swimming, walking and jogging [33]. At present, more and more doctors apply exercise prescriptions to the clinical treatment of asthma [34]. Sports prescriptions have been recommended as an important part of asthma management [35]. In this article, the author will focus on the pathogenesis and treatment of asthma, discussing whether asthma patients need exercise training and how to improve asthma.

25.2 Pathogenesis of Asthma

Asthma is a chronic airway inflammatory disease involving the interaction of various inflammatory cells and inflammatory mediators. Airway inflammation is a common pathological feature of various types of asthma in all types [36]. Airway inflammation is characterized by airway epithelial damage and shedding, multiple inflammatory cell infiltration by eosinophils, airway microvascular dilatation, increased permeability and increased exudate, and inflammatory mediators in the airway lumen increased (such as histamine, leukotrienes, platelet-derived factor, prostaglandins, and a variety of inflammatory biochemokines) [37]. A variety of inflammatory cells (including mast cells, basophils, neutrophils, lymphocytes, macrophages, platelets, vascular endothelial cells, and airway epithelial cells), which are mainly eosinophils, mediate airway inflammation [38]. Mast cells and basophils are the starting cells of the airway inflammatory response [39]. Chemical mediators and chemokines released by inflammatory cells and other inflammatory mediators cause bronchoconstriction, airway hypersecretion, plasma exudation, airway hyperresponsiveness, and airway structure changes (airway smooth muscle and collagen fiber proliferation, gas Road remodeling) [40]. The function, growth and differentiation of various cells in asthmatic airway inflammation, and the interaction between cells are regulated by various cytokines [41]. Cytokines are important informers between cells and determine the type and duration of the inflammatory response [42].

Asthma is a chronic airway inflammation involving a variety of inflammatory cells such as eosinophils, mast cells, and T lymphocytes [43]. At the same time, structural cells such as epithelial cells and smooth muscle cells may also contribute to the inflammatory environment [44]. These cells together produce inflammatory molecules such as cytokines, chemokines, and cysteinyl leukotrienes, which cause inflammation and promote airway stenosis [45]. Airway stenosis is a gradual and constant pathological process [46]. Structural changes associated with airway remodeling include increased smooth muscle, increased

distribution of subepithelial tissue, thickening of the basement membrane and subepithelial deposition of various structural proteins, and the loss of normal airway dilatation [47]. It can be seen that asthma is a disease associated with allergies. Several classic types of asthma are now described below.

25.2.1 Bronchial Asthma

Asthma is a chronic inflammatory disease of the airways, in which many cells and cellular components are involved [48]. Bronchial asthma is mainly caused by genetic or environmental factors. As the disease progresses, a series of airway structural changes occur, also known as airway remodeling [49]. Pulmonary function and symptoms in asthma patients often worsen between midnight and early morning [50]. Bronchial asthma patients suffer from mental stress due to their high risk, so bronchial asthma patients are easy to develop anxiety and depression [51].

25.2.2 Cardiogenic Asthma

Cardiac asthma is a paroxysmal asthma caused by left heart failure and acute pulmonary edema. The clinical manifestations of the onset of the disease are similar to those of bronchial asthma, accompanied by frequent cough and bloody sputum [52]. The pathogenesis of cardiogenic asthma: when the left ventricle develops myocardial lesions (because of coronary heart disease, acute myocardial infarction, dilated cardiomyopathy, hypertrophic cardiomyopathy, myocarditis, etc.), as the left ventricular end-diastolic pressure increases, the left atrium and pulmonary venous pressure increase accordingly, which in turn causes increased pulmonary capillary pressure, and eventually lead to pulmonary congestion and pulmonary edema [53].

25.2.3 Cough Variant Asthma

Cough variant asthma is based on airway allergic inflammation and airway hyperresponsiveness, which causes asthma due to inhalation-induced factors [54]. The average total serum IgE in asthma patients is usually 200 IU/ml higher than in the general population [55]. The recent work of Heymann et al. and Green et al. suggested the interaction between rhinovirus and allergies mainly occurs in patients with a total IgE > 200 IU/ml [56]. Meanwhile, the different characteristics of allergens may affect the prevalence and severity of asthma [57]. Cough variant asthma usually is accompanied with irritating dry cough with pain and sternal discomfort, but it is generally with no sputum or other manifestations of respiratory inflammation. Therefore, it is not beneficial to treat with antibiotics and other drugs which relieve cough and reduce sputum. In addition, the appearance of cough has a certain seasonality, which occurs mostly in the spring and autumn when the climate is changeable [58].

25.2.4 Exercise-Induced Asthma

Asthma induced by exercise is called exercise-induced asthma (EIA). During exercise, the patients contract bronchial smooth muscle due to increased breathing; in addition, loss of heat and moisture in the respiratory tract causes contraction of bronchial smooth muscle [59]. If you exercise in a dry and cold environment, dry and cold air will stimulate the respiratory tract. When mast cells and eosinophils are stimulated, they will release inflammatory mediators, causing respiratory inflammation and airway hyperresponsiveness [60]. The typical symptoms are chest tightness, coughing, and wheezing, and even obvious breathing difficulties after 5–10 min physical activity. Most of this reaction is transient and reversible; apart from that it will be relieved after about 20–30 min [61].

25.2.5 Drug-Induced Asthma

Drugs such as aspirin can induce or aggravate existing asthma symptoms, which is known as drug-induced asthma. Aspirin is a commonly used antipyretic analgesic, a nonsteroidal drug, and the pathogenesis of drug-induced asthma is believed to be related to allergic reactions [62]. In recent years, it has been further recognized that as a cyclooxygenase inhibitor, aspirin inhibits the activity of airway epoxidase, produces more metabolites such as leukotrienes, and cause bronchial smooth muscle airway inflammation and smooth muscle contraction, which eventually lead to acute exacerbation or exacerbation of asthma [63].

25.3 Asthma Therapy

With the continuous research on the pathogenesis of asthma, the treatment of asthma has also made great progress and breakthrough. In the 1970s, bronchial asthma was thought to be caused by bronchial smooth muscle spasm. Therefore, short-acting B2 receptor agonist (SABA) became the leading treatment for asthma at that time. Although it could improve the symptoms of asthma patients in a short period of time, the mortality rate was rising on the other hand [64]. After the 1980s, in-depth studies found that bronchial epithelial shedding, submucosal eosinophils (EOS), and T and B lymphocytes were destroyed in asthmatic patients. The chronic inflammation theory of bronchial asthma gradually became popular and it was found that inhaled corticosteroids (ICS) had a wide range of anti-airway inflammation effects [65]. In the 1990s, it was reported that the airway of asthma patients showed thickening of the basement membrane, deposition of the parenchyma of the lower pancreas, and smooth tissue changes of the smooth muscle cells. Asthma was then considered to be an airway heavy plastic disease [66]. Numerous studies have confirmed that ICS is by far the most effective drug for controlling airway inflammation, regulating target cell transcription, inhibiting the activation and release of various inflammatory cells, reducing the leakage of microvasculature, and increasing the sensitivity of beta receptor, and thus prevent airway remodeling. ICS has gradually gained recognition in the treatment of asthma, becoming the basis of asthma treatment [67]. With the accumulation and extensive publication of a large number of evidence-based medical trails for asthma treatment, the effects of many traditional drugs in the treatment of asthma has been re-recognized. The continuous development and emergence of new drugs for asthma prevention and treatment have also resulted in incremental improvement and breakthrough in the treatment of asthma. Asthma is currently cannot be completely cured. However, long-term standardized treatment can make asthma symptoms well controlled, or even not onset [68]. The goal of asthma treatment is to control symptoms for a long time, prevent future risks, and ensure that patients work and live like healthy people. Asthma should be comprehensively controlled from two aspects: drug treatment and exercise training regulation [69].

25.3.1 Traditional Medication Therapy

Traditional asthma drugs mainly include corticosteroids (ICS), leukotriene receptor antagonists (LTRA), β-2 adrenergic agonists (LABA) and theophylline [70]. In addition, glucocorticoid hormone is an effective anti-allergic inflammation drug [71]. Its mechanism of action mainly includes interfering with arachidonic acid metabolism; reducing the synthesis of leukotrienes and prostaglandins; inhibiting the chemotaxis and activation of eosinophils; inhibiting the synthesis of Th2 cytokines and IgE; reducing microvascular leakage; and synthesis of β2 receptors on cell membranes [72]. In most cases, patients should first be treated with a low dose of corticosteroids (ICS) or a leukotriene receptor antagonist (LTRA) before further increasing the ICS dose and using a beta-2 adrenergic agonist (LABA) [73]. Routes of drug administration include inhalation, oral, and intravenous administration [74]. By inhalation administration, the drug acts

directly on the respiratory tract, and the required dose is small. Most of the drugs that enter the blood through the respiratory tract are inactivated by the liver, and therefore systemic adverse reactions are small [75]. Inhalation aerosol represented by Pulmicort is one of the currently effective treatments for asthma. According to clinical observations, after asthma patients have basic control of symptoms in the acute phase, the dose of Pulmicort inhaled is 600–1000 μg, and can be reduced after 2–3 months [76]. For seasonal episodes of asthma, inhaled hormones can be started 1 month before the onset, until 1 month after the season, usually for 6 months [77]. There are several advantages of Pulmicin inhalation therapy as followed. Pulmicort is a drug composed of non-deuterated glucocorticoids, which has stronger local selection and lower side effects than its analog drugs. It can improve the lung function of patients and relieve symptoms. It can effectively control airway hyperresponsiveness, and long-term regular use plays a positive role in the prevention of asthma, and can replace oral hormones in critically ill patients, thereby relieving the inhibition of oral hormones on the human adrenal axis, and indirectly promoting functional recovery of adrenal cortex [78].

25.3.2 Exercise Therapy

In clinical medicine and rehabilitation medicine, medical and sports applications are very extensive, but they are used less for the treatment of respiratory diseases, especially bronchial asthma. Drugs are not ideal for the treatment of asthma, and are easy to relapse, so research of asthma therapy is of great significance [79]. Rasmussen et al, who studied 757 children in a 10 year research, concluded that the decline in physical fitness during childhood was significantly associated with the onset of asthma in adolescence [80]. Huovinen et al., in their 17-year study of 262 pairs of twins, found that among the twins, the one who participated in exercise conditioning reduced the risk of asthma [81]. Therefore, patients can participate in appropriate physical exercise according to their own conditions to benefit their health. However, excessive exercise should be avoided, and outdoor exercise should not be carried out in cold and humid climates [82]. For asthma patients, walking and swimming are good exercises. Studies have shown that for people who walk for a long time, their blood vessel capacity will expand [83], thereby enhancing blood circulation. More importantly, walking improves the body's breathing function, increases lung capacity, and promotes deep breathing [84], which is especially beneficial to elderly patients. Because the ribs of the elderly are calcified, the scope of the thoracic activity is small, and the vital capacity is significantly reduced, resulting in a decrease in the oxygen supply in the body [85]. Besides, fibrosis of the blood vessels in the lungs causes gas exchange disorders, which is very unfavorable for asthma [86]. However, if you insist on walking, you can improve your lung capacity [87]. Due to the improvement of capacity, exercises improve blood distribution in the lungs and respiratory function, which will greatly improve asthma symptoms [88]. Swimming is also a great exercise for asthma patients [89]. Swimming can make the muscles and internal organs of the whole body participate in rhythmic activities [90], enhance lung capacity, accelerate blood circulation, and promote the body's metabolism [91]. Because of the particularity of the movement of body in the water, that the mouth is extended to the surface of the water for a very short time when swimming [92], so it is required to be quick and powerful when inhaling, and the lung needs to accommodate as much air as possible [93]. On the other hand, since the density of water is larger than that of air, it is more difficult to breathe than other sports [94]. When swimming, the chest has to bear a certain pressure, which puts higher demands on the respiratory muscles [95]. In addition, since there is a sufficient amount of water, most asthma patients do not suffer asthma recurrence during exercise [96]. Therefore, people who swim for a long time not only benefit the heart, but also induce benign adaptive changes in the respiratory system [97]. The study found that the average person's lung capacity is about 3500 ml [98]. When the elasticity of the lungs is greatly

increased, the respiratory muscle strength is also increased [99]. People who often exercise swimming have the lung capacity that is 1000 ml larger than that of average people [100]. In addition, swimming can also deepen the breathing and improve the efficiency of breathing [101]. The number of people who swim frequently can be reduced to 8–12 times per minute, while that of average people is 12–16 times [102]. The advantage is that exercise can make the respiratory muscles have more rest time [103]. Because of the shallow breathing, the average person only has about 300 ml of breathing, and the athletes can reach 600 ml [104]. Finally, people who lack exercise often become obese, and obesity is also a potential cause of asthma [105]. The main reason is that obesity reduces the number of deeps [106], and the tracheal stenosis is caused by smooth muscle atresia, which reduces the expiratory flow from 25 to 75%, eventually leading to bronchoconstriction, increased wheezing and increased inflammatory factors [107]. JM Bogaard et al. evaluated the effects of physical exercise on children with asthma. Through participation in sports training for 47 children with clinically diagnosed asthma, it was found that participating in physical exercise not only enhanced physical fitness but also improved their ability to cope with asthma [108].

25.4 Discussion

Because exercise has the potential to induce asthma, safety is of great concern for asthma patients to participate in physical exercise [109]. A large number of studies have shown that designing the appropriate time for exercise, training in non-acute asthma attacks, and adequate preparation activities before exercise are helpful to avoid asthma [110]. For patients who are prone to asthma during exercise, inhaling ventolin before each exercise and taking exercise after 5–10 min can reduce asthma [111]. Some foreign studies have also shown that as long as the medication is appropriate, it is safe for children with asthma to participate in exercise. Studies have shown that in swimming, basketball, badminton, table tennis, skipping, aerobics and jogging, the incidence of swimming-induced asthma is the smallest, only 1.27%, which may be due to the swimming environment, so it is less likely to induce asthma [112]. In summary, studies have shown that appropriate exercise can improve the symptoms of asthma in children, reduce the amount of emergency drugs, and improve lung function. At the same time, under proper management, is safe for children with asthma to participate in exercise. Our recommendation is that it is safe to exercise for no less than 20 min/day for 3 days a week, which is good for children's asthma control [30]. Exercise is conducive to children's skeletal development, training of motor skills, improving cardiovascular adaptability and fostering self-esteem [113]. For children with asthma, exercise is equally important to their normal growth and development [79]. Due to the possibility of exercise-induced asthma, the traditional view is that children with asthma should participate in exercise less. However, according to the global initiative for asthma (GINA) and childhood asthma prevention guidelines, asthma patients should still participate in sports moderately, and normal physical activity is considered the best way to control asthma [114]. In recent years, some local studies have also shown that as long as the management is appropriate, it is safe for asthma patients to participate in exercise [30]. There is evidence that aerobic training improves health and health-related quality of life [115], reduces exercise-induced bronchoconstriction and corticosteroid consumption, and reduces airway inflammation levels, and breathing exercises also reduce anxiety and depression, which greatly improves the symptoms of asthma [116]. Physical exercise focuses on improving physical ability, improving cognition and learning to cope with asthma. When exercising outdoor, patients can warm up for 15 min in advance, and endurance and circulation training in the later stage, including 30 min for upper and lower limbs and using diaphragm breathing and mouth breathing to improve ventilation [117].

Asthma is a chronic airway inflammatory disease characterized by difficulty breathing and

repeated asthma [118]. Most patients can be controlled with medication, but if the asthma is in an uncontrolled state, or if the patient continuously stays in a high-risk environment, the patient may still develop acute asthma which will get worse and even become fatal [119]. The number of patients with asthma is large and is increasing year by year in China, whereas the overall control rate of asthma patients is not optimistic [120]. The economic burden is caused by repeated illnesses in many recurrent patients of asthma after reducing drugs application [121]. Therefore, simple drug treatment cannot control the spread of asthma [122]. Slow and healthy aerobic exercise such as swimming and walking are very beneficial for the control of asthma [123]. In the existing study, the cardiopulmonary function of patients with frequent exercise has been significantly improved [124]. In recent years, the standardized treatment of asthma has been widely promoted nationwide, which has significantly improved the control rate of asthma patients in China, but it is still lower than that of developed countries [125]. Sports prescriptions have been recommended as an important part of asthma management [126], but at present, research on exercise treatment of asthma is still very scarce in China. Therefore, finding sports prescriptions suitable for Chinese asthma patients is an important future task for researchers and medical workers.

Competing Financial Interests The authors declare no competing financial interests.

