Kazuyuki Kanosue *Editor in Chief*

Satomi Oshima
Zhen-Bo Cao
Koichiro Oka *Editors*

Physical Activity, Exercise, Sedentary Behavior and Health

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ISBN 978-4-431-55332-8 ISBN 978-4-431-55333-5 (eBook)
DOI 10.1007/978-4-431-55333-5

Library of Congress Control Number: 2015939583

Springer Tokyo Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer Japan KK is part of Springer Science+Business Media (www.springer.com)

Introduction to the Series

Waseda University of Japan has a tradition of producing great athletes amongst its graduates, such as Mikio Oda, the first Japanese ever to win an Olympic gold medal. Waseda University strongly supports coaching techniques that embody a practical application of the knowledge gained from the fundamental research findings of sports science. Waseda University also takes pride in providing athletes with medical care that utilizes leading-edge sports medicine, and formulates management strategies that combine all these elements. This approach has led to a strong tradition of sports-based research—what we like to call "Waseda Sports"—which has enjoyed an unprecedented level of success. This tradition was enhanced by the Faculty of Sport Sciences in Waseda University in 2009 when they initiated the Global COE (Center of Excellence) Program, entitled "Sport Sciences for the Promotion of Active Life". The Global COE Program is under the aegis of the Japanese Ministry of Education, Culture, Sports, Science, and Technology; this Ministry supports the development of international centers of education and research excellence.

While life expectancy in Japan is the highest in the world, large-scale societal changes here and elsewhere have led to an increase in health problems due to a decrease in activity and physical fitness. In the aging population there has been a deterioration of overall health, much of which can be attributed to inactivity and excess body weight. It is especially troubling that similar problems are increasing among children and are associated with severe physical and mental disabilities. The international scope of the above problems provided the impetus for Waseda University to form the Global COE Program. This effort involved the construction of an international hub of education and research specifically designed to develop and encourage talented researchers to create sports programs that would contribute to an active and vital lifestyle. The program emphasizes the development of specialist knowledge in conjunction with a broad understanding and awareness of the diverse world of sports. One of our goals was to focus not just on improving the individual health of mind and body, but also to develop an understanding of the conditions present in regions and societies that facilitate such improvements in the lifestyle of individuals.

The sports sciences have created and are extending an important body of knowledge. It is critical that this information be utilized to produce an active, two-way interaction between the investigators and the active participants of sporting events. In order to provide a focus for developing this reciprocal intercommunication, the Global COE program identified three strategic project themes: (1) Active Children Project, (2) Active Elderly Project, and (3) Elite Athlete Project. The COE Program was proactive in seeking out mature graduate students who were returning to higher education after a period of work, thereby facilitating a meaningful contribution to the formation of academic careers for specialists who were active in the practical domain of sports. Many graduate students from abroad, especially from Asian countries, joined the program and have contributed to our goals via both the creation of academic knowledge and direct participation in the sports relevant to their area of investigation.

The formal funding for the Global COE Program came to an end in March 2014, but the projects initiated by the program and the activities of the graduates continue unabated. The accomplishments made during the 5 years of the program have been documented in a series of four books with the overall theme of "Sports Science and an Active Life". We are proud to present this substantial body of research in the following series of books: Vol. 1: *Sports Management and Sports Humanities* (Kohei Kogiso, Daichi Oshimi, Munehiko Harada, Eds.), Vol. 2: *Physical Activity, Exercise, Sedentary Behavior, and Promoting Health* (Satomi Oshima, Zhen-Bo Cao, Koichiro Oka, Eds.), Vol. 3: *Sports Performance* (Tomoyuki Nagami, Jun Tsuchiya, Eds.), and Vol. 4: *Sports Injuries and Prevention* (Tetsuya Ogawa, Mako Fukano, Toru Fukubayashi, Eds.). The series was written by the dedicated faculty members and young graduate students and postdoctoral researchers under the guidance of investigators who took part in the Global COE program. The series was also contributed to by leading researchers around the world, most of whom belong to Waseda University's research institute or university partners. I appreciate their contributions as well as their participation in the Global COE program. During the 5 years of the program, an international network of individuals and universities doing active research in the area of sports sciences has been established. I expect this network to grow wider and stronger in the future and to contribute to the solution of many of the health problems that plague modern societies. We will all continue to work hard to involve sports activities in the solutions to these problems, and in the process, aid in advancing the sports activities themselves.