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Exercise and Cystic Fibrosis

26

Shengguang Ding and Chongjun Zhong

Abstract

Cystic fibrosis (CF) is an autosomal recessive, inherited congenital disease caused by the mutation of the family autosomal CF gene, with cumulative exocrine secretion characterized by inflammation, tracheal remodeling, and mucus accumulation. With the development of modern medical technology, CF patients are living longer lives and receiving more and more treatments, including traditional drugs, physical therapy, and gene therapy. Exercise is widely used to prevent and treat metabolic diseases such as cardiovascular diseases, obesity, diabetes, and metabolic syndrome. Regular exercise is beneficial to aerobic capacity and lung health. Exercise therapy has been of great interest since people realized that CF can be affected by exercise. Exercise alone can be used as an ACT (airway clearance technique), which promotes the removal of mucosal cilia. Exercise therapy is more easily accepted by any society, which helps to normalize the lives of CF patients, rather than placing a psychological burden on them. In this chapter, we will review the latest research progress about exercise in CF.

Keywords

Cystic fibrosis · Exercise · Physical therapy · Research progress

26.1 Introduction

Cystic fibrosis (CF) is an autosomal recessive, inherited congenital disease caused by the mutation of the family autosomal CF gene, with cumulative exocrine secretion. Half of the patient's siblings have recessive genes, and the probability of getting sick is one-fourth [1, 2]. It has been suggested that CF was proposed be distinguish from celiac disease since medical workers found that patients had lung lesions and sweat electrolyte abnormalities [3–5]. CF mainly occurs in white people in some European countries in, and few cases have been found in Asian countries [6, 7]. Studies have shown that the main reasons for the thickening of secretions in CF patients may be the defect of chlorine channel regulation in upper dermal cells [8, 9], which will hinder water and electrolytic transport across the mucous membrane and increase the content of acid glycoprotein in the secretion of mucous glands, which, in turn, change the characteristics of mucous rheology [10, 11]. CF is a kind of "polytropic" disease, which means that many different and unrelated clinical manifestations are controlled by the same gene [12–14]. CF is an autoimmune disease affecting multiple systems.

S. Ding · C. Zhong (✉)
Department of Thoracic and Cardiovascular Surgery, The Second Affiliated Hospital of Nantong University, Nantong, China

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_26

Riordan et al. have shown that some of the autoimmune diseases are, indeed, related to corresponding gene mutations, for example, Delta F508 is the most common mutation caused by CF [15]. Up to now, about 2000 CFTR mutations have been reported. It is worth noting that the severity of CF is affected by factors other than CFTR mutations, such as modified genes, environment and lifestyle, so individuals with the same CFTR mutation may respond differently to the same treatment [16, 17]. However, the molecular alterations in DNA sequences are not equivalent to the surface reactivity or function change of the proteins [18, 19]. In some CF diseases, no association has been established between the genotype and the phenotype, so it is impossible to generalize the problem [20, 21].

One of the most important clinical manifestations of CF patients is the adverse effect on respiration system, which is also the major cause of death in CF patients [22, 23]. Inflammation, tracheal remodeling, and mucus accumulation are the three main features of CF patients, and the breakdown of the invasive segregation is a common feature of CF patients affecting epithelial organelles [24–26]. The reduction of HCO3– secretion in the lungs of patients with CF leads to acidification of the surface layer of the respiratory tract, leading to damage, inflammation, excessive secretion and adhesion of mucus, and weakening of the cilia of the attenuated mucosa [27–30]. Normal CFTR protein is needed to drive the neutralization of neutral HCO3– by anion exchange, but in CF patients only a small part is transported to the apical end by CFTR, and the secretion of HCO3– in the small intestine tissue of CF patients is significantly reduced [31–35]. HCO3– ensures proper folding and expansion of the mucin, which is necessary to maintain its normal fluidity, so as to avoid sticking to the surface of the mucous membrane [36–38]. Increased viscosity in intestinal mucus and pancreatic enzyme deficiency affect protein digestion [39, 40]. Therefore, about 10% of CF newborns suffer from meconium obstruction, which may lead to meconium ileus, rectal prolapse, and distal intestinal obstructive syndrome [38, 41–43]. The intestinal absorption of lipids is essentially caused by the lack of exocrine pancreatic function [44, 45]. However, defects in the formation of chylomicron, the main transport vehicle for dietary fat, are usually associated with abnormal absorption [46, 47].

Exercise is widely used to prevent and treat metabolic diseases such as cardiovascular diseases, obesity, diabetes, and metabolic syndrome [48]. Pedersen, Currie, and Edgeworth found that lifestyle changes and metformin treatment reduced the incidence of diabetes in high-risk groups [49–51]; and lifestyle interventions were suggested more effective than metformin [52, 53]. Although exercise has been shown to be more effective than drug therapy in some cases, the mechanism is unclear [38, 54–56]. The benefits of exercise for most adults far outweigh the risks [38, 57–59]. Regular exercise programs beyond daily life activities can improve cardiorespiratory function, flexibility, and neuromotor performance; therefore, exercise training is essential for most adults to maintain physical health [38, 60, 61]. There are many reports that exercise effect on the treatment of diseases [49, 62]. Some scholars pointed out that aerobic exercise compared to drug intervention has better effect in treating depression [63]. The study reported that exercise seemed to improve symptoms of depression in patients with depression; but in the experiment, it found that the mechanics and moderate intensity of exercise did not have good treatment effect [64–66]. So specific exercise treatments for certain diseases have not yet been well defined [67, 68]. The ACSM recommends that most adults should have moderate-intensity exercise of cardiopulmonary training for ≥30 min/day on ≥5 days/week (≥150 min/week), and vigorous-intensity cardiorespiratory exercise training for ≥20 min/day on ≥3 days/week (≥75 min/week); or a combination of moderate- and vigorous-intensity exercise to achieve a total energy expenditure of ≥500–1000 MET min/week. On 2–3 days/week, adults should also perform resistance exercises for each of the major muscle groups, and neuromotor exercise involving balance, agility, and coordination on 2–3 days/week [60, 69, 70]. There have also been many studies about the effect of exercise inten-

sity on the improvement of diseases [71–73]. Some researchers have confirmed that high intensity exercise is not related to the hippocampal volume of the elderly, while low intensity daily walking activity is related to the hippocampal volume of the elderly [74]. They also suggested that these findings suggest that physical activity has more cognitive benefits for women [75–77].

26.2 The Treatment of Cystic Fibrosis

With the development of modern medical technology, CF patients are living longer lives and receiving more and more treatments, including traditional drugs, physical therapy, and gene therapy [78, 79]. Different treatments can be used according to the severity of the disease [80, 81]. Conservative treatments of CF include airway clearance, airway surface liquid and mucus alteration treatments, antimicrobials, pulmonary exacerbations, anti-inflammatories, and CFTR modulators [82–84]. The CFTR modulator is a current hot spot of research that involves precision medicine or personalized therapy combining prevention and treatment [85–87]. The focus of CF therapy is shifting from symptomatic treatment to the treatment with pharmacologic restoration of CFTR-mediated chloride transport [88, 89]. Evidence of the beneficial effects of regular exercise on lung health and aerobic capacity has been accumulating over the past few years [90–92]. Although most data are obtained from small laboratory studies or clinical trials, the observed results are encouraging and make a good reason to implement exercise in the care of CF patients [93, 94].

26.3 Exercise Therapy

Back in 1986, it was found that forced breathing not only achieved the purpose of physical exercise but also improved the treatment outcome of patients with CF [95–97]. Therefore, researchers considered that exercise can, indeed, treat CF, which can achieve the effects of pathological therapy [53]. Although, there was no explanation for the mechanism of the exercise treatment back then. In 1992, it was proposed that the therapeutic effect of exercise on CF was associated with arterial oxygen desaturation during the late stage of CF with severe pulmonary disorder [98–100]. Researchers observed 22 patients with CF who had poor lung function [101], graded exercise stress tests, and found that inhaling oxygen during aerobic exercise increased exercise endurance and aerobic capacity [102–104]. Exercise therapy has been of great interest since people realized that CF can be affected by exercise [105, 106]. Now sports therapy has been incorporated into the physical therapy practices in Australia and New Zealand, which has a good guiding significance for future CF management [61, 107, 108]. It has been reported that the muscular system of CF patients and healthy children have the same endurance for high-intensity exercise, but the lung function is different, including the respiratory reserve index and the oxygen saturation and exercise ability of CF patients [109–111]. CF patients have lower exercise ability, higher respiratory reserve index, and higher oxygen saturation [104, 112–114]. But in the past 5 years, there has been considerable interest in the implementation of the method in patient clinical evaluation [62].

26.4 Clinical Therapy

The benefits of exercise therapy have been well-documented [61, 115]. In one study, the authors searched the data of CF disease research centers in Europe and North America, and found out that patients with poor lung function, poor nutritional status, and poor cloud capacity were particularly benefited from exercise testing, and the exercise prognosis of patients in the early stage became very important [89, 116, 117]. Supporters believe that exercise alone can be used as an ACT (airway clearance technique), and the evidence supporting this point is two systematic reviews that evaluate and summarize the effect of exercise on CF patients [118]. In addition to PD&P, FVC, and FEV1, exercise can improve physical fitness, self-confidence, and quality of life. In another

review, the authors suggested that exercise can promote the removal of mucosal cilia [119–122]. Mucosal cilia's viscosity decreased significantly when the patients were doing running exercises and concussion exercises [116, 123]. Exercise therapy is more easily accepted by any society, which helps to normalize the lives of CF patients, rather than placing a psychological burden on them [111, 124, 125].

26.5 Clinical Applications

Although there is a large amount of evidence supporting exercise therapy of CF, there are many problems in its clinical practice. Some scholars systematically evaluated the literature related to CF exercise therapy practice [126, 127]. According to the advice of the national health and medical research council, quality of sports management for clinical practice need to be improved [128]. Current researches mainly contain two aspects: a larger number of clinical investigation and limited data of movement experiments, because the movement is restricted by a variety of conditions, including the type of movement, the frequency, intensity, gender, age, and disease progression [129].

Multiple randomized parallel trials were designed in CF patients to compare physical activity vs. non-physical activity, short-term vs. long-term, adult vs. child, male vs. female, aerobic vs. anaerobic [130, 131]. The results showed that after short-term experimental exercise training, the patient's exercise endurance was significantly improved, but long-term training had no therapeutic effect [132, 133]. For adults with CF, a higher level of physical activity is associated with a lower level of general and physical fatigue when controlling for lung function and level of depression [134–136]. Physical activity may be used as a means of mitigating the levels of general and physical fatigue in people with CF [137, 138]. The Radtke paper is a remarkable collaborative effort [139, 140]. It raised important points that confirmed well-described relationships between nutritional and pulmonary status and exercise tolerance and challenged notions about CFTR classes and their effects [141–143]. David Orenstein and colleagues also confirmed the relationship between CFTR genotype and exercise tolerance [144, 145]. The results of some scholars have confirmed that the height and gender of CF adult patients affect their exercise health [146, 147]. Duration of exercise therapy and best training components (such as type, frequency, intensity, and duration) for the treatment of CF need to be determined through further researches in the future [148, 149]. National Center for Advancing Translational Sciences (NCATS) funded a project—Supramax exercise, in which volunteers were recruited to simulate the treatment of CF through movement and the obtained data was analyzed with modern methods [150–152]. However, due to the patients and the difference between data, the results were not ideal, so the clinical CF researches are still insufficient and further development is needed [153].

26.6 Perspective

In recent studies, many scholars used the Internet to analyze data and obtain motion-related parameters based on the massive data, for example, cardiovascular test values, lung function, and muscle function [148, 154, 155]. They have used swimming, tai chi and jogging as the best exercise models, and the results were all effective [156, 157]. Most participants were enthusiastic about the reports [103, 158]. Exercise therapy is essentially a form of physical therapy [159]. There is growing interest in nonmedical treatments for CF, and researchers may hope to further investigate the effects of this inexpensive treatment on CF in the future [160–162]. It is hoped that, in the future, sports medicine and precision medicine can be combined to improve the health condition of patients with CF [163, 164].

Competing Financial Interests The authors declare no competing financial interests.

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Part VIII

Exercise and Immunity

Exercise Regulates the Immune System

27

Jing Wang, Shuqin Liu, Guoping Li, and Junjie Xiao

Abstract

The profound effect of exercise on the normal functioning of the immune system has been well-known. Exercise and immune regulation are interrelated and affect each other. Exercise changes immune regulation by affecting leucocytes, red blood cells, and cytokines, etc. Regular exercise could reduce the risk of chronic metabolic and cardiorespiratory diseases, partially by the anti-inflammatory effects of exercise. However, these effects are also likely to be responsible for the suppressed immunity that make our bodies more susceptible to infections. Here we summarize the known mechanisms by which exercise—both acute and chronic—exerts its immune regulation effects.

Keywords

Acute exercise · Chronic exercise · Innate immune system · Adaptive immune system

J. Wang · S. Liu · J. Xiao (✉)
Cardiac Regeneration and Ageing Lab, Institute of Cardiovascular Sciences, School of Life Science, Shanghai University, Shanghai, China
e-mail: junjiexiao@shu.edu.cn

G. Li
Cardiovascular Division of the Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

27.1 Background

A complex network of cells and molecules construct the immune system, which function to protect our bodies from invading microorganisms, facilitate wound healing, and prevent disease. The immune system contains innate (nonspecific, nature) and adaptive (specific, repetitive) immunity, and both immune systems work synergistically in the overall immune response. In the immune response, adaptive immune cells function to release messenger molecules and cytokines that regulate immune system especially innate immune cell function, while cells from innate immune system help facilitate specific immune responses through antigen presentation [1, 2]. The immune system not only protects our bodies against infection but also influences other physiological systems and their processes, including metabolism, sleep/fatigue, tissue repair, mental health, and thermoregulation [3–5]. Based on the recognition that stress responses mediated through the endocrine and nervous systems play a key role in determining exercise-induced immune changes and that the immune system mediates many exercise effects, the exercise immunology has developed into its own discipline during the past four decades [6].

Compared with many branches of the exercise sciences, exercise immunology has quite a short history. The modern era of careful epidemiological investigations and precise laboratory studies

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_27

began in the mid-1980s. The early work of David Nieman piqued the interest in the effect of exercise on the immune system, by reporting that people with a more serious commitment to regular exercise may experience less infectious episodes such as upper respiratory tract infections (URTI) than their sedentary peers because of both direct and indirect effects on immunosurveillance; conversely, those engaged in stressful race experience appeared to be at a greater risk of infection than those who remained sedentary [7–9]. Thus, the link between exercise and the immune system in people who exercise has become a prominent focus area in the sports science and medicine communities since the formation of the International Society of Exercise and Immunology (ISEI) in 1989 [10, 11]. It is generally recognized that regular moderate-intensity exercise is beneficial for our bodies, while prolonged periods of intensive exercise training can depress immunity [12]. The immune responses to exercise are organized, and specific immune cells are redistributed for defined functional purposes. Most studies about the effects of exercise on the immune system are focused on the impact of the chronic effects of exercise training as well as the acute bouts of exercise. Both acute and chronic exercise have shown significant response in the area of leukocyte redistribution, activity, trafficking, and function [11, 13]. The intensity, duration, and volume of exercise have been reported to influence the redistribution of immune cells into the circulation associated with exercise [14–17]. In most of the exercise immunology studies, which type of exercise training can improve immune function in athletes, the elderly, and diseased patients is of great concern. In this chapter, we will describe the effects of chronic and acute exercise on immune responses and some strategies for restoring immune function after exercise.

27.2 The Effects of Exercise on Innate Immune Cells

As one of the two main immunity strategies found in vertebrates, the innate immune system is also known as the nonspecific immune system or in-born immune system, which is a semi-specific and widely distributed form of immunity [18]. The innate immunity includes both cells and soluble factors, which represents the first line of defense against pathogens. Major cells of this immune system include neutrophils, macrophages, dendritic cells (DCs), and natural killer (NK) cells. Soluble factors of the innate immune system include complement proteins and antimicrobial peptides [19]. Beside these innate immune cells and factors, many host cells can also initiate responses to a pathogenic infection. Here we will focus on exercise and the innate immune cells and the inflammatory cytokines which constitute the products of these immune cells.

27.2.1 Exercise and Neutrophils

Neutrophils, as the first-line defenders against bacterial infection in innate immunity, has been a popular cell type to study in the field of exercise immunology. A single bout of exercise has a profound effect on the total number and composition of circulating neutrophils [11]. Following a bout of high-dose resistance exercise, the neutrophils may remain elevated and peak up threefold post exercise [20–23], whereas prolonged endurance exercise (0.5–3 h) may cause neutrophil count to increase up to fivefold [24]. Although the increased number of not only neutrophils but also other immune cells is often indicative of infection and inflammation, exercise-induced immune cell counts typically return to pre-exercise levels within 6–24 h after exercise cessation [25].

Regular exercise training studies in leukocytes reported that leukocyte count in blood circulation does not change, including that of neutrophils [26]. In endurance aerobic exercise training studies, neutrophil counts significantly decreased after exercise therapy in those with chronic inflammatory conditions. This count was correlated with percent changes in insulin sensitivity index, body mass index, maximal oxygen uptake (VO2max), and fasting triglyceride analysis [27]. Whether this effect is deleterious or beneficial is dependent upon the context. Of note, in a resistance exercise study, it was found that the change in the number of circulation neutrophils can occur more rapidly following a bout of higher-volume/lower-intensity (5 × 10 reps, 80%-1 RM) vs. lower-volume/higher intensity (15 × 1 reps, 100%-1 RM) resistance exercise [28]. However, in another high-dose resistance study, there were no detected changes in neutrophil count [29]. It is not clear till now to determine clearly why different exercise temporal profiles vary for neutrophils in the literature.

The change in the number of neutrophils in blood was rapid and profoundly raised the first time after acute exercise, followed by a second, delayed increase a few hours later, which was associated with both the duration and intensity of the exercise [16, 30]. These immediate and delayed neutrophilic leukocytoses induced by exercise are mediated respectively by catecholamine and cortisol [31]. The ability to adhere to the endothelium is the initial step of neutrophil migration to sites of infection or injury. However, acute intensity exercise was reported to enhance neutrophil chemotaxis and phagocytosis but not their ability to adhere to the endothelium [32, 33]. The acute bout of exercise could reduce the oxidative burst and degranulation of neutrophils in response to bacterial stimulation that can last for long times. Also, this exercise could increase the unstimulated neutrophil phagocytosis, degranulation, and oxidative burst activity [16, 30, 34]. All these results indicated that acute exercise might reduce neutrophils' ability to respond to exogenous stimulation but mobilize highly functional neutrophils into the circulation blood and increase spontaneous neutrophil degranulation [35]. Although there are more studies of neutrophils in acute and chronic exercise training, little is known about the influence of exercise training on neutrophil function, which needs further study.

27.2.2 Exercise and Monocytes/Macrophage

Monocytes are the largest type of leukocytes that circulate in the blood and then migrate into tissues, where they mature into macrophages and myeloid lineage dendritic cells. These maturations are essential in tissue regeneration, recovery, and repair through processes including promotion of minisatellite cell stimulation and phagocytosis [36]. Classical ($CD14^{hi}CD16^{-}$) and nonclassical ($CD14^{low}CD16^{+}$ or $CD14^{hi}CD16^{+}$) are two main populations of monocytes. The inflammatory nonclassical ($CD14^{low}CD16^{+}$) monocytes express 2.5 times as much cell surface TLR4 as the other classical monocytes, which is driven by TNF-α [37]. Regular exercise appears to reduce the number of inflammatory monocytes ($CD14^{low}CD16^{+}$) in blood at the resting state. In the studies of cross-sectional and longitudinal exercise training, people with physically training exhibit a lower percentage of inflammatory monocytes, lower surface TLR4 expression, and reduced circulation monocyte inflammatory responses to lipopolysaccharide (LPS) [38–43]. The anti-inflammatory effect of exercise on these monocytes in tissue is still unclear. But in the mouse model studies, induced inflammatory responses of peritoneal macrophages were induced by exercise training, indicating a possible different effect of exercise on circular blood monocytes and tissue macrophages [44–46]. In obese mice studies, regular exercise training reduced systemic inflammation in high fat diet-fed mice [47, 48]. The macrophage infiltration into other sites of chronic inflammation has also been reported to be reduced by regular exercise training [49]. All these animal studies showed more evidence to demonstrate the anti-inflammatory effect of regular exercise.

After a single, acute bout of intense exercise, there was a transient increase in the number of inflammatory monocytes, which then returned to the baseline number during recovery [50]. This transient (~2 h) increase in monocytes most likely represents a migration of monocytes from the margins to the circulating pool [51]. In response to acute exercise, the preferential mobilization of $CD14^+CD16^+$ monocytes exhibited an inflammatory phenotype relative to $CD14^+CD16^-$ monocytes [52, 53]. Then the percentage of these $CD14^+CD16^+$ monocytes reduced in recovery, practically due to tissue recruitment or remarginalization [50]. These cells had a more inflammatory function to entry into tissues and were knocked off the endothelium in response to exercise. The cytokine production of monocytes was also influenced after acute exercise. Although spontaneous cytokine levels of $CD14^+$ monocytes did not change so much, the interleukin-6 (IL-6), IL1-α, and tumor necrosis factor-α (TNF-α) were significantly reduced post acute exercise, perhaps due to the reduced expression of LTR on the surface of monocytes [54–57]. In resistance exercise studies, an acute bout of resistance exercise also induced an acute increase in the number of circulation monocytes. The monocyte values returned to baseline between 15 and 30 min after high-dose resistance exercise or peaked at 120 min after the exercise cessation, due to different exercise doses [21, 22, 28].

Macrophages can be divided into two separate states: M1 and M2 macrophages. M1 macrophages always produce IL-6, nitric oxide, and TNF, which is an inflammatory state, whereas M2 macrophages produce anti-inflammatory cytokines and arginase [58]. Because there are little macrophages in circulation blood and most of them are matured in tissue, the study of acute exercise and macrophages in human are limited. In animal studies, prolonged exercise could reduce the antigen presentation ability of macrophages and the surface MHC II expression [59–61]. Acute exercise was reported to have potent stimulatory effects on M1 and M2 macrophages phagocytosis, nitrogen metabolism, chemotaxis, antitumor activity, and reactive oxygen [51, 62, 63].

27.2.3 Exercise and Dendric Cells

In human exercise studies, a single bout of dynamic exercise by healthy adults enhanced the generation of monocyte-derived DCs, but the functional consequences of this observation remained poorly understood [64]. The circulating number of DCs was detected to be increased after exercise, and this mobilization of DCs may be less prone to drive inflammatory processes [65, 66]. In animal models, the mixed leukocyte reaction, surface MHC II expression, and IL-12 production were significantly increased in DCs from regular exercise training; however, the costimulatory molecule of these DCs such as CD80 and CD86 showed no difference after training [67, 68]. During aerobic exercise, there is a preferential mobilization of plasmacytoid DCs. Due to the functional repertoire of plasmacytoid DCs, which includes production of interferons against viral and bacterial pathogens, exercise may improve immune-surveillance through preferentially mobilizing these DC effector cells [69]. However, there is very little information on the effects of exercise on DCs, which needs more investigation.

27.2.4 Exercise and Natural Killer Cells

Since NK cells are easy to study and exhibit a large magnitude change in response to exercise, they have received significant attention in the exercise immunology literature [11]. There existed much controversy on the effects of exercise training on NK cells, despite the fact that many results demonstrated the effects of exercise on NK cell function and number. Like other circulation leukocytes, through increased catecholamine-induced downregulation of adhesion molecule expression and shear stress, NK cells were immediately mobilized into the circulation in response to acute exercise [70, 71]. But after prolonged exercise, the number of NK cells in peripheral blood circulation was decreased, partially due to the tissue migration or remarginalization [71]. In a high-dose resistance exer-

cise (60–100%-1 RM at different volumes), the number of NK cells can be increased and sustained 15-min post exercise [21, 22]. Additionally, $CD16^+/CD56^+$ NK cell number was reported to reestablish to baseline values by 3-h post the prolonged aerobic exercise [20]. The varied count of $CD16^+/CD56^+$ NK cells was associated with the intensities and volumes of exercise. However, in contrast to other lymphocytes, there was no change in $CD16^+/CD56^+$ NK cell count under a low-dose bout of resistance exercise [72].

The key function of NK cells is innate cytotoxicity; NK cells are primarily known to characteristically secrete interferon gamma (IFN-γ) and induce cell death of infected cells. NK cell cytotoxicity was an well-known major functional measure of NK activity [73]. Early intervention or cross-sectional studies detected modest increases in NK cell cytotoxicity after moderate exercise training [74–76]. Beside this, A single bout of exercise could cause an increase in NK cell cytotoxicity, then quickly followed by a delayed suppression during exercise recovery [77]. The changes in the cytotoxic activity of NK cells was mostly driven by the changes in the proportion of NK cells among the peripheral blood mononuclear cell (PBMC) fraction. Indeed, both high- and moderate-intensity exercise were associated with significant shifts in circulating proportions of NK cells which significantly influence the interpretation of NK cell cytotoxicity [77]. However, the studies by other groups challenged this concept by using a wide range of tumor target cells (e.g., K562) in the detection of the effects of exercise on NK cell cytotoxicity [78]. They proposed that exercise evokes a preferential redeployment of NK cell subsets with a high differentiation phenotype and augments cytotoxicity against HLA-expressing target cells [78, 79]. Thus, till now it remains unclear if changes in NK cell function simply reflect exercise-induced alterations in the count of NK cells and NK cell subset distribution, or whether exercise affects the functional capability of NK cells at the individual cell level.

27.2.5 Exercise and Other Innate Immune Cells

The studies on effects of exercise on other innate immune cells such as basophils and eosinophils was collected and presented in Table 27.1.

27.3 The Effects of Exercise on Adaptive Immune Cells

Adaptive immunity is also known as acquired immunity or specific immunity, which is designed to protect our bodies by destroying invading microorganisms and preventing colonization [90]. The immunological memory that is created by adaptive immunity after an initial response to a specific pathogen leads to an future intensive response to subsequent encounters with that pathogen [19]. The main cells that are involved in the adaptive immunity are T and B lymphocytes, which are a subset of leukocyte. T cells play a large role in cell-mediated immune responses, whereas B cells are intimately involved in the humoral immune response [19]. It is widely accepted that proportional to exercise duration and intensity, there exists a lymphocytosis during and immediately after exercise. In this part, we will focus on exercise and the main adaptive immune cell function.

27.3.1 Exercise and B Cells

After immune activation, B cells undergo proliferation and differentiation and mature into memory and plasma cell. As the major cells involved in the creation of blood plasma and lymph antibodies, plasma cells produce IgA, IgD, IgE, IgM, and IgG immunoglobulin (Ig), each of which recognizes a unique antigen in the humoral immunity [91]. The effect of exercise on humoral Ig function has been evaluated through measurements of mucosal and serum Ig concentration. Brief or prolonged exercise studies reported that

Table 27.1 Effects of exercise on immune cells

Gender	Type	Exercise protocol	Rest periods	Key findings	References
Male	Lower body	Leg press	1 min/3 min	LE ↑	1996 [29]
Female	Upper and lower body	Leg press, leg extension, bench press, overhead press, leg curls, seated rows, biceps curls	3 min	LE ↑ at 90 min and 180 min post (untrained only)	2001 [80]
Female	Full body	Squat	2 min	$CD16^+/CD56^+$ NK and T cells ↑ by 0 min in all the group; B cells ↑ by 0 min post in high-strength group only (which performed more total work than low strength)	2001 [81]
Female	Full body	Squat	2 min	In control and training status, all tested LE ↑ by 0 min post	2003 [82]
Male	Circuit	Bench press, latissimus dorsi pull, leg press, shoulder press, leg extension, crunch, pull-up, biceps curls, leg extension, triceps exercise	1 min	All tested LE ↑ by 0 min post control and training status; NK ($CD16^+/CD56^+$) cells ↑ approx. 250% then ↓ blow BL by 30 min post; T ($CD4^+$) cells ↑ approx. 20% then ↓ blow BL by 30 min post; T ($CD8^+$) cells ↑ then ↓ blow BL by 30 min post; NE and MO remained ↑ and peaked at 2 h post (final time-point)	2003 [22]
Male	Circuit	Shoulder press, seated rows, lag press, leg extensions, leg curls, latissimus dorsi pull-downs, abdominal crunches, chest press	1:2 (work:rest) ratio	MO, NE, LY, NK cells, $CD8^+$ and $CD4^+$ T cells ↑ by 0 min post, then ↓; $CD8^+$ T cells ↓ to baseline by 15 min post; MO, LY, NK, and $CD8^+$ T cells except NE ↓ to baseline by 30 min post	2004 [21]
Male	Upper and lower body	Bench press and leg press, hamstring curl, knee station, biceps curls	Not provided	LY and LE (NE and MO accounted for the majority) ↑ post and remained ↑ at 3 h post; $CD8^+$ T and $CD16^+/CD56^+$ NK cells ↑ by 0 min post and ↓ to baseline by 3 h post; B cells ↑ by 3 h post	2003 [20]
Male	Circuit	Bench press, leg press, leg extension, shoulder press, pull-up, biceps curls, triceps exercise, crunch, latissimus dorsi pull, vertical row	1 min	NE ↑ by 0 min post (untrained or resistance trained)	2004 [83]
Male	Lower body	Leg press	1 min/3 min	LE, LY, MO, NE ↑ by 0 min post; The change of MO and LY was greatest in 1 min rest group	2005 [84]
Male	Upper limb eccentric	Eccentric contractions of the elbow flexors	1 min/3 min; 2 s rest between reps	LE and NE ↑ by 3 h post; MO and LY no change	2006 [85]
Female	Circuit	Arm curl, dead lift, triceps extension, back extension, bench press, seated row, squat, overhead press, leg curl	1 min between rounds	LE, LY, and NE ↑ by 0 min post in all exercise groups	2010 [86]

(continued)

Table 27.1 (continued)

Gender	Type	Exercise protocol	Rest periods	Key findings	References
Male	Circuit	Leg curl, biceps curls, leg press, shoulder press, latissimus pulldowns, bench press, seated row	2 min rest between exercise and 3 min rest between rounds	LE, LY, and NE ↑ by 3 h post and returned to baseline by 24 h post	2012 [23]
Male	Circuit	Biceps with barbell, triceps with barbell, trunk extension, sit-up, squat, knee flexion, standing shoulder flexion, dead lift, sitting paddle lift with device, supine bench press	1 min rest between rounds	No change was detected	2012 [87]
Male	Lower body	Leg press	3 min/2 min	LE remained ↑ by 0 min post, then ↓ to baseline; NE, LY ↑ by 0 min post then ↓ to baseline by 30 min post	2014 [28]
Male	Upper limb: isometric	Thumb exertion: lateral pinch	1 min	LE and LY ↑ by 0 min post; MO ↑ by 60 min post (resistance trained/untrained); T and B cells ↑ by 20 min post, then ↓ to baseline by 60 min post	2015 [88, 89]

Abbreviations: *BA* basophils, *EO* eosinophils, *LE* total leukocytes, *MO* monocytes, *NE* neutrophils, *LY* total lymphocytes, *post* post exercise

serum Ig concentration appears to remain either slightly increased, or unchanged [92–94]. The mucosal immune system protects the mucosal surfaces of the nasal passages, intestines, and the respiratory tract. The secretory IgA (SIgA) that is produced by plasma cells is the major effector function of the mucosal immune system providing the pathogens [95, 96]. The effect of exercise on the changes of the secretion of SIgA in saliva has been widely studied [97]. Training status, intensity of the exercise bout, and duration of the exercise could influence the response of SIgA [11]. High levels of saliva SIgA was important to enhance basic immune capacity and was associated with low incidence of URTI in athletes. Substantial transient falls in saliva SIgA could increase the risk of URTI [98, 99]. Although some early studies indicated falls in saliva SIgA concentration in endurance athletes or during intensive periods of training [99–102], the majority of studies reported that the saliva SIgA concentration in athletes was the same as non-athletes except when athletes are engaged in heavy training [103, 104]. This decreased saliva SIgA in athletes after high-intensity exercise is partly due to a withdrawal of the inhibitory effects of the parasympathetic nervous system [11]. Thus, acute bouts of moderate exercise showed little impact on plasma cell Ig expression, but prolonged heavy exercise and intensified training could evoke decreases in saliva SIgA secretion.

Except their Ig antibody secretion role in humoral and mucosal immunity, B cells were also engaged in initiating T cell-mediated immune responses and played a key role [105]. B cell number was mildly increased during and immediately after exercise and was proportional to exercise duration and intensity. But this enhanced number of B cells falling below pre-exercise levels during the early stages of recovery and returning to basal level within 24 h [25, 106]. Besides that, a consistent elevated circulation B cell number was detected either during or after high-dose resistance exercise (evident after 3 h rest, 60–100%-1 RM at different volumes) [20, 81, 82]. The elevated circulation B cell count was also detected even in low-dose resistance exercise [107]. Well, except the high- and low-dose exercise, bouts of different dose exercise could be admitted that induced an acute lymphocytosis

with occurs either during or immediately after exercise. Furthermore, higher exercise doses should be augmented to measure the effect of different types of exercise on the circulation B cell count, and further research is needed to clarify the effects of exercise training on immunological function of B cells.