Finally, I express my appreciation to the editors of each volume, who not only did a fine job of organizing the volumes but also wrote chapters that were important scientific contributions to the overall effort. We would also like to thank the Global COE staff for their efficient work and the kind support they extended to the graduate students. Drs. Larry Crawshaw and Candace S. O'Connor are thanked for their enthusiastic editorial assistance.

Program Leader
Global COE "Sport Sciences for the
Promotion of Active Life"
Waseda University

Kazuyuki Kanosue

Preface

The aim of this book is to present current views about physical activity and the benefits of physical activity in preventing and ameliorating various health conditions that are of worldwide concern. This book was developed as a compilation of the accomplishments of the 5-year Global COE (Center of Excellence) "Sport Sciences for the Promotion of Active Life" Program at the Faculty of Sport Sciences of Waseda University, Saitama, Japan. The first part establishes the research methodology and discusses the current status of physical activity. Topics covered include the prevalence of physical inactivity and highly sedentary behavior in different populations as well as strategies that can be adopted to promote physical activity. The second part focuses on the physiological effects of physical activity. Topics covered include physiological responses to exercise by the autonomic nervous system, the endocrine system, vascular functioning, postprandial blood glucose control, and inflammatory processes. The relationship between exercise and appetite is discussed, as is the influence of exercise on food intake and weight regulation. Additionally, the influence of exercise on protein regulation and posttranslational modifications is introduced. The final part discusses the role of physical activity in preventing lifestyle-related health issues and improving the quality of life, especially for the elderly. The contents should be of interest to anyone who is concerned with the human physiologic response to exercise and the promotion of healthy lifestyles, including sports and exercise science researchers as well as those involved with medicine, public health, physiology, nutrition, and elder care.

This book was written by distinguished researchers in this field all around the world as well as by dedicated faculty members and young graduate students and researchers of Waseda University who took part in the Global COE program. We feel extremely fortunate that this group of globally renowned researchers have contributed to this book. Without their involvement the book would not exist. We are especially grateful for the contribution of the following researchers and their students or collaborators: Dr. Stuart J.H. Biddle, Victoria University, Melbourne, Australia; Dr. Takemi Sugiyama, Swinburne University of Technology, Melbourne,

Australia; Dr. Neil King, Queensland University of Technology, Australia; Dr. Todd A. Hagobian, California Polytechnic State University, San Luis Obispo, U.S.A.; and Dr. Zsolt Radák, Department Chairman of the Sports Science Department, Semmelweis University, Hungary. Japanese contributors include Dr. Toshio Moritani, Kyoto University; Dr. Kiyoshi Sanada, Ritsumeikan University; Dr. Shizue Masuki, Shinshu University; and Drs. Yoshiko Ishimi and Shigeho Tanaka, National Institute of Health and Nutrition. To organize manuscripts from the divergent fields into one book that promotes exercise physiology was no easy task. However, now the book has become a reality.

Saitama, Japan — Satomi Oshima
Shanghai, China — Zhen-Bo Cao
Saitama, Japan — Koichiro Oka

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Part I
Current Status of Physical Activity and Sedentary Behavior Research

Chapter 1
Physical Activity Levels and Physical Activity Recommendations in Japan

Zhen-Bo Cao

Abstract The significant roles that physical activities play in improving the public's health and preventing and controlling chronic diseases are now well established, and physical activity has become recognized as a major health-enhancing behavior. This chapter provides an overview of the current recommendations for physical activity in Japan and briefly summarizes current information on the status of objectively-measured physical activity in Japanese adults. Physical Activity Guideline for Health Promotion 2013 established by the Ministry of Health, Labour and Welfare of Japan recommended that adults (20–64 years) should engage in at least 60 min of moderate- to-vigorous-intensity physical activity (MVPA) per day (equivalent to 23 metabolic equivalent (MET)-h per week of MVPA) while older adults (65 years and older) should engage in at least 40 min of physical activity at any intensity per day (equivalent to 10 MET-h per week of MVPA) to maintain health and fitness. According to direct studies of step-count equivalents to the current physical activity guidelines, 10,000 steps/day represented the optimal threshold for likelihood of accumulating at least 23 MET-h per week of MVPA. The National Health and Nutrition Survey of Japan (NHNS-J 2012) showed that the majority of Japanese adults perform inadequate amounts of exercise; only 36 % of men and 28 % of women aged 20 years or older regularly exercise for at least 30 min two or more times a week. Prefectures with relatively low levels of ambulatory physical activity are concentrated in the northeast and west. According to both population-based research and national surveys, Japanese adults take between 6,200 and 9,700 steps/day which is below the recommended 10,000 steps/day. Time trends for physical activity as measured by steps has shown that mean steps/day declined from peak values in 2003–2005 to values in 2008 by 550 steps/day among men and by 817 steps/day among women.