27.3.2 Exercise and T Cells

After antigen challenge, T cells proliferate and differentiate into multiple effector T cell clones. These expanded T cells can be divided into several subsets of cells, each with a distinct function [108]. Some of them are able to recognize the antigen that causes the initial response and regulated the immunological events in both humoral and cell-mediated immunity. The cell surface cluster of differentiation (CD) markers and the cytokines profiles that T cell produced can be used to classify different T cell phenotypes. $CD4^+$ helper/inducer T cells can be divided into type 1 (Th2), type 2 (Th2), Th17, and T follicular helper cells [109]. Th1 cells function to eliminate intracellular pathogens and are associated with organ-specific autoimmunity. Conversely, Th2 cells mount responses to extracellular parasites and indirectly regulate inflammatory activity through secretion of cytokine IL-4, IL-5, IL-6, and IL-13 [110]. Through the secretion of the regulator cytokine IL-10, Th2 cells could also negatively regulate inflammation. The cytokines that are released from Th2 cells could activate B cells, leading B cells to proliferate and differentiate into memory and plasma cells [111]. Like $CD4^+$ T cells, $CD8^+$ T cells are classified into type 1 (Tc1) and type 2 (Tc2) cells according to their cytokine profiles. These $CD8^+$ T cells are also known as cytotoxic T cells, which are central to resistance against intracellular pathogens [112]. Different types of T cells in adaptive immunity play different roles; hence, differential analysis of T cell subtypes is necessary.

Several studies have uncovered a decreased T cells proliferation both during and after exercise [11]. The function of T cells appears to be sensitive to increases in training load in well-trained athletes undertaking a period of intensified training, together with a decreased circulating Th1 T cell counts, which suggested that a long period of intensified training exhibits decreases in T cell functionality. However, a lymphocytosis is observed during and immediately after exercise, with numbers of cells falling below pre-exercise levels during the early stages of recovery [113]. These variations of T cells number in different exercises might be proportional to exercise intensity and duration [55, 114]. In resistance exercise studies, the responses of $CD4^+$ T cells to resistance exercise were different based on the different study groups. It was reported that $CD4^+$ lymphocytosis existed immediately after high-dose resistance exercise [21, 22, 82], or increased during 0–60 min following very low-dose resistance exercise [89]. Then the counts of $CD4^+$ T cells returned to baseline within 30 min following the high-dose exertion [21], or remained elevated at 60 min succeeding a low-dose exertion [89]. In contrast to exercise induced T cell number, following a body resistance exercise protocol (60–70%-1 RM at different volumes), there was no detected change in $CD4^+$ T cell count (despite an increase in total lymphocytes) [20]. Actually, in the resting stage (more than 24 h resting after the last training session) of athletes, the circulating lymphocyte (include all type of T cells) and functions appeared to be broadly similar to those of non-athletes [115].

As in the case of $CD4^+$ T cells, a $CD8^+$ T cell lymphocytosis has been detected to exist immediately following high-dose resistance exercise (60–70%-1 RM), which reportedly returned to baseline levels by 15 min succeeding exercise or decreased below pre-exercise levels by 30 min of rest, and then returned to baseline values by 3 h post exercise [20, 21, 82]. During the very low-dose resistance exercise, the count of $CD8^+$ T cells increased from 0 to 60 min post exercise training and returned to baseline between 20 and 60 min post exercise [89]. Slight variances in exercise volume or differences in the timing of blood collections after exercise might be related to the number of non-consistent CD8+ T cells that were reported in different papers.

Till now, it has been accepted that exercise is somehow correlated with T cell function. However, it is debated whether T cell proliferation is truly impaired during or after exercise. Thus, further research is necessary to clarify the relationship of T cell count and function in different exercise training programs.

27.4 Perspective

During exercise, no matter acute or chronic, there exists a marked difference in the circulating levels of immune cells and other factors that have immunomodulatory effects by influencing leukocyte trafficking and functions. The effects of exercise on the normal functioning of the immune system have been widely agreed to be profound [116–118]. It is already known that the single exercise bouts only induce a transient immune response. However, these effects cumulated over time and formed the immunological adaptations to chronic exercise training. Based on exercise dose, prolonged periods of intensive exercise training could depress immunity [119, 120], while there was no doubt that regular exercise training may reduce the risk of disease such as the URTI due to its anti-inflammatory, thymic-activity reinvigorated, and boost-immunity effects. However, more rigorous standardization of studies is required to reveal reliable data which could assist in improving the safety of exercise and health status.

Data accumulated from preclinical experiments have demonstrated that exercise can directly regulate the immune system and has the potential to indirectly affect cancer, asthma, chronic disease, and cardiovascular disease through the regulation of immune response [121–126]. Essentially, this points to a new direction for exercise immunology studies, which may aim to exploit exercise training as one of the new compound therapy strategies. To this end, the molecular mechanisms of immune cell infiltration and functional regulation and inflammatory cytokines occurring during exercise need much broader and deeper investigations.

Acknowledgments This work was supported by the grants from National Natural Science Foundation of China (81722008, 91639101, and 81570362 to JJ Xiao), Innovation Program of Shanghai Municipal Education Commission (2017-01-07-00-09-E00042 to JJ Xiao), the grant from Science and Technology Commission of Shanghai Municipality (17010500100, 18410722200 to JJ Xiao), the development fund for Shanghai talents (to JJ Xiao), and the Sailing Program from Science and Technology Commission of Shanghai (19YF1415400 to J Wang).

Competing Financial Interests The authors declare no competing financial interests.

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Part IX

Exercise and HIV/AIDS

28 Effects of Exercise on the Immune Function, Quality of Life, and Mental Health in HIV/AIDS Individuals

Mostafa Dianatinasab, Simin Ghahri, Aria Dianatinasab, Sasan Amanat, and Mohammad Fararouei

Abstract

Physical exercise is a common type of planned physical activity in order to enhance or maintain a person's physical fitness. Physical exercise may act as an effective strategy to take control of certain conditions associated with HIV-1 infection. HIV infection and its related treatments not only affect the immune system but also cause several musculoskeletal disorders including pre-sarcopenia or sarcopenia, myalgia, and low bone mineral density. Moderate- to high-intensity aerobic exercise, progressive resistance exercise, or a combination of both is considered as a complementary part of medical care and treatment of HIV-infected individuals. In the present chapter, the results of recent investigations regarding the effects of physical activity on muscle strength and function, mental health, and immune system of HIV infected individuals will be discussed.

Keywords

Exercise · HIV · AIDS · Immune function · Quality of life · Mental health

M. Dianatinasab (✉)
Department of Epidemiology, Center for Health Related Social and Behavioral Sciences Research, Shahroud University of Medical Sciences, Shahroud, Iran
e-mail: dianatinasab@sums.ac.ir

S. Ghahri
Department of Sport Physiology, Shahrood University of Technology, Shahrood, Iran

A. Dianatinasab
Department of Biochemistry, Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran

S. Amanat
Department of Nutrition, School of Health, Larestan University of Medical Sciences, Larestan, Iran

M. Fararouei
Faculty of Public Health, Department of Epidemiology, Shiraz University of Medical Sciences, Shiraz, Iran
e-mail: fararouei@sums.ac.ir

28.1 Background

Since 1996, the year in which highly active antiretroviral therapy was introduced, the number of patients who died from AIDS and opportunistic infections has significantly decreased (by two-thirds). On the other hand, new health problems including lipids and glucose imbalance and body fat among the patients have gained more attention among physicians and health professionals [1]. In addition, a significant number of newborns who are infected with HIV perinatal infection reach older age causing adolescent HIV epidemics in many parts of the world. Adolescents with congenital HIV cope with several stressors such

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_28

as other chronic illnesses, ongoing medical treatments, hospitalization, pain, and social problems. In fact, the patients face a wide range of psychosocial problems that are highly stigmatized and may make adolescence a very difficult period for them [2]. Moreover, the HIV-related disabilities are associated with patient's impairment in daily activities and less exercise. Several scientific findings indicated that exercise training increases aerobic capacity, muscle strength, flexibility, and functional ability in patients with HIV or AIDS [3]. Therefore, as suggested by rehabilitation professionals, keeping up physical activities and regular exercise are key strategies in medical and social care of HIV/AIDS patients. Both symptomatic and asymptomatic HIV-infected patients can develop cardiopulmonary dysfunction characterized by a decrease in both oxygen uptake at submaximal and peak exercise levels and workload capacity. Statistics demonstrated that the most common cardiovascular diseases diagnosed among HIV/AIDS patients were coronary atherosclerosis, angina pectoris, and myocardial infarction. Moreover, HIV patients were more likely to suffer from chronic obstructive pulmonary disease. Patients with HIV-associated pulmonary hypertension had poor prognosis, among whom the vascular endothelial cells were chronically exposed to viral proteins which can be produced by HIV-infected cells in the lung. The loss of skeletal muscle mass and lean tissue mass, known as HIV-associated wasting, is a common disorder among HIV-infected individuals. About 20% of HIV patients with rapid disease progression could suffer from wasting, which is closely related to an increase in morbidity. Metabolic disorders such as dyslipidemia and abnormal glucose metabolism, appear frequently in HIV-infected patients leading to a significant imbalance in body composition and less quality of life [4]. Today, exercise is proven to have a significant role in diseases that are not primarily known as disorders of the locomotive apparatus [5]. Different types of physical exercises are considered as efficient non-pharmacological interventions for patients with chronic diseases [6]. For example, it has been shown that osteoporosis, deterioration of bone tissue, disruption of bone architecture, and compromised bone strength that predispose patients to an increased risk of fracture are common among HIV-infected patients. These conditions are likely to become an important cause of morbidity and mortality alongside of aging process of the HIV-infected people. For example, osteoporosis leads to a higher risk of osteoporosis-related fractures, which might be associated with increased risk for osteonecrosis of the hip and other bones. It has been shown that practicing 30 min of weight-bearing (jogging, dancing, walking) and muscle-strengthening exercises (i.e., weight training) for at least 3 days a week may increase bone density and prevent osteoporosis and its related fractures [7]. In addition, a large number of studies reported that regular aerobic and resistance exercises can promote cardiovascular performance in elderly people by increasing the volume of O_2 uptake, reducing blood pressure, improving glucose and lipid metabolism, and decreasing risks of cardiovascular diseases.

Exercise can also prevent osteoporosis and osteoarthritis, and improve neuropsychological health. Resistance exercise also showed beneficial in enhancing muscles strength and function in older HIV patients [4]. The American Psychiatric Association recognizes the diagnosis of a life-threatening illness as a potentially traumatic stressor that may lead to the development of posttraumatic stress disorder (PTSD) [8]. In that regard, it is a truly huge stressful experience to be diagnosed with HIV infection. Kamitani et al. (2017) suggested physical exercise among HIV infected patients as a good strategy to prevent AIDS related complications [9]. Similarly, Quigley et al. (2018) found that physical activity may play an important role in preserving or even improving cognitive performance of people living with HIV [10]. Jaggers (2018) concluded that people living with HIV/AIDS, regardless of disease status, can gain short-term health benefits from routine physical activity. Another study reported that after a moderate level of routine exercise for 5–6 weeks, a significant improvement was obtained in psychological and physiologic statuses of the participants [11]. In an interventional study, a better body image in

people living with HIV/AIDS was observed after taking part of a physical exercise program [12]. To define the factors affecting the willingness of patients in doing physical exercise, Mabweazara et al. (2018) evaluated the effects of social support and socioeconomic status of individuals with HIV on their levels of physical activity. In addition, some resources introduced socioeconomic barriers that prevent HIV people from doing physical exercises. It was also reported that social support plays important roles in promoting physical activity and counteracting the other barriers of physical activity in people with low socioeconomic status living with HIV/AIDS [13].

28.2 Immune Function and Exercise

Exercise is known to have a profound effect on the functioning of the immune system. It is generally believed that prolonged periods of intensive exercise training can depress function of the immune system, whereas, exercise with regular to moderate intensity is beneficial to the immune system. Regular moderate-intensity exercises are "immuno-enhancing" and have been used to effectively increase vaccine responses in immune-compromised patients. The observed improvements in the functioning of the immune system after regular exercise of moderate intensity may be explained by significant reduction in the levels of inflammatory factors, maintenance of thymic mass, alterations in the composition of "older" and "younger" immune cells, enhanced immune surveillance, and/or the amelioration of psychological stress. Indeed, exercise is a powerful behavioral intervention that has the potential to improve immune and health outcomes in the elderly, the obese, and patients living with chronic viral infections such as HIV [14]. However, when it turns to HIV positive patients, there are conflicting results regarding the effects of exercise on the immune function. Neto et al. (2015) demonstrated that the stability of immunological and virological measures during regular exercise can be seen as evidence for the safety of these types of interventions [6]. According to Kamitani et al. (2017), CD4 counts were better improved by interventions with interval aerobic or 41–50 min of exercise three times per week compared with other types and durations of exercises [9]. On the other hand, in a study on the impact of a 12-week aerobic and resistance exercise training program on mental health and CD4 counts among female HIV+ patients, Dianatinasab et al. (2018) found no significant change in CD4 cell counts after the intervention program. In contrary, according to a pre-post analysis study, although both intervention and control groups experienced a decline in CD4 count over time, patients who practiced a 12-week exercise experienced less decrease in CD4 count. High variation and small sample size were possible reasons that the rate of reduction in CD4 counts in the intervention group was not statistically significant [15]. In another study, a combined (resistance plus aerobic) exercise training program completed by ten HIV infected sedentary adults induced a significant increase in the number of TCD4+ cells as well as CD4+/CD8+ ratio reflecting an important benefit to the immune system of HIV+ participants. However, no effect of training on viral load of the participants was detected. These findings strongly suggest that exercise training programs improve the efficiency of immune defense system with no apparent risk to the patients [16]. Interestingly, no study has shown any exercise-induced reduction in immune cell count or function at any exercise intensity when looking specifically in HIV-infected patients. Jaggers and Hand (2016) suggested that aerobic and/or resistance exercise at any intensity neither helps nor hinders immune function or viral load for people living with HIV/AIDS at any stage of HIV infection [17]. However, it is believed that while moderate-intensity physical activities improve the immune function in people with HIV/AIDS, high-intensity exercise may have immunosuppressive effects in people living with HIV/AIDS [12].

28.2.1 Exercise and CD4/CD8

The effect of exercise on CD4 count is still under debate. This is because few studies suggested that exercise programs may increase CD4 count [17], whereas others found no significant association [15]. Kamitani et al. (2017) suggested that regular aerobic exercise, up to 50 min, three times per week, appears to positively affect CD4 counts among people living with HIV [9]. After summering several studies on effects of any type/intensity of exercise on CD4+ counts, Jaggers and Hand (2016) conducted that there is a potential benefit in maintaining CD4+ cell count when routine moderate-intensity aerobic exercise is done while HIV/AIDS patients were taking ART [17]. In a Nigerian study, 45–60 min, 3 times/week for 8 weeks of moderate intensity exercise resulted in an increase in CD4 cells versus conventional therapy involving ART only [18]. Ten sedentary adult participants with HIV exhibited a significant improvement in several important immunological indexes after completing a 20-week combined resistance–aerobic exercise training program. Although the participants' serum viral load remained unaltered throughout the period of the exercise program, the number of TCD4+ cells increased by 31% and a significant augmentation in CD4+/CD8+ ratio was observed. The improvement in the number of TCD4+ lymphocyte and CD4+/CD8+ ratio highlights the importance of combined exercise training program in the functioning of immune system among HIV positive participants [16]. Another study on people living with HIV/AIDS, who were receiving ART treatment, revealed a significant decrease in systolic blood pressure, diastolic blood pressure and increase in CD4 count and maximum O_2 volume uptake (VO_2 max) after aerobic exercise with moderate intensity (between 60 and 79% of heart rate reserve) quantified by jogging on a treadmill. Furthermore, the results indicated a significant positive correlation between change in VO_2 max and change in CD4 count. These findings suggest that moderate intensity aerobic exercise is an effective complementary therapy in lowering blood pressure and increasing CD4 cell count in people living with HIV/AIDS [19]. From a different point of view, Grace et al. (2015) noted that considering the stage of HIV/AIDS disease is critical not only for tracking and monitoring the HIV epidemic but also for the clinical management of the disease. Physical exercise therapists should therefore be aware of the stages and the varying needs of the HIV patients in order to prescribe the effective exercise. For the aerobic exercise for HIV-positive individuals, the researchers recommend 40–60% of exercise intensity of VO_2R (difference between VO_2max and resting VO_2) or heart rate reserve. Progressive resistive exercise intensity can be measured as percentage of 1RM (1 Repetition Maximum: maximum amount of weight that a person can lift for one repetition). Intensities of the exercises prescribed to HIV-infected individuals most often include progressive resistive exercise start at moderate intensity of 50–60% 1 RM, and then gradually to higher level of intensity (75–80% 1 RM) after 4–12 weeks of training. Although training at higher intensities of up to 85% 1 RM reported no adverse effects, a progressive resistive exercise at 60–80% of 1 RM for 2–3 sets of 8–10 repetitions are recommended. For HIV-infected individuals, 20 min of steady-state exercise has been suggested to gain positive results though, with a longer session of up to 1 h also showing positive results. In most observational studies, regular training that included alternate moderate-and high-intensity exercises were also associated with improved CD4 counts [20].

28.3 Exercise and Quality of Life in HIV Positive People

It has been shown that HIV declines muscle function and reduces physical activity, so maintaining muscle strength via adequate physical activity is of crucial importance for people living with HIV/AIDS [18]. People of all ages infected with HIV have abnormally lower level of cardiorespiratory fitness, a reduction in which sedentary lifestyle should have a significant effect [11]. Several experts declared that HIV-infected adults seem to experience aging faster at earlier age compared to

the general population. Despite adequate ART, the life expectancy of infected individuals is still lower than that of the general population. This means that HIV infected people can have declined health and physical function and experience higher prevalence of physical frailty at younger age compared to healthy individuals. Some of the functional impairments seen in HIV-infected individuals are similar to a physiological sense with those sometimes seen in 10–15 years older people who are uninfected. It is well known that even moderate physical activity can enhance physical function and quality of life among older adults. However, the majority of older adults do not exert physical activity enough to gain its benefits. Documented scientific findings suggest that physical frailty in HIV-infected patients is potentially reversible and it is believed that low physical activity is positively associated with depression [21]. This may suggest the positive effect of increasing physical activity on control of depression among patients. Moreover, most of the side effects attributable to HIV medication/treatment are associated with metabolic processes, which lead to the risk of metabolic syndromes, lipodystrophy, insulin resistance, hyperglycemia, and redistribution of body fat as well as diarrhea, nauseas, vomit, agitation, and insomnia. However, regarding thermos regulation hypothesis (the increase in body temperature facilitates the sleep induction), regular physical exercise, provides better sleeping. In addition, physical exercise improves energy conservation in order to get a positive energetic balance, preparing a normal sleeping cycle condition and thereby a well-being enhancement [22]. Additionally, as the life expectancy of HIV infected individuals increases, aging is going to become a factor affecting brain structure and its function. In addition, aging causes neurocognitive impairment, which influence the sense of well-being [23]. DuFour et al. (2013) have conducted a research that, based on self-reported activities (with increased heart rate in the last 72 h), the HIV adult participants were divided in to "exercise" and "no exercise" groups. The researchers conducted comprehensive standardized neurocognitive test battery that covers seven cognitive domains commonly affected by AIDS. The domains included, verbal fluency, working memory, speed of information processing, learning, recall, executive function, and motor function neurocognitive impairment. The results indicated that HIV infected adults in the exercise group had approximately half the chance to show neurocognitive impairment as compared to those in the no exercise group [24]. Resistance training, aerobic exercise, and concurrent training are proven to be incontestably associated with improvements in body composition, muscle strength, and cardiopulmonary fitness in adults living with HIV/AIDS. Short-term resistance exercise has shown to have physiologic benefits and has positive effects on body composition and musculoskeletal health. In addition, aerobic exercise and concurrent training increase aerobic capacity and have a positive effect on body composition, muscle strength, and quality of life. In addition to reduction in body weight, resistance exercise training improves outcomes related to body composition by increasing the lean body mass, mid-thigh cross-sectional muscle area, muscle strength, and bone mineral density. These parameters might have positive impacts on the individual's quality of life. Aerobic exercise training improves body composition by balancing body weight, total body fat and the waist-to-hip circumferences ratio (WHR). Aerobic exercise also increases aerobic capacity, measured as maximum/peak volume of O_2 uptake (VO_2max/VO_2peak) or time on treadmill. Similarly, concurrent training positively alters body composition by increasing lean body mass, muscle thigh volume, and mid-thigh cross-sectional muscle area. Additionally, this type of training seems to reduce thigh muscle adiposity, the percentage of body fat and WHR. Thereby, concurrent training provides significant improvement in all evaluated outcomes, making it as the best type of exercise in patients with disabilities and problems related to HIV infection/treatment [3]. It is reported that a 6-month supervised exercise program (90 min, 3 times per week) at a fitness club, caused better social relationships, better quality of life, better self-esteem, better body image and less emotional stress [18].

Kamitani et al. (2017) found that physical exercise is associated with improvements in physiological and psychological health. Moreover, researchers claimed that like aerobic exercise, progressive resistance exercise appears to reduce adiposity and increase body weight and muscle mass in HIV/AIDS patient living with wasting syndrome. Moreover, aerobic exercise with or without progressive resistance exercises appears to improve patients' anaerobic capacity, depression, and mood [9]. As a result, as a structured form of self-management strategy of physical activity, physical exercise can address different types of mental, physical, and social problems in people with HIV/AIDS.

The exercises also optimized lipid profile and glucose tolerance in HIV/AIDS patients. Progressive resistive exercise are shown to be especially beneficial in medically stable adults living with HIV. This kind of exercise can increase body weight, peripheral girth and interestingly can reverse muscular atrophy process. These effects can undoubtedly cause a better psychological status and better quality of life and lipid profile (by lowering triglycerides) [20]. These benefits also include positive effects on HIV infection and the treatment-related toxicities, (i.e., impaired glucose tolerance, fatigue, increased blood lipid profile, chronic inflammation, anxiety, depression, circulating cortisol). Obviously, the response and adaptation to exercise training vary depending on several factors including current fitness level, disease status and whether or not the patient is currently on an ART [17]. Safeek et al. (2018) reported that regular physical activity may improve the function of cardiorespiratory system and functional independence in people living with HIV/AIDS. Also, researchers have found an association between inactivity and poor physical function in older patients [25]. According to a notable number of observational studies, more physically active persons living with HIV/AIDS have significantly better sleep quality, total sleep time, efficiency of sleep, decreased number of awakenings and improvement of sleeping disorders (insomnia), disorders which significantly deteriorate the patient's health and consequently their quality of life [22]. In that regard, Neto et al. (2015) suggested that combined aerobic and resistance exercise should be considered as a component of care of HIV-infected individuals [6]. Physical activities in HIV patients are able to improve the quality of life by attenuating anxiety and depression [15].

Pain is another disturbing and common outcome of AIDS, such that severe pain would be experienced by 80–98% of those with advanced HIV. Expectedly, disturbances in physical, psychological, and social functioning have been found to be greater in patients experiencing pain compared to pain-free patients. Several studies demonstrated the adverse impact of pain on the patient's sense of well-being [26]. Training via increasing muscle strength and stability and the irritant that induces the pain would be reduced [5]. After undergoing a 12-week progressive resistance exercise trial involving HIV infected participants with moderate-to-severe neuropathy, a significant improvement was observed in the quality of life of the intervention group when compared to the control group. As a result, it was suggested that progressive resisted exercise have some positive effects on the health-related quality of life in subjects with HIV/AIDS-related distal symmetrical polyneuropathy [27]. Dudgeon et al. (2012) designed a 6-week moderate-intensity combined aerobic and resistance exercise for HIV+ men participants and observed a significant improvement in salivary cortisol levels, physical performance, and body composition. The researchers showed that the exercise caused transient increase in anabolic factors (Growth Hormone) and decreased catabolic factors (salivary cortisol). These changes led to a significant increase in lean tissue mass in the exercise group, with no changes in total body mass or fat mass. In addition, significant improvement was observed in muscle strength within the exercise group [28]. It is shown that moderate to high-intensity physical activities such as walking, cycling, swimming, stair climbing and rowing are the most beneficial types of exercise for HIV populations. To achieve the most benefits, a 6 weeks aerobic training at least 3 days per week for 20–40 min is recommended. Also, 5–10 min

of stretching major muscle groups are necessary before and after aerobic exercise. The appropriate heart rate during exercise is between 70 and 80% of the estimated maximum heart rate. Patients are suggested to begin at a lower intensity, and gradually increase the intensity of the exercise to a higher level. For muscle strength training, patients are recommended to start with 1–2 sets of 6–8 repetitions at 60% of the maximum weight, including knee extension, grip strength, shoulder flexion, and chest press. Later, patients may lift for only one repetition (1-RM) and progressively increase to 3 sets of 8–10 repetitions at 80–90% of 1-RM. It is important that prolonged intensive exercise are probably to have negative effects on HIV patients. Statistics from the American College of Sports Medicine (2003) reported that exercise for more than 90 min in healthy adults may alter the circulating levels of inflammatory cytokines and decrease the function of natural killer cells which target HIV-infected cells in the body [29]. Thus, prolonged exercise may also increase the patients' susceptibility to the virus, especially among immune-compromised HIV patients. Moreover, patients are recommended to exercise with a group of training partners which help to increase motivation [4]. The functional impairments of a patient should determine the type of exercises and activities prescribed. In fact, the use of multiple conditioning components to address both neuromuscular strength and cardiovascular health has become an important part of most recommended exercise programs. It is important to emphasize that qualified professionals should supervise the exercise training in order to prevent any injury and to optimize the benefits. Exercise prescription is defined by several factors including: frequency, intensity, duration of the training, the type of exercise, and the initial functional status. Determining the appropriate type of exercise also depends on patient health status and safety issues regarding the stage of the disease. A minimal intensity level is likely required to gain any benefit. There is no exact or absolute value and the minimal intensity level may vary from one person to another. Although the optimal intensity cannot be defined based on available information, most of the observed exercises, which were associated with good health, were at least at moderate intensity. Resistance training, at a moderate intensity (set at 60–80% of the 1RM) and progressively increasing, would be the most efficient type of exercise if one is focusing on large muscle groups such as the chest, brachial biceps, quadriceps, and hamstrings. Overload should be adjusted according to a level at which a patient can safely and comfortably perform 8–12 repetitions. For people who wish to focus on improving muscular endurance, a lower intensity (i.e., 50% of the 1RM; light to moderate intensity) would be appropriate to complete 15–25 repetitions per set, with the number of sets not exceeding two. Aerobic exercises are preferred to be practiced at a moderate intensity that would be 50–85% of the maximum heart rate, or 45–85% of the VO_2max/peak, from 11 to 14 based on the Borg Rating of Perceived Exertion Scale. The frequency of exercise should be increased until the patient can tolerate three to five sessions weekly for 30–60 min per session. For the best result, sessions need to be started with a warm-up period and finished with a cooldown period [3]. Clinical exercise therapists are needed to consider various factors when prescribing an exercise program for HIV-infected individuals. Considerations supported by the American College of Sports Medicine (ACSM) for the general population are also applicable to those HIV patients who experiencing additional medication-related physical and psychological problems such as gastrointestinal disfunction (especially diarrhea), neurological complications (i.e., peripheral neuropathy), lethargy, malaise, fatigue, anemia, mitochondrial toxicity, and myopathy. In addition, designing any physical exercise, the following factors are recommended to be taken in to account: (1) the functional limitations and likes/dislikes of the individual, (2) availability of time and required equipment, (3) exercise parameters (e.g., desired effect, type of exercise, (4) intensity, duration, and frequency of training) and (5) coordination among members of the multidisciplinary training team [20].

As physical function is a predictor of quality of life regardless of age, comorbidities, and

immune function, the promotion of physical activity has become a public health priority worldwide. However, since HIV-infected patients, particularly HIV-infected older adults, tend to be socioeconomically disadvantaged and live in isolation because of the stigma, they more suffer from depression, negative perceptions, and multiple comorbidities. Interventions aimed at measuring the effects of increasing physical activity on emotional well-being are seriously needed to control physical frailty and depression in this target population. Interventions are needed to raise the needed psychological satisfaction from physical activity. This can boost emotional well-being and help in alleviating some of the emotional barriers that would normally prevent HIV-infected adults from engaging in physical activity. Improvements in self-guarded motivation can not only contribute to maintaining physical activity but also can potentially provide improvements in physical activity-related physiologic outcomes [21].

28.4 Exercise and Mental Health in HIV-Positive People

Exercise is a regular activity that can start a positive cycle, that is, a person engaging in physical exercise is more likely to feel physically and psychologically normal. Being occupied by physical activity at a relatively high-intensity level makes a simultaneously negative and stressful emotion more difficult. This is because physical activity can act as a healthy efficient distraction from sad thoughts. In addition, depressed people often suffer from fatigue and the feeling that life is insurmountable, which can lead to a sedentary behavior and lifestyle. As a result, they face loss of fitness and increased fatigue. On the other hand, regular exercise increases aerobic capacity and muscle strength, self-confidence, and physical well-being. There are also various theories that hormonal changes occurring during physical activity can have positive effects on mood via altering beta-endorphin and monoamine concentrations [5]. People living with HIV/AIDS suffer from a wide variety of psychological issues associated with the virus itself, the related medications, or a combination of both. The common symptoms of HIV which being experienced by the patients reduce their quality of life and well-being. The frequency and severity of the symptoms are affected by disease progression, functional capacity, adherence to pharmacological treatment, self-medication, psychological distress as well as anxiety and depression [17]. Long-term HIV survivors and perinatal HIV infected individuals are known to be at higher risk of mental health complications because of exposure to biomedical, family, and environmental factors. For example, significant and subtle neurocognitive deficits are reported in perinatal HIV+ children. These defects affect the children's school achievement, social relationship and autonomy. The suggested mechanism is the possible effect of HIV on subcortical white matter and front striatal systems involved in the regulation of emotion and behavior. This further place the patient at higher risk of mental problems during adolescence. For youths experiencing severe HIV symptoms, hospitalizations, perceived risk of mortality, missing school and social opportunities, and delayed puberty, the mental pressure is huge, and the risk of mental issues is significant. The permanent impact of these experiences and deficits, even though the immune system is reconstituted, may affect the ability of HIV-infected youths in completion of the mandatory education, finding job, and doing social activities. These stressful conditions may have a reciprocal influence on mental health and well-being of the patients [2]. In that regard, properly designed exercises, which can affect psychological complications like anxiety or stress are recommended [30]. For example, a recently published meta-analysis suggested that exercise have beneficial effects on reducing both depression and anxiety symptoms in people living with HIV/AIDS [31]. The authors of this review recommended that professionally guided aerobic exercises for three or more times a week can improve the symptoms in those living with HIV/AIDS [31].