Keywords Physical activity guideline • Physical activity status • Metabolic equivalent • Pedometer • Accelerometer

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_1

1.1 Introduction

Physical activity refers to all movement produced by skeletal muscles that increases energy expenditure resulting in energy expenditure above the resting level (ACSM 2013). The association of regular physical activity with increased health benefits has been well documented. People who are physically inactive are at higher risk of several non-communicable diseases (NCDs) and mortality (Haskell et al. 2007; Lee et al. 2012). In 2009, the World Health Organization (WHO) highlighted the importance of physical inactivity and identified physical inactivity as the fourth leading risk factor for global mortality (WHO 2010). Lee et al. (2012) reported that 9.4 % of deaths from any cause are attributable to physical inactivity; physical inactivity causes 6 % of the burden of disease from coronary heart disease, 7 % of type 2 diabetes, 10 % of breast cancer, and 10 % of colon cancer worldwide. In Japan, physical inactivity is identified as the 3rd greatest risk factor of mortality due to NCDs, preceded only by smoking and hypertension (Ikeda et al. 2012).

During the last half of the twentieth century, physical activity became recognized as a major health-enhancing behavior. However, current global physical activity trends show that more than 30 % of adults are physically inactive (Hallal et al. 2012). Accordingly, promoting physical activity has become a public health priority worldwide (WHO 2010), and numerous physical activity guidelines have been published by government agencies, professional organizations, and associations to provide information and guidance on the types and amounts of physical activity sufficient to offer substantial health benefits (Haskell et al. 2007; WHO 2010; Tremblay et al. 2011; Department of Health, United Kingdom 2011; Australian Government Department of Health and Ageing 2013; Ministry of health and Japan 2013).

Because it is a health-enhancing behavior, it is essential to have a clear understanding of the current status of physical activity and of evaluation criteria that can be used to determine the prevalence of physical activity or inactivity. This chapter will provide an overview of the current recommendations for physical activity in Japan and briefly summarize current information on the status of physical activity, especially objectively-measured physical activity, in Japanese adults.

1.2 National Physical Activity Guidelines for Japan

Usually, physical activity guidelines are expressed in terms of time or energy expenditure (metabolic equivalent, MET). One MET is defined as the amount of oxygen consumed while sitting at rest and is equal to 3.5 ml/kg/min of O_2. A number of international and national health authorities have produced similar guidelines recommending that adults accumulate at least 150 min of weekly moderate- to vigorous-intensity physical activity (MVPA) in bouts of at least 10 min (Haskell et al. 2007; WHO 2010; Tremblay et al. 2011).

1.2.1 National Physical Activity Guidelines for the Japanese People

In 2000, the Ministry of Health, Labour and Welfare of Japan established "National Health Promotion in the twenty-first century (Health Japan 21)" which focused on primary prevention, extended healthy life expectancy, and enhanced quality of life, and set specific targets to serve as an index for national health/medical standards and to promote healthy living objectives based on assessments. As a legislative support for health promotion and disease prevention in citizens, with special reference to "Health Japan 21", the Health Promotion Law was formulated in 2002 and various programs for health promotion have been introduced since then. Health Japan 21 set a physical activity goal of adding 1,000 steps to one's current daily total. In spite of the efforts represented by "Health Japan 21", the average number of steps/day has failed to increase during the past 10 years. However, an increase in the percentage of people possessing awareness about the importance of physical activity and exercise was observed. The Ministry of Health, Labour and Welfare of Japan revised "Health Japan 21" in 2012 [Health Japan 21 (2nd edition)], setting a new national step count target of 8,500 and 9,000 steps/day for adult, non-elderly females and males, respectively (Table 1.1). Furthermore, the "Smart Life Project" was launched with the slogan "Firstly, physical activity and exercise. Secondly, diet and complete smoking cessation. Lastly, medication". This places further emphasis on the important role of physical activity and exercise in health promotion and the prevention of chronic disease.