Depression affects adherence to ART, CD4 counts, and serum viral load of the patients. Yoga,

as a physical exercise, augment current treatment modalities of HIV infected patients Yoga helps in improving many psychological conditions such as anxiety, depression, schizophrenia, and overall well-being and quality of life in many chronic diseases. Several studies reported the potential role of yoga in controlling disorders of cellular immunity, regarding all these significant reduction in depression and improvement in CD4 counts was observed at the end of one month of integrated yoga practice, as compared to the control group [32]. Physical exercise has a positive impact on depression, which is of the most common psychological impairments among people living with HIV/AIDS. It has been shown that, aerobic exercise can eliminate depression symptoms in general population. It might therefor be an efficient intervention if manage depression symptoms among HIV individuals [9]. Many studies demonstrated that HIV stigma may also cause various psychological problems among people living with HIV/AIDS. These problems include depression, hopelessness, anxiety, low self-esteem, and perceived lack of social support. In a study, by controlling perceived stigma the association of self-stigma with depressive symptoms was reduced to a nonsignificant level [33]. It seems that the perceived-stigma mediated the relationship between distress and HIV-related changes in physical appearance [33]. Jaggers and Hand (2016) found that 60 min of moderate intensity (60–80%VO_2 peak) aerobic exercise conducted 3 days a week can be suggested as an effective method for improving the psychological disturbances experienced by people living with HIV/AIDS [17]. In addition, Vancampfort et al. (2018) suggested that more physical activity may raise self-efficacy, perceived physical functioning and general health. In their research, higher levels of depressive symptoms, and pain were reported among those with no physical activity when compared to physically active patients. However, the patients' emotional functioning was unrelated to the physical activity levels. Owing to physical manifestations of AIDS including lipodystrophy which is viewed as a visible marker of the disease progress might on its turn cause stigmatization and social isolation. Positive experiences when being physically active can improve the physical comfort and body satisfaction in people living with HIV/AIDS [12]. In a cross-sectional study, Fazeli et al. (2015) showed that greater levels of moderate physical activity is associated with less neurocognitive and better physical functioning among older adults living with HIV. The researchers suggested that moderate physical activities come with better neurologic outcomes. They also suggested that the underlying effects of physical activity on neurocognitive functioning is possibly due to changes in the brain activity (e.g., via neuroplasticity, neurogenesis, and/or increased cerebral blood flow) and indirect effect via physical activity reduced cardiovascular comorbidities (e.g., diabetes, hypertension), or a combination of both direct and indirect mechanisms [23]. In addition, Monroe et al. (2017) suggested that physical activity have therapeutic effects on psychomotor speed performance in HIV-infected individuals [34]. After 12-week aerobic and resistance exercise, Dianatinasab et al. (2018) observed significant improvement in all psychological subscales including anxiety disorder, social function, depression, and mental health in the exercise group compared to the control group. The researchers concluded that exercise training can be included in all health care programs in order to improve the mental health status of women with HIV infection [15]. Both aerobic and resistance exercises found to have independent and combined positive effects on various indicators of mental health in people living with HIV [35]. As recommended by the American College of Sports Medicine's Exercise Management for Persons with Chronic Disease and Disabilities (4th edition) exercise programs for people living with HIV/AIDS are similar to those recommended for the general population. These recommendations area moderate-intensity aerobic and resistance training regimen with 150 min of moderate-intensity physical activity throughout a week, as well as 2 days of full-body resistance training at approximately 60% of 1 repetition maximum intensity. Although this recommendation is known to be safe for anyone without underlying heart problems, it may not

necessarily be practical for someone with HIV [11]. A descriptive qualitative study on adult participants living with HIV conducted by Simonik et al. (2016) developed a framework to describe readiness to be engaged in physical exercises and the interaction of some other factors with readiness among adults with HIV and the related morbidities. Accordingly, personal perceptions and beliefs about physical exercise, personal experience with exercise, and financial accessibility, readiness was found to be influenced by the complexity and episodic nature of HIV and its related morbidities including physical impairments, mental problems, and other health conditions. The authors suggested that any successful measure to increase readiness to physical exercise should consider the importance of social and financial factors as well as AIDS related symptoms and morbidities [36]. As conclusion, it is proven that in addition to medical treatments and social support, physical exercise is beneficial to HIV/AIDS patient's clinical status. Physical exercise also improves physiological/psychological and social status of the patients. Physical exercise is beneficial to self-management, functional capacity, and perceived well-being of the patients. Physical exercise is necessary and urgently needed to be prescribed for HIV/AIDS patients in order to let them have a more healthy and efficient life. To become a routine care for the HIV/AIDS patients, physical exercise requires global and governmental support.

Ethics Statement We did not conduct any experiment on animals or cell lines for the work presented in this chapter.

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Part X

Exercise and Neuropsychiatric Disorders

29 Effects of Exercise on Memory Interference in Neuropsychiatric Disorders

Lindsay Crawford and Paul D. Loprinzi

Abstract

There are several mechanisms that cause memory impairment, including motivated forgetting, active forgetting, natural decay, and memory interference. Interference occurs when one is attempting to recall something specific, but there is conflicting information making it more difficult to recall the target stimuli. In laboratory settings, it is common to measure memory interference with paired associate tasks—usually utilizing the AB-CD, AB-AC, AB-ABr, or AB-DE AC-FG method. Memory impairments are frequent among those with neuropsychiatric disorders such as depression, schizophrenia, and multiple sclerosis. The memory effects of each condition differ, but are all related to alterations in brain physiology and general memory deterioration. Exercise, or physical activity, has been demonstrated to attenuate memory interference in some cases, but the mechanisms are still being determined. Further research is needed on memory interference, in regard to exercise and neuropsychiatric disorders.

Keywords

Memory interference · Proactive interference · Retroactive interference · Schizophrenia · Depression · Multiple sclerosis

29.1 Memory

Memory is a compilation of everything you have experienced and learned within your lifetime. It is unique and is what defines us as individuals. The process of creating a memory includes encoding, consolidation, and retrieval [1–3]. Encoding occurs when a stimulus results in the formation of a new memory [4]. This memory, or memory trace where neurons store the memory, is susceptible to decay and other disturbing influences [4]. Consolidation occurs when the memory trace is slowly stabilized and assimilated into previous knowledge [4]. Retrieval, the final stage, is when the stored memory is accessed and recalled [4]. Forming memories typically occurs in this order, but not always. During shocking events, like trauma, our brains go through all three stages at one time, creating a long-term "flash bulb" memory instantaneously.

Memories are broken into two temporalities: short term and long term. Short-term memory is defined as memory that lasts less than 2 min, and it also usually stores a small amount of information [5, 6]. An example of this may be temporarily

L. Crawford · P. D. Loprinzi (✉)
Department of Health, Exercise Science, and Recreation Management, Exercise and Memory Laboratory, The University of Mississippi, MS, Oxford, USA
e-mail: pdloprin@olemiss.edu

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_29

remembering a phone number someone is telling you as you write it down. This example uses working memory, the shortest type of memory, which usually lasts several seconds [5, 6]. Long-term memory consists of memories that last longer than 2 min [6]. There are multiple subsets within long-term memory, including explicit and implicit memory. Explicit, also known as declarative memory, is comprised of memories where the individual is consciously aware of encoding a particular event [5]. Explicit memories can be semantic or episodic. Semantic memory is defined as facts about the world, whereas episodic can be thought of as autobiographical memories [5]. Episodic memories include a what, where, and when aspect [7–9]. An example of semantic memory may be knowing that dogs are an animal, whereas an episodic memory would be remembering the first time you were ever barked at or attacked by a dog. Implicit, or nondeclarative memories, can be procedural or priming [5]. Procedural memories are comprised of motor skills (e.g., walking, tying your shoes) and other activities we complete automatically without conscious thought (e.g., buckling your seat belt when entering a car). Priming occurs when exposure to a stimulus influences your response to another stimulus [5]. A common example includes how individuals are able to recall word-pairs significantly better when the words are highly related, for example, "butter—toast" versus "butter—tower" [5].

29.2 Forgetting

So why do we forget some information, yet remember others? There are two types of forgetting—passive and active—which are both thought to include three distinct mechanisms [10–13]. Passive forgetting may occur when (a) context cues are lost over time, making retrieval difficult, (b) there is interference, or (c) there is natural decay of the memory trace [11]. Biological decay of an engram may eliminate all traces of the memory or erode various sections, both of which may cause an incomplete engram to be unresponsive, causing the inability to recall [11]. Active forgetting may occur through interference, motivated forgetting, or retrieval-induced forgetting [11]. Interference, which will be detailed more below, occurs when retrieval is difficult due to similar, competing information [11]. Motivated forgetting happens when an individual actively suppresses a memory, or part of a memory, due to an unpleasant quality of the memory (e.g., embarrassment or guilt) [11]. Retrieval-induced forgetting occurs when only portions of a memory are recalled, which suppresses the recall of other parts related to the particular memory [11].

29.3 Memory Interference

As stated previously, there are several mechanisms that cause memory impairment, including motivated forgetting, active forgetting, natural decay, and memory interference [10, 14–18]. For this chapter, we will focus heavily on memory interference, specifically its two forms, proactive and retroactive interference. Interference occurs when one is attempting to recall something specific, but there is conflicting information making it more difficult to recall the target stimuli [19–21], for example, trying to unlock a door with a set of keys, but not remembering which one is the correct key to use. The multitude of keys may interfere with your memory, making it more challenging to recall the correct key. As stated previously, there are two types of memory interference. Proactive interference, often abbreviated as PI, occurs when older (or previously acquired) information interferes with the recall of newly attained information (old → new) [19]. Retroactive interference (RI) occurs in the opposite direction; new information interferes with the recall of older, previously acquired information (old ← new) [19].

In an experimental setting, there are multiple ways to measure memory interference [19, 22–28]. Most commonly, paired associate tasks are used to evaluate memory interference [29–32]. These are memory tasks that contain lists of images or word-pairs (e.g., ♣◆ or "table house"). The participants memorize and subsequently recall the lists. During the recall scenario, the participant is exposed to the stem, or first word/

image, and attempts to recall the second part of the pair (e.g., table—"___"). There are several distinct types of word-based paired associate tasks, including AB-CD, AB-AC, AB-ABr, and AB-DE AC-FG. In these models, each letter in the name (e.g., AB-CD) stands for one word (A = house B = table), and the combined letters (e.g., AB) represent one word-pair (house table). The word-pairs may or may not be related to each other, depending on the research question (e.g., cheese mouse, shovel cloud). The format for each associate model's structure will be explained in the narrative that follows.

AB-CD As stated previously, each letter in the title represents one word, where the combined letters represent one word-pair. AB signifies the first list of words the participant is exposed to, and CD represents the second list. The A and B words are non-repeating, as are the C and D words. There are no repeating words in this paired associate task, for example, AB house table, pencil dog, etc. and CD glasses tea, flower bucket, etc. Participants may be exposed to both lists and then asked to recall only one of them, with interference then measured by how many words were recalled correctly. For measuring proactive interference, the participants would learn list 1 (AB), learn list 2 (CD), and finally recall list 2. For retroactive interference, participants would learn list 1 (AB), learn list 2 (CD), and finally recall list 1.

An example of an AB-CD model is provided below.

List 1	List 2
AB	*CD*
BLOUSE TOOTH	NICKEL HORSE
BRAIN SUPPER	GRASS COFFEE
RIVER ELBOW	FLAME STAIR
DOCTOR MIRROR	WINDOW TOILET
BRUSH ZIPPER	CLOCK STONE
DOLLAR CHALK	BUTTON STREET

AB-AC Similar to the previous model, the A and B words from the first list (AB) are non-repeating. When observing the second list, AC, we can already see that A is the same between the lists, meaning the second list will have the same stem words (A) as list AB, for example, AB *house* table, *pencil* dog, etc. and AC *house* straw, *pencil* car, etc. The lists share the same stem words (A) house and pencil, but the second part of the word-pair changes (B, C). Participants may be exposed to both lists and then asked to recall only one of them, with interference then measured by how many words were recalled correctly. For measuring proactive interference, the participants would learn list 1 (AB), learn list 2 (CD), and finally recall list 2. For retroactive interference, participants would learn list 1 (AB), learn list 2 (CD), and finally recall list 1.

An example of an AB-AC model is provided below.

List 1	List 2
AB	*AC*
BLOUSE TOOTH	BRAIN HORSE
BRAIN SUPPER	BRUSH COFFEE
RIVER ELBOW	DOLLAR STAIR
DOCTOR MIRROR	DOCTOR TOILET
BRUSH ZIPPER	BLOUSE STONE
DOLLAR CHALK	RIVER STREET

AB-ABr For this model, again, we have repeating letters between the lists. The first list (AB) will be comprised of non-repeating words, but the second list (ABr) will contain all of the same words as AB, but they will be rearranged and in a different order, for example, AB house table, pencil dog, straw car, etc. and ABr car table, house dog, pencil straw, etc. Participants may be exposed to both lists and then asked to recall only one of them, with interference then measured by how many words were recalled correctly.

An example of an AB-ABr model is provided below.

List 1	List 2
AB	*ABr*
BLOUSE TOOTH	SUPPER BLOUSE
BRAIN SUPPER	ZIPPER DOLLAR
RIVER ELBOW	ELBOW CHALK
DOCTOR MIRROR	MIRROR BRUSH
BRUSH ZIPPER	DOCTOR RIVER
DOLLAR CHALK	BRAIN TOOTH

AB-DE AC-FG This model is perhaps the most difficult to conceptualize. The two lists are comprised of two separate types of word-pairs, interfering pairs (AB and AC) and control pairs (DE and FG). AB and AC may cause interference because they have repeating stem words (A), similar to previous models. DE and FG have no repeating words. The first list contains AB and DE word-pairs, and the second contains AC and FG pairs, for example, AB-DE house table (AB), pencil dog (DE), etc. and AC-FG house straw (AC), flower bucket (FG), etc. In this model, participants encode the first list, recall it, encode the second list, recall it, and then complete the Modified Modified Free Recall (MMFR) list. The MMFR is a list that contains all of the word-pairs learned (AB, DE, AC, and FG). When exposed to a stem word that has more than one answer (A–B/C words), the participants recall both simultaneously.

An example of an AB-DE AC-FG model is provided below.

List 1 *AB*, DE	Cued recall 1 *A*__, D__	List 2 *AC*, FG	Cued recall 2 *A*__, F__	MMFR *A*__ __ D__ __ F__ __
SUPPER RECORD	COFFEE _____	*CHILD LETTER*	DOCTOR _____	*DRIVER* ____ ____
CHILD TICKET	*TRUCK* _____	HOTEL TEACHER	*SLEEVE* _____	WHISKEY ____ ____
WHISKEY STAIR	*SLEEVE* _____	*TRUCK TOAST*	PENNY _____	DOCTOR ____ ____
SLEEVE COLLEGE	TABLE _____	PENNY BROTHER	*CHILD* _____	*SLEEVE* ____ ____
TABLE STREET	*CHILD* _____	*DRIVER CANDY*	DOCTOR _____	SUPPER ____ ____
DRIVER SALAD	*DRIVER* _____	WINDOW MONEY	WINDOW _____	COFFEE___ ___
COFFEE PANTS	SUPPER _____	DOCTOR KETTLE	*DRIVER* _____	*TRUCK* ____ ____
TRUCK PENCIL	WHISKEY _____	*SLEEVE BRUSH*	*TRUCK* _____	HOTEL ____ _____
				SUPPER ____ ____
				CHILD ____ ____
				PENNY ____ ____
				TABLE ____ ____

29.4 Neuropsychiatric Disorders

Depression Depression is the most common type of mental illness [33]. It is a mood disorder with many variations, including persistent depressive disorder, postpartum depression, seasonal affective disorder, and psychotic depression [34]. Most of these forms share similar signs and symptoms, including, but not limited to, persistent sadness or anxiety; feelings of hopelessness, guilt, or worthlessness; loss of interest; decreased energy; difficulty concentrating, remembering, or making decisions; and difficulty sleeping [34]. Diagnosis typically includes a physical exam, lab tests to rule out other possibilities, and a psychiatric evaluation [35–38]. To be diagnosed with depression, an individual must show symptoms for at least 2 weeks [34]. It is often diagnosed in adults and is treated with medication, such as antidepressants, psychotherapy, or both [34]. There are many risk factors for depression, including personality traits (e.g., low self-esteem), traumatic events (e.g., physical or sexual abuse), family history, alcohol or drug abuse, history of other mental disorders (e.g., anxiety or post-traumatic stress disorder), serious or chronic illness, and certain medications [35, 39–52]. The Mayo Clinic provides a few tips for preventing depression: take steps to control stress, reach out to family and friends, get treatment at the earliest sign, and consider getting long-term maintenance treatment to help prevent relapse [35]. According to the Centers for Disease Control and Prevention, 8.1% of Americans reported being diagnosed between 2013 and 2016, and women were almost twice as likely as men to have ever had depression [41]. Participating in physical activity, or exercise, has been demonstrated to produce psychological and emotional benefits that may help manage mental health conditions such as

depression [53]. Exercise releases endorphins, which are cannabis-like brain chemicals that enhance your sense of happiness. It also can take your mind off of stressful aspects of your life, increase your self-esteem, and provide a healthy coping mechanism [53].