In 2006, the Ministry of Health, Labour and Welfare of Japan revised its previous physical activity guidelines to provide information and guidance on the amount of physical activity recommended to maintain health and fitness and recommended that Japanese adults should engage in a minimum of 23 MET-h per week of MVPA, which is more than twice the volume of activity in the recommendation of 150 min/week of MVPA. The Ministry of Health, Labour and Welfare of Japan revised the physical activity guideline in 2013 (Physical Activity Guideline for Health

Table 1.1 National physical activity guidelines for Japan

	Physical activity guideline for health promotion 2013	Healthy Japan 21 (2nd edition)
Ages: 18–64	60 min/day of MVPA (equivalent to an activity lasting approx. 23 MET-h/week at an intensity of 3 METs), of which 60 min/week should be active exercise (equivalent to an exercise lasting approx. 4 MET-h/week at moderate- to vigorous-intensity)	9,000 steps/day for men
		8,500 steps/day for women
Ages: 65+	40 min/day of physical activity at any intensity (the equivalent to an activity lasting approx. 10 MET-h/week)	7,000 steps/day for men
		6,000 steps/day for women
Ages: 18+	Walking in 10 min increments once every day; 30 min of moderate- to vigorous-intensity exercise twice or more per week	

Promotion 2013), with slight changes to recommendations of aerobic activity for different age groups (Table 1.1). Significant additions included a physical activity recommendation that adults aged 65 years and older undertake at least 40 min of physical activity per day at any intensity (equivalent to an activity lasting approximately 10 MET-h/week). In addition, the Physical Activity Guideline for Health Promotion 2013 also recommends that Japanese people should walk in 10 min increments once a day and engage in 30 min of moderate- to vigorous-intensity exercise two or more times per week. Unlike other physical activity guidelines, the Physical Activity Guideline for Health Promotion 2013 does not refer to MVPA in bouts of at least 10 min. Recent studies found that the association of sporadic MVPA (activity in bouts of <10 min) with several cardiovascular risk factors and metabolic syndrome was similar to the association for bouts of MVPA (activity in bouts of ≥10 min) (Glazer et al. 2013; Clarke and Janssen 2014).

1.2.2 Steps/Day Translation of the National Physical Activity Guidelines for Japan

Steps/day is an increasingly popular indicator of physical activity volume. Tudor-Locke and Bassett (2004) proposed a graduated step index to classify pedometer-determined habitual physical activity in adults: (1) <5,000 steps/day ('sedentary'); (2) 5,000–7,499 steps/day ('low active'); (3) 7,500–9,999 steps/day ('somewhat active'); (4) 10,000–12,499 steps/day ('active'); and (5) ≥12,500 steps/day ('highly active'). Previous physical activity guidelines in Japan have encouraged adults to achieve 10,000 steps/day (an amount equivalent to at least 20–30 min of moderate-intensity walking or other exercise most days of the week). This steps/day recommendation can be traced to the 1960s when Japanese walking clubs embraced a pedometer manufacturer's (Yamasa Corporation, Tokyo, Japan) nickname for their product: manpo-kei (literally translated, "ten thousand steps meter") (Hatano 1993). Yoshiro Hatano (1993) reported that 10,000 steps/day is approximately equal to an energy expenditure of 300 kcal/day for an average middle-aged Japanese man. Health Japan 21 (2nd edition) set a national step count target of 8,500 and 9,000 steps/day for females and males, respectively (Ministry of Health Labour and Welfare of Japan 2013). Steps/day recommendations are also directed towards current physical activity guidelines, so as to provide further options for achieving those goals. Recent Japanese physical activity guidelines encourage at least 23 MET-h/week of MVPA and indicate that 23 MET-h/week of MVPA is approximately equivalent to 60 min of MVPA or 8,000–10,000 steps/day (Ministry of Health Labour and Welfare of Japan 2013). However, this step count recommendation is not evidence-based. It is based on an assumed daily level in Japanese adults of 2,000–4,000 steps/day of low intensity unconscious activity (<3 METs), with each additional 60 min of MVPA adding 6,000 steps. There is a need to adopt evidence-based steps/day recommendations to ensure harmony with existing physical activity guidelines.