Schizophrenia Schizophrenia is a chronic and serious mental disorder that affects an individual's entire way of life. It is uncommon and usually affects individuals between the ages of 13 and 30, and the symptoms can be debilitating [54]. There are three categories of schizophrenic symptoms: positive, negative, and cognitive [54]. Positive symptoms consist of psychotic behaviors such as hallucinations and delusions [54]. Negative symptoms disrupt emotions and behaviors, such as lack of interest, flat affect, and difficulty completing tasks [54]. Cognitive symptoms range from subtle to severe and affect memory [54]. This often involves poor executive functioning (the ability to plan, focus, remember instructions, and multitask) and problems with working memory (remembering temporary information while completing an activity) [54]. Other symptoms include extremely disorganized or abnormal motor behavior and disorganized thinking [54]. Teenagers tend to have different symptoms than adults; typically they are less likely to have delusions and more likely to hallucinate [55]. The cause of schizophrenia is unknown; therefore, treatment options only target its symptoms [54]. Options often include antipsychotics, psychosocial treatment, and coordinated specialty care [54, 56–65]. Risk factors for developing schizophrenia include family history, increased immune system activation, pregnancy or birth complications (e.g., malnutrition), and taking mind-altering drugs during adolescence (e.g., psychoactive or psychotropics) [55, 66–72]. Diagnosis typically includes a physical exam, lab tests to rule out other possibilities, and a psychiatric evaluation [54, 73]. If left untreated, schizophrenia can lead to a multitude of problems, including suicide, self-injury, anxiety disorders, abuse of alcohol or other drugs, homelessness, social isolation, and other health and medical problems [55]. According to the Mayo Clinic, there are no effective ways to prevent schizophrenia, only methods to treat it [55]. It is difficult to ascertain the prevalence of schizophrenia, due to the difficulty of diagnosis, but internationally it is estimated to be 0.33–0.75% among non-institutionalized individuals [73]. The National Institute of Mental Health reports that half of individuals with schizophrenia have co-occurring mental or behavior health disorders and typically have an increased risk of premature death [73].

Multiple Sclerosis Multiple sclerosis (MS) is an autoimmune disease of the brain and spinal cord [74]. The body's immune system attacks the myelin sheath that covers and protects nerve fibers [74]. This can cause miscommunication between your brain and body, causing the nerves to become damaged or to completely decayed [74]. The cause of MS is uncertain, but risk factors include age (15–60 years), sex (females are twice as likely to develop MS), race (Caucasian descent), family history, climate (temperate climates), and smoking [74–80]. Certain infections and viruses (e.g., Epstein-Barr) and autoimmune disorders (e.g., thyroid disease, type 1 diabetes, or inflammatory bowel) have also been associated with MS [74]. Symptoms vary wildly and depend on the extent of myelin sheath damage and which nerves have been affected [74]. Common symptoms include numbness or weakness of limbs, loss of vision, tingling of body parts, electric-shock sensations, tremor, fatigue, or problems with bowel and bladder function [74]. There is no cure for MS, and severe cases can lead to the inability to walk or function independently [74]. MS is usually relapsing-remitting, meaning individuals may experience phases of symptoms and phases where they are asymptomatic [74]. There is no direct diagnostic test for MS, but common measures include blood tests to rule out other diseases, MRIs to determine if there are any lesions on the brain or spinal cord, lumbar puncture, and evoked potential tests [74]. Treatment options focus on reducing symptoms and helping patients recover from

symptomatic phases—corticosteroids, plasmapheresis, physical therapy, and muscle relaxants are common options [74]. Exercise is also a remedy for MS, as it improves strength, muscle tone, balance, and coordination [74]. Reducing stress and eating a balanced diet can also assist with the maintenance of symptoms [74]. Globally, MS affects approximately 2.5 million people with symptoms typically occurring between the ages of 20 and 50 years old [81].

29.5 Neuropsychiatric Disorders and Memory Interference

Depression and Memory Interference (MI) Individuals with depression are more likely to experience memory impairment [82–91]. There are several reasons behind this observation—depression is associated with decreased hippocampal volume, and alterations in hippocampal volume are associated with a number of factors, including dendritic retraction, neuronal death, and suppression of adult neurogenesis [86]. These alterations in brain functions can lead to impairments in memory, with the strongest effect on episodic (autobiographical) memory and less substantial effects on semantic memory (facts about the world) and spatial memory when compared to healthy subjects in a virtual town navigation test [86]. There is evidence that the use of antidepressants may reverse these shortcomings [86]. One characteristic of individuals with depression that has been observed repeatedly is that participants with major depressive disorder (MDD) tend to "ruminate," or ponder, on negative stimuli—which in turn may increase memory interference [85, 86]. Joorman et al. report that "we did find that depressed participants exhibited difficulties removing irrelevant negative material from short-term memory" [85], and Shelton et al. report similar findings: "these findings indicate that depression is associated with difficulties removing irrelevant negative material from working memory. Results also indicate that the increased memory interference from irrelevant negative material is associated with rumination" [86]. Deficits in memory interference may be attributed to the tendency to ruminate on certain stimuli [86].

In regard to pattern separation, an ability imperative to memory, depression is negatively associated with its performance—meaning those with higher scores of depression tend to do worse on pattern separation activities [86]. Shelton et al. demonstrated that those with high levels of depression may be more likely to overgeneralize moderately similar stimuli as equal even though they have distinct differences that healthy participants are able to distinguish between [86]. Interestingly, Dery et al. performed a pattern separation experiment on two healthy adult groups, with the experimental group receiving a 6-week aerobic regime and the control group receiving no exercise instruction [92]. The results demonstrated that those who increased their fitness level had a greater degree of change on the pattern separation task—demonstrating that exercise may have a favorable effect on pattern separation due to an exercise-induced increase in hippocampal neurogenesis [92].

Schizophrenia and MI As stated previously, schizophrenia can be detrimental to one's working memory and executive function, which may increase the opportunities for memory interference to occur. In experimental studies, patients with schizophrenia tend to score significantly lower on memory tests compared to healthy controls [23, 93–97]. The memory interference effects for those with schizophrenia, however, are not consistent across the literature. Elevag et al. hypothesized that patients with schizophrenia would perform poorly on an AB-AC and AB-ABr paired associate tasks with unrelated words compared to the same tasks comprised of related words [98]. The authors also hypothesized that the patients would score significantly lower on recall from the second lists (AC and ABr), but neither hypothesis was supported by the results [23]. The authors suggest that the interference effects in schizophrenic patients are largely due to general memory problems that accompany the condition [23, 99, 100]. Conversely, Kaller et al. demonstrated that patients with schizophrenia

may have diminished vulnerability to proactive interference despite working memory impairments [95]. Again, this phenomenon is yet to be understood completely. One proposition that Kaller et al. ruled out is the superior function of the inferior frontal gyrus and anterior insula, which are thought to decrease PI vulnerability [95]. These brain regions are typically functionally reduced in patients with schizophrenia, again, leaving the question unanswered [95]. One important shortcoming of memory-related experiments on patients with schizophrenia is the limited sample size—due to it being an uncommon disorder.

Multiple Sclerosis and MI Multiple sclerosis (MS) impairs multiple cognitive domains, but primarily learning and memory [101]. This includes, but is not limited to, diminished verbal long-term memory, difficulty acquiring new information, hippocampal dysfunction, greater information loss during early consolidation, long-term potentiation impairment, and overall worse memory [24, 101]. Griffiths et al. found that, compared to healthy individuals, those with MS appeared equally susceptible to proactive interference, but had greater (more) retroactive interference [24]. Individuals with MS have difficulty retrieving previously acquired (old) information after learning new, semantically related information (RI) [24]. This may signify difficulty using source and contextual information to ease retention and help distinguish between competing stimuli—which is linked to medial prefrontal cortex dysfunction [24, 25]. This issue with retaining old information may be linked to poor encoding or consolidation of new information due to hippocampal dysfunction—which is evident in many MS patients [101]. Hippocampal synaptic density is also likely to be reduced in those with MS, which, again, correlates with general memory problems and poor early consolidation [101]. Overall, individuals with MS are likely to suffer from physiological and anatomical changes of their brain structure, due to their immune systems attacking their myelinated sheaths, which causes inflammation and alterations to brain structures that are imperative for learning and memory [24, 101].

29.6 Exercise and Memory

Exercise has repeatedly been demonstrated to improve brain plasticity, cognition, and well-being [4, 14, 33, 102–133]. Exercise has also been reported to induce structural and functional changes in the brain, creating many biological and psychological benefits [33, 102, 134]. Physical activity or "any bodily movement produced by skeletal muscles that requires energy expenditure" is often used interchangeably with exercise, but in this case, we are specifically referring to structured and planned exercise [33]. In human studies, structural changes are indicative of increased hippocampal and prefrontal cortex volume, increased gray matter volume, white matter integrity, and increased neurotrophin levels such as brain-derived neurotrophic factor (BDNF) [25, 33, 135–139]. The benefits are vast and can help improve quality of life at every stage. For the aged, exercise may even help to prevent cognitive decline and reduce risk of developing dementia [6, 33, 121, 129, 130, 140–144]. These changes may all facilitate improved memory performance. Emerging work tends to focus on how exercise improves memory among older adults, since they are at an increased risk of memory loss, but impairments have been shown to occur in young adults in their 20s—making this field a topic of interest among many researchers [102, 145].

29.7 Exercise and Memory Interference

Effects of Exercise in MI There is evidence that physical activity influences cognition and memory through a variety of mechanisms [146–153]. Brain-derived neurotrophic factor (BDNF) has long been established to be integral in learning and memory function [135, 137, 154–164]. Increases in BDNF can be found in the hippocampus of mice after training and learning various

mazes, tasks, and fear conditioning, demonstrating the link between BDNF and hippocampal learning [154]. According to Cunha et al., BDNF proteins have the highest expressions in the hippocampus, neocortex, cerebellum, and amygdala—all of which are responsible for cognitive functions [128, 154]. Exercise, or physical activity, is associated with increased prefrontal cortex (PFC) and hippocampal volume, along with increased BDNF production in the brain [25]. This is one of the many mechanisms which may lead to increased cognition and improved memory [137]. Exercise also stimulates the PFC and hippocampus, resulting in increased neuronal excitability within two of the regions imperative for encoding, retrieval, and distinguishing between conflicting memories (memory interference) [25]. Research has mainly focused on acute aerobic exercise-induced increases of BDNF, but evidence demonstrates that both acute aerobic and resistance exercises are effective at increasing BDNF levels [163].

Physiological changes, such as this, may be one of the reasons physical activity may attenuate memory interference effects [26, 28, 137, 165]. Research in this area is sparse, but is continuing to grow. Roig et al.'s paper from 2013 details how cardiovascular exercise *prior* to memory testing demonstrates a significant improvement on memory performance, compared to exercising during and after a memory task [147]. This exercise and memory temporality has been tested repeatedly, showing similar results in combination with memory interference tasks [26, 28, 165]. Haynes and Loprinzi demonstrated that a short bout of exercise prior to memory encoding was beneficial for improving retrospective episodic memory compared to during encoding, after encoding, and a control group [26]. Frith et al. evaluated a short bout of high-intensity treadmill exercise (jogging) and demonstrated that exercise may help to attenuate a proactive interference effect [165]. Compared to a control group, the exercise group showed a non-significant inclination to attenuate proactive interference [165]. Wingate et al. examined the effect of acute exercise on proactive and retroactive interference [28]. The results from this study suggest that acute exercise, 15 min at a self-selected "brisk walking" pace, may be more beneficial for retroactive interference compared to proactive interference, but further research is needed [28].

Mechanisms Mediating the Effects of Exercise in MI As stated previously, acute and chronic exercise can improve cognitive function [146]. The mechanisms behind the chronic exercise effect may include induced neurogenesis, gliogenesis, angiogenesis, and increased cerebral circulation [146]. The mechanisms behind acute exercise-induced memory performance have fewer concrete mechanisms established. Two strong hypothesized mechanisms are by means of the muscle spindle pathway and the vagus nerve [146]. When skeletal muscles contract, muscle spindles are activated, generating action potentials which are then transmitted to the dorsal spinal cord. From the spinal cord, the action potentials travel to the brainstem, activating the prefrontal cortex (PFC), amygdala, and hippocampal structures (CA3 and CA1)—all of which are involved in memory [146]. The vagus nerve, which is the longest cranial nerve in the body, is activated during exercise by various tissues, such as the lungs, and/or exercise-induced increases in catecholamines [146]. The afferent sensory fibers within the nerve transmit information from peripheral tissues (e.g., respiratory tract, heart) to the NTS, which again has direct communication with hippocampal structures (CA1) [146]. This brainstem stimulation can lead to increases in neurotransmitters such as norepinephrine, which is also associated with memory [146]. These mechanisms are hypothetical but provide direct pathways in which exercise-induced physiological changes may occur and therefore improve memory performance and, possibly, attenuate MI.

29.8 Summary

Memory interference is one of the many mechanisms behind forgetting. It occurs when similar information competes and disrupts the recollection of the target information. Memory impairments are

common in individuals with neuropsychiatric conditions such as depression, schizophrenia, and multiple sclerosis. Conditions that affect memory can deteriorate a person's quality of life and memory and leave them dependent on others. Exercise has been shown to reduce memory impairments and even increase certain types of memory performance, including an attenuation of memory interference. The literature is still sparse on the topic, but as it continues to grow, we will learn more about how exercise-induced physiological changes can improve memory and perhaps help combat memory impairments brought on by a myriad of diseases.

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30 Effects of Exercise on Long-Term Potentiation in Neuropsychiatric Disorders

Paul D. Loprinzi

Abstract

Various neuropsychiatric conditions, such as depression, Alzheimer's disease, and Parkinson's disease, demonstrate evidence of impaired long-term potentiation, a cellular correlate of episodic memory function. This chapter discusses the mechanistic effects of these neuropsychiatric conditions on long-term potentiation and how exercise may help to attenuate these detrimental effects.

Keywords

Exercise · Functional connectivity · Memory physical activity

30.1 Long-Term Potentiation

As we have thoroughly discussed elsewhere [1, 2], long-term potentiation (LTP) is referred to as the functional connectivity of neurons and neuronal circuits, characteristically shown by sustained postsynaptic excitatory potentials [3]. It is not within the scope of this review to provide a detailed explanation of LTP and its antecedents, as this is heavily research and influenced by a multitude of factors [4–76]. Briefly, LTP is often classified into an early (E-LTP) and late-phase (L-LTP), with E-LTP often considered as a non-protein synthesis process whereas L-LTP involving a protein synthesis process. In E-LTP, after neurotransmitter (e.g., glutamate) release from a presynaptic neuron, the neurotransmitter binds to its respective membrane receptor on the postsynaptic neuron. Following this, an ionotropic receptor, such as AMPA, will allow for the influx of sodium and efflux of potassium. Upon sufficient sodium influx, depolarization of the postsynaptic neuron will occur. Through an electrostatic repulsion process, involving postsynaptic depolarization and glycine and glutamate binding with the NMDA receptor, the magnesium block from the NMDA receptor will be repelled. This will then allow for an influx of calcium ions through the NMDA receptor. Intracellular calcium, in conjunction with intracellular kinases, will help facilitate the phosphorylation of AMPA receptors, ultimately subserving LTP. Protein synthesis-dependent L-LTP involves the phosphorylation of transcription factors (e.g., CREB), ultimately producing new proteins (e.g., BDNF, PKM-zeta) to facilitate synaptic plasticity and, in turn, strengthening the connectivity of communicating neurons and neural circuits.

P. D. Loprinzi (✉)
Department of Health, Exercise Science, and Recreation Management, Exercise and Memory Laboratory, The University of Mississippi, Oxford, MS, USA
e-mail: pdloprin@olemiss.edu

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_30

30.2 Depression and Long-Term Potentiation

Depression is a mood disorder typically characterized as a persistent perception of sadness and loss of interest [77–84]. It is the leading cause of disability, and the global prevalence of depression has been increasing in recent decades, with a lifetime prevalence ranging from 20 to 25% in women and 7–12% in men [85]. In addition to gender, depression prevalence estimates also vary by morbidity status, including asthma (27%), COPD (25%), and stroke (30%) [85]. In alignment with these findings, a recent systematic review among outpatients showed that the prevalence of depression or depressive symptoms was 27%, ranging from 17 to 53% [86].

Various risk factors for chronic depression have been identified [87]. These include younger age at depression onset, longer duration of depression, family history of mood disorder, anxiety disorders, personality disorder, and comorbid substance abuse. From a behavioral perspective, accumulating research demonstrates that regular participation in physical activity may help prevent and treat depression symptomology [88–95]. Potential mechanisms through which physical activity may prevent and treat depression are likely to occur through various physiological (e.g., thermogenic, endorphin, and monoamine) and/or psychological (e.g., self-efficacy) mechanisms [96]. Regarding the physiological mechanisms, the monoamine mechanism indicates that physical activity may reduce depression symptoms by increasing the availability of select brain neurotransmitters, such as serotonin, dopamine, and norepinephrine [96]. Physical activity may also be contributory by enhancing self-efficacy [97–99], including coping self-efficacy [100] and problem-focused coping [101].