Researchers have attempted to establish the association between current physical activity guidelines and steps/day recommendations and to translate physical activity recommendations into a pedometer-based step goal for the Japanese population. Murakami et al. (2012) performed a study to determine daily step counts corresponding to 23 MET-h/week of MVPA in a large sample of Japanese adults. They reported that 8,500–10,000 steps/day, a number similar to the recent Japanese physical activity recommendation of 8,000–10,000 steps/day, was indicated as the optimal daily step count for achieving 23 MET-h/week of MVPA. However, subjects in their study had high levels of physical activity (subjects walked an average of 9,600 steps/day, and approximately 48 % of subjects achieved ≥23 MET-h/week of MVPA) compared to the general population (men in the general population average 7,139 steps/day, and women average 6,257 steps/day). In addition, the activity monitor (Actimarker EW4800; Panasonic Electric Works, Japan) used in their study undercounted steps at slow walking speeds, and its production and sales have been suspended. Cao et al. (2014) measured steps and MVPA with the an accelerometer-based activity monitor (Kenz Lifecorder; Suzuken, Nagoya, Japan) in a large sample of Japanese adults ($n = 940$) and analyzed the data with a linear regression model and Receiver Operating Chacteristic (ROC) methodology to determine the optimal number of steps/day needed to meet the current physical activity guidelines. They reported that approximately 10,000–11,000 steps/day, corresponding to the "active" level of a graduated step index for healthy adults, are needed for Japanese adults to exert at least 23 MET-h/week of MVPA. They found that current recommended step counts of 8,000–10,000 steps/day in Japan are equivalent to only 12–19 MET-h/week, falling short of the recommended 23 MET-h/week of MVPA. They also found that the current recommended 8,000–10,000 steps/day actually overestimate the proportion of their subjects who are meeting physical activity guidelines (23 MET-h/week of MVPA) by 17–40 %. Such an overestimation could be dangerous because it could lead individuals to underestimate their own health risks. Thus, 10,000 steps/day is a reasonable daily step count for achieving 23 MET-h/week of MVPA for Japanese adults. Cao et al. (2014) also reported that subjects who accumulated 7,700–8,000 steps/day were highly likely to accumulate ≥150 min/week of MVPA.

1.3 Levels of Physical Activity in Japanese Adults

Subjective self-reporting questionnaires have served as the primary means to assess physical activity during the last 50 years (Haskell WL 2012). However, self-reported physical activity measures can suffer from vulnerability to social pressure and recall biases (Tudor-Locke et al. 2011), and perhaps their greatest limitation is their inability to accurately assess unstructured and incidental ambulatory physical activity, which may account for a greater proportion of total physical activity in sedentary people (Cao et al. 2014). Advances in electronic sensor technologies have prompted a shift away from self-reporting methods in favor of objective monitoring (e.g., accelerometers and pedometers) for physical activity assessment.

1.3.1 Research Findings of Physical Activity Levels

Several studies have objectively assessed physical activity in Japanese adults via pedometry or accelerometer (Nawata et al. 2006; Kishimoto et al. 2010; Inoue et al. 2011; Murakami et al. 2012; Oshima et al. 2012; Cao et al. 2014). The average daily step count in these studies has ranged from 6,500 to 9,669 steps/day. According to the findings in two of the six studies (Nawata et al. 2006; Oshima et al. 2012), Japanese adults would be categorized as 'low activity' on average (i.e., taking <7,500 steps/day); other studies (Kishimoto et al. 2010; Inoue et al. 2011; Murakami et al. 2012; Cao et al. 2014) would classify Japanese adults as 'somewhat active' (i.e., taking 7,500–9,669 steps/day).

Cao et al. (2014) identified the objectively-measured physical activity levels of 940 Japanese adults (480 women, 460 men) aged 20–69 years who took part in the Exercise and Physical Activity Reference and Guide for Health Promotion Study (EPARGHP) conducted in four Japanese cities (Tokyo, Chita-gun, Okayama, and Matsumoto) from 2007 to 2009. All participants wore an accelerometer (Lifecorder, SUZUKEN Co Ltd., Japan) for 7 consecutive days to record their step count data and the amount of their physical activity-related energy expenditure (PAEE) that was spent in MVPA. The results showed that minutes and PAEE spent in MVPA and number of steps averaged over 7 days were 28.2 min/day, 2.1 MET-h/day, and 8,776 steps/day, respectively, in this cohort. They reported that the amount spent in MVPA, including both minutes and PAEE, was higher in men (29.7 min/day; 15.2 MET-h/week) than in women (26.8 min/day; 13.9 MET-h/week), but no significant difference in step count per day existed between men (8,793) and women (8,760). In addition, 62.6 % of men and 54.8 % of women met the recommendation of 150 min/week of MVPA, while 18.5 % of men and 15.0 % of women met the current physical activity recommendation of 23 MET-h/week of MVPA.

Inoue et al. (2011) reported on accelerometer-measured (Lifecorder, SUZUKEN Co Ltd., Japan) step counts in Japanese adults. They analyzed data from 790 individuals (421 women, 369 men) aged 20 year or older who took part in a cross-sectional mail survey that was conducted in four Japanese cities (Koganei, Tsukuba, Shizuoka, and Kagoshima) from February 2007 to January 2008. They reported that men and women took an average of 8,763 steps/day and 8,242 steps/day, respectively, while 29.0 % of men and 27.8 % of women took 10,000 steps/day.

Kishimoto et al. (2010) studied the physical activity levels of 1,878 Japanese adults (1,111 women, 767 men) aged 20 years or older in Hisayama Town of Fukuoka Prefecture from June to August 2009. The study participants were asked to wear an accelerometer (Active Style Pro HJA-350IT, Omron Healthcare Co., Ltd, Japan) for more than 7 days to record their step count data. On average, adults in Hisayama Town took fewer than 6,500 steps/day; men took more steps/day (6,499) than women did (6,061). An age-related decline in steps/day was observed.

Murakami et al. (2012) investigated the objectively-measured physical activity levels of 1,837 Japanese adults (989 women, 848 men) aged 23–69 years who participated in the Nutrition and Exercise Intervention Study (NEXIS, $n=773$)

conducted in Tokyo and the Saku Control Obesity Program (SCOP, $n=1{,}064$) conducted in Saku, Nagano prefecture. All participants were instructed to wear an accelerometer (Actimarker EW4800, Panasonic Electric Works, Japan) for more than 14 days to record their step count data and the PAEE spent in MVPA. They found that adults took an average of 9,564 steps/day, 9,594 steps/day in men and 9,537 steps/day in women. They also reported that approximately 48 % of adults met the recommendation of ≥23 MET-h/week of MVPA; adults in NEXIS took more steps/day (10,517) than those in SCOP (8,871).

Oshima and colleagues (2012) reported objectively-measured physical activity levels of 455 Japanese adults (224 women, 231 men) living in Kyoto prefecture using a triaxial accelerometer (HJA-350IT, Active style Pro, Omron Healthcare Co., Ltd. Japan). Their findings showed that mean PAEE spent in MVPA and steps/day were 28.0 MET-h/week and 7,293 steps/day in men, 26.4 MET-h/week and 6,607 steps/day in women.

Nawata et al. (2006) examined the relationship between the number of steps measured by a Yamasa pedometer (BIG EM-285, Yamasa Co. Ltd., Tokyo, Japan) and body mass index (BMI) among 310 Japanese male workers aged 30–59 years in the Tokyo metropolitan area. They reported that male workers attained an average physical activity level (PAL) of 1.5 and took an average of 10,682 steps/day on working days and 7,135 steps/day on holidays.

Ishikawa-Takata et al. (2008) investigated total energy expenditure (TEE) and PAL determined by the doubly-labeled water (DLW) method in 150 healthy Japanese adults (76 women, 74 men) aged 20–59 years. They reported that the average TEE and PAL were 10.78 ± 1.67 MJ/day and 1.72 ± 0.22 for males, and 8.33 ± 1.31 MJ/ day and 1.72 ± 0.27 for females. The minimum of the average PAL values in sex and age groups was 1.58 ± 0.29 for females in their 20s and the maximum was 1.78 ± 0.20 for 30-year-old males. PAL for 20- to 29-year olds was lower than in the other age groups; however, there were no significant differences in TEE and PAL among age groups, sexes, and areas.

1.3.2 National Physical Activity Level Surveys

The National Health and Nutrition Survey of Japan (NHNS-J) has collected nationally-representative data on levels of physical activity measured by a spring-levered pedometer (AS-200, Yamasa Co. Ltd., Tokyo, Japan) and as reported using a questionnaire since 1989. According to the most recent NHNS-J (2012), the average steps/day taken by Japanese residents aged 20 years and older was less than 7,000 steps/day, with Japanese men taking 7,139 steps/day and Japanese women taking 6,257 steps/day. These values decreased steadily throughout the age groups until they averaged approximately 5,223 steps/day in men and 4,285 steps/day in women over 70 years of age (Fig. 1.1). This is far below the recommended 10,000 steps/day. Time trends for physical activity as measured by steps taken showed that mean steps/day declined by 550 steps/day among men and by 817 steps/day among

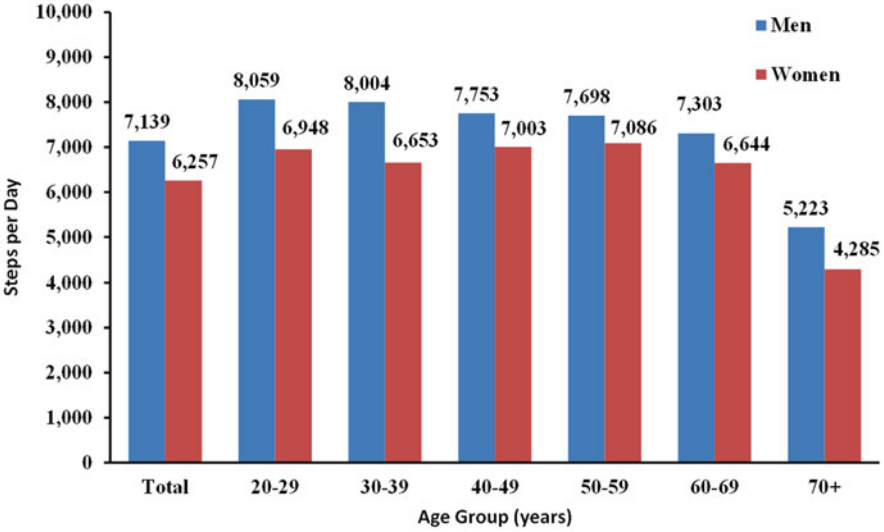

Fig. 1.1 Pedometer-determined physical activity levels (steps/day) in Japanese adults (aged 20 years or older, by gender/age categories) (The data were obtained from the National Health and Nutrition Survey Japan, 2012)

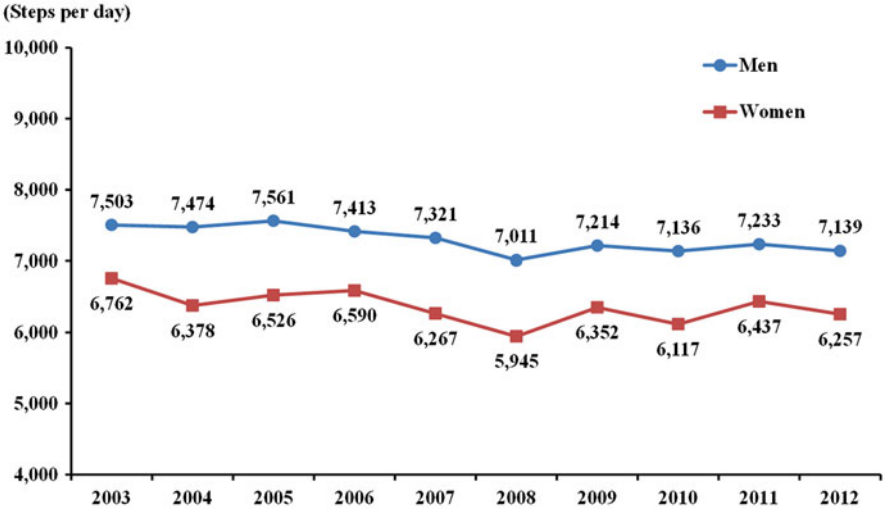

Fig. 1.2 Annual variation in the physical activity levels (steps/day) in Japanese adults (aged 20 years or older, by gender categories