Emerging research demonstrates that major depression disorder is associated with reduced levels of key neurotrophins (e.g., BDNF) that influence LTP [102]. For example, serum and plasma BDNF levels are decreased among individuals with untreated major depressive disorder. Per the neurogenic hypothesis of depression, reduced hippocampal neurogenesis may, in part, underlie the pathoetiology of depression [103]. However, anti-depressive treatment for at least 4 weeks can help restore BDNF levels and, thus, attenuate depression-induced impairments in synaptic plasticity [103]. Further, such treatments may help promote neurogenesis, synaptogenesis, and neuronal maturation, all of which may subserve LTP. As stated, NMDA receptors play a critical role in LTP. Accumulating research also demonstrates that NMDA receptors play an important role in the neurobiology and treatment of depression [104].

30.3 Alzheimer's Disease and Long-Term Potentiation

As we have thoroughly discussed elsewhere [105], Alzheimer's disease (AD) is a debilitating neuropsychiatric disorder, including both genetic and environmental etiologies [106–125]. Globally, 44 million adults have AD, occurring most commonly in Western Europe [126]. Within the United States, an estimated 5.5 million adults (5.3 million among people 65+ years) have AD, as of 2017 [127]. Among elderly individuals (65+ years), the average survival of AD is 4–8 years, with some living up to 20 years post-diagnosis [128].

Classic characteristics of AD include accumulation of amyloid beta (Aβ) and intracellular neurofibrillary tangles. Other notable characteristics include, for example, alterations in presenilins, tau, vesicle transport/release, calcium dysregulation, AMPA/NMDA receptor function, nicotinic acetylcholine receptors, PKC/PKA, and BDNF. Consequences of AD often include neuronal loss, astrocytosis, and microgliosis. These factors, among others, may morphologically alter medial temporal lobe structures, namely, the hippocampus, which may have profound effects on episodic memory function.

Encouragingly, regular participation in physical activity may help to reduce the risk of AD. Norton and Matthews [129] indicated the population-attributable risk of AD for physical inactivity ranged from 12.7 to 20.3%. In 2017, Stephen et al. [130] employed a systematic review to evaluate the association between physical activity and AD

incidence. Of the 24 evaluated prospective studies, 18 studies (75%) provided evidence that physical activity is inversely associated with AD risk. Similar results have been reported by other systematic reviews. Guure et al. [131] evaluated 17 prospective studies and reported a 38% reduced incidence of AD with sufficient engagement in physical activity. Other meta-analyses also support these findings [132, 133].

Various mechanisms have been identified through which physical activity may reduce the risk of AD. These included, for example, physical activity-induced changes of Aβ and brain structure changes, as well as attenuation of inflammation, oxidative stress, insulin/glucose dysregulation, and mitochondrial dysfunction [134–149]. Further, physical activity may attenuate the progression of AD via alterations in various proteins and intracellular pathways that inhibit neuronal apoptosis [143]. Further, physical activity may enhance or preserve memory function among AD patients by altering changes in molecular pathways related to AD [150].

Alzheimer's disease may impair LTP via various pathways. For example, Aβ may induce neuronal dysfunction through Ca^{2+} dysregulation [151]. Relatedly, Aβ may also decrease certain NMDA subunits (e.g., NR2B) [152], which play a crucial role in subserving learning and memory [1]. For example, Aβ binds to acetylcholine receptors and activates phosphatases (e.g., PP2B), which ultimately may induce dephosphorylation of NR2B [153]. In addition to influencing LTP via NMDA receptors, AMPA receptor expression and functionally may also be reduced in neurons treated with Aβ [154]. Certain kinases, such as PKC, which have been shown to be negatively influenced by AD brains [155], help regulate Aβ by binding to it and then facilitating its inactivation and, ultimately, its clearance [156].

30.4 Parkinson's Disease and Long-Term Potentiation

As we have detailed elsewhere [157], a major hallmark of Parkinson's disease (PD) is dopaminergic loss in the basal ganglia. Behaviorally, PD often involves bradykinesia, tremor, rigidity, and postural instability [117, 158–169]. Parkinson's disease may also involve memory-related impairments [157].

A variety of memory types can be influenced by PD. These include, for example, verbal memory [170, 171], nonverbal memory [172], procedural memory [173], semantic memory [174, 175], and working memory [176]. Increasing evidence has shown that physical activity may be beneficial to prevent PD risk [177–180]. Several mechanisms have been proposed through which physical activity may help to prevent PD risk. These include the regulatory effects of exercise on dopamine level, oxidative stress, inflammation, and neurotrophic factor levels [181–183]. These same mechanisms may help explain, in part, the beneficial effects of physical activity on memory function among those with PD [184–196].

Further, PD is also associated with impairments in various molecular processes that influence LTP. For example, reduced levels of dopamine may reduce dendritic spine density, as dopamine plays an important role in activating transcription factors (e.g., CREB) via cAMP and PKA signaling. Dopamine can also regulate LTP through targeting NMDA receptors [197]. Activation of D_1 receptor leads to NMDA potentiation through PKA signaling pathway [198, 199]. As stated previously, NMDA activation may increase intracellular Ca^{2+} levels and phosphorylate various transcription factors subserving L-LTP.

30.5 Effect of Exercise on Long-Term Potentiation

Before discussing the effects of exercise on LTP, it is important to discuss the effects that exercise has on memory function. We have recently reviewed the underlying mechanisms through which exercise may improve memory function [1, 2, 200]. These include, for example, exercise-induced alterations in LTP, neurotrophins, select hormones, and psychological-related parameters (e.g., enhanced encoding via attentional processes).

Research also demonstrates that both acute and chronic exercise can enhance memory function [1, 2, 201–226].

Emerging work within both animals [47, 227–242] and humans [243–245] provides suggestive evidence that exercise, particularly chronic exercise, may subserve LTP. These studies demonstrate that when exercise occurs either before or during LTP induction, enhanced LTP ensues. A candidate mechanism through which exercise may influence LTP is through exercise-induced alterations in the structure and function of NMDA receptors. Exercise has been shown to induce phosphorylation of NR1 and NR2 subunits of cerebral cortex NMDA receptors [246]. Further, exercise may also increase the NMDA channel opening rate. Other work demonstrates that exercise training increases the expression of NR1, NR2A, and NR2B mRNA in the rat hippocampus [247].

30.6 Summary

Various neuropsychiatric disorders, such as depression, Alzheimer's disease, and Parkinson's disease, are associated with reduced memory function. Although memory function is a complex phenomenon involving multiple brain regions and underlying molecular pathways, a mechanistic correlate of episodic memory function is long-term potentiation. The evaluated neuropsychiatric conditions demonstrate evidence of impaired long-term potentiation, providing a potential mechanistic explanation of their reduced memory function. Emerging work demonstrates that exercise may enhance memory function among each of these neuropsychiatric conditions and may also facilitate long-term potentiation. Future longitudinal work is needed to evaluate the extent to which chronic exercise training may preserve memory function among these populations and whether long-term potentiation mediates these effects.

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Part XI

Future Prospects

31 Prospective Advances in Beneficial Effects of Exercise on Human Health

Zuoxu Hou, Xing Zhang, and Feng Gao

Abstract

Physical inactivity increases the chance of many adverse health conditions. It has been well recognized that exercise exerts widespread beneficial effects in health promotion and disease prevention. However, there remain many unknowns in the understanding of the complex biology and performance behind diversity in response to exercise among populations and individuals. The exercise-afforded health benefits are not sufficiently researched, which to some extent holds back the translation of exercise biology to society and the widespread adoption of physical activity promotion. A comprehensive understanding of the physiology of exercise and pathogenic processes underpinning physical inactivity-associated disorders will facilitate the development of new preventative and therapeutic strategies to improve health and well-being at the whole-body level. In this chapter, we will discuss some important questions that remain to be addressed in the research of health-promoting benefits of exercise.

Keywords

Health promoting · Personalized exercise · Exerkine

Substantial evidence shows that physical inactivity is a significant risk factor for many noncommunicable diseases including obesity, type 2 diabetes, cardiovascular diseases, and cancer, and shortens life expectancy. From the evolutionary perspective, human beings are born to be physically active. Our genetic makeup is largely shaped to support physical activity pattern. To some extent, modern lifestyle that enables inactive way of living is blamed to be the culprit of chronic diseases that constitutes a major health problem and a huge economic burden [1]. There is strong experimental and epidemiological evidence on the beneficial effects of regular physical activity by positively affecting all organ systems of the body. The study on exercise beneficial effects will help improve the understanding of how our body works (human physiology per se),

Z. Hou · X. Zhang · F. Gao (✉)
School of Aerospace Medicine, The Fourth Military Medical University, Xi'an, China
e-mail: fgao@fmmu.edu.cn

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_31

and the true meaning of health. Empowered with this knowledge, people will be more willing to make changes in their lifestyle, to reshape themselves both physically and psychologically, and to get reward from the changes.

31.1 High Priority of Increasing Physical Activity Participation and Health Perceptions

On the eve of the 2012 summer Olympic Games, *The Lancet* published its first series on physical activity, which identified physical inactivity as a global pandemic and urgent public health priority [2]. It requires all sectors of governments and societies to take immediate action to increase physical activity levels worldwide. Four years later, the second *Lancet* physical activity series came out in 2016 indicated that general physical activity levels have not increased over the Olympic quadrennium, and that about a quarter of adults and 80% of adolescents were inactive globally [3]. Thus, getting people moving should become a priority of all sectors, including researchers, policymakers, and communities. Although scaling up physical activity interventions in populations across the varying cultural, geographic, social, and economic contexts worldwide is challenging, it is feasible because the efforts from all over the world has grown substantially [4]. The more intensive and extensive research, from experimental studies and clinical trials, on health-promoting effects will undoubtedly support public education on health and increase public awareness of well-being.

Beside the efforts of shifting populations to a more active way of life, it is also important to consider the physical and psychological road blocks that deter people from undertaking exercise on a regular basis, especially for the aged. It remains unknown why some individuals enjoy exercise and for others it is a chore. Further research should be undertaken to elucidate the effects of genetic background, psychological state, behavior, and other factors on exercise performance and to find ways to motivate people to adopt and maintain a physically active lifestyle. This will have a greater impact on individual and population health than searching for potential pharmacological treatments.

31.2 Personalized Exercise Regimes in Health Promotion and Disease Prevention

It is generally accepted that exercise is an important part of maintaining a healthy body and a "polypill" in intervention of diseases, which combines preventive and therapeutic effects with little adverse consequences and at lower cost [5]. However, the response to physical activity and its performance vary from individual to individual [6]. Recent progress has been made regarding personalized exercise regimes to optimize health benefits of exercise to individuals, yet it is still a big challenge. The most important factor that affects the performance of exercise is individual difference of genetic background, psychological state, behavior, pathological profile, culture, and social environment. There remains much to be solved about the complex biology behind diversity in response to exercise among individuals and populations, especially for the aged and those with diseases.

Although exercise is beneficial for health, the exercise dose significantly affects the biological effects of exercise. The World Health Organization recommends that adults aged between 18 and 64 years should accumulate at least 150 min of moderate-intensity aerobic physical activity throughout the week, or undertake at least 75 min of vigorous-intensity aerobic physical activity, or perform a combination of both forms of physical activity [7]. However, exercise capacity and exercise performance are markedly influenced by individual physiological and pathological profiles. The existing exercise guideline is not suitable for everyone. Recently, a study of 55,000 people from the Aerobics Center Longitudinal Study showed that runners had impressive reduc-

tions in all-cause mortality of 30%, with an average increase in life expectancy of 3 years. Notably, substantial benefits were obtained with exercise training doses much lower than current major physical activity guidelines. Running even at relatively low doses (5–10 min per day) was sufficient for substantial mortality benefits [8]. In addition, it is still largely unknown how much dose of exercise for a certain group of people is needed for producing health beneficial effects.

Furthermore, exercise is classified by the type, intensity, frequency, and duration of activity, which makes the accurate personalized exercise regimes more complicated. The biological functions of various types of exercise such as aerobic/anaerobic exercise, resistance exercise, and high-intensity intermittent exercise have been extensively studied. However, few studies have compared the effects of different exercise types in humans in settings of health and disease. Since the often-heard complaint is that they "don't have the time" to exercise, further studies on new effective and time-saving exercise programs are warranted.

In addition, recent studies showed that the time of day is a critical factor to amplify the beneficial impact of exercise on both metabolic pathways within skeletal muscles and systemic energy homeostasis [9, 10]. The circadian rhythm controls a huge variety of physiological processes including the sleep–wake cycle, metabolism, and cell proliferation. Several studies have investigated the circadian regulation of exercise performance and health-promoting effects, but still many aspects remain to be addressed as to how precisely this is managed. In the future, individualized exercise prescription may include the time of day to perform exercise. Furthermore, many effects observed in animals frequently differ from those seen in humans in vivo; in particular, exercise is usually a voluntary activity which is more than muscle contraction in human, while it is usually a forced activity with significant stress in animal studies. Therefore, the differences must be carefully considered when assessing the potential of translating findings from animal experiments to humans, and care should be taken when extrapolating responses from one set of conditions or a given experimental model to another [11]. Multicenter studies and large cohort studies in general population are warranted in the future.

31.3 Searching for Exerkines and Exploiting the Beneficial Effects of Exercise

Another challenge in studying exercise is to decipher the precise mechanisms by which exercise promotes whole-body health. By comprehensively understanding the factors underlying the protective properties of exercise, we can improve our understanding of the pathogenic processes underpinning the numerous contemporary physical inactivity-mediated disorders and develop preventative and treatment strategies. However, it is challenging to define the full complement of molecular and cellular changes associated with exercise given that exercise represents a dynamic stimulus affecting numerous organs and systems in the body. It is also unclear whether mechanisms identified in exercise training models in animals reflect mechanisms that occur in humans. With the ability to profile the genome, transcriptome, proteome, and metabolome in far greater depth than ever before, exercise biologists are getting new opportunities to define the multiplicity and complexity of cellular networks involved in exercise responses. It is now possible to identify thousands of factors that are regulated in response to exercise. However, many signaling pathways are not linear. They constitute a complex network, with a high degree of cross talk, feedback regulation, and transient activation. Analyzing of huge data sets generated from "omics" technologies to delineate the key drivers and complex processes underlying exercise-induced responses is still challenging. The application of artificial intelligence to problems in exercise biology should facilitate future progress.

Exercise-induced bioactive factors which act as exercise pills or messengers and play important roles in exercise-induced health benefits are collectively termed exerkines [5]. The exerkines

identified are secreted from skeletal muscles or other organs/tissues and released into circulation, and carried to other organs/tissues. Such "cross talk" between tissues and organs provides a framework for understanding how exercise mediates many of its beneficial systemic effects. Interest in this research field has grown with the increased knowledge that the majority of the exerkines are found in extracellular vesicles such as exosomes and microvesicles. Extracellular vesicles, small endogenous membrane vesicles secreted by most cell types, have been shown to play important roles in mediating cross talks between organs via the transmission of a variety of signaling molecules including protein and nucleic acids. Recent studies demonstrate that long-term exercise affects not only the quantity but also the quality of circulating exosomes. The differentially expressed miRNAs cargoed in exercise-induced exosomes are released mainly from endothelial cells triggered by such a simple mechanical force, that is, increased blood flow–associated shear stress. These miRNAs exert cardioprotective effects, indicating a cross talk between blood vessels and the heart in exercise-associated cardioprotection [12]. Future studies will be required to identify more exerkines and develop bioengineered or modified exosomes to incorporate one or many of known exerkines for the treatment of obesity, diabetes, and other aging-associated metabolic disorders, especially for those with restricted physical activity.

Future research in the field of exercise biology requires increasingly sophisticated approaches to understand the underlying mechanisms of physical activity-exerted beneficial effects with integrated observations from genes, molecules, cells, organs, and other aspects in a physiological or pathological context. The progress in exercise research will enhance our understanding of how exercise-induced systemic and tissue-specific changes lead to health improvement at the whole-body level and facilitate the development of preventative and therapeutic strategies for chronic diseases associated with modern lifestyle.

Acknowledgments This work was supported by the grants from National Natural Science Foundation of China (81870273 to F Gao and 31500932 to X Zhang).

Competing Financial Interests The authors declare no competing financial interests.

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Correction to: Exercise and Osteoarthritis

Lei Chen and Yan Yu

Correction to:
Chapter 15 in: J. Xiao (ed.),
***Physical Exercise for Human Health*,**
https://doi.org/10.1007/978-981-15-1792-1_15

This chapter was inadvertently published with incorrect details in reference 57. Reference 57 has been updated in the chapter as below:

Favero M, Belluzzi E, Trisolino G et al (2019) Inflammatory molecules produced by meniscus and synovium in early and end-stage osteoarthritis: a coculture study. J Cell Physiol 234:11176–11187. https://doi.org/10.1002/jcp.27766

The updated version of this chapters can be found at https://doi.org/10.1007/978-981-15-1792-1_15

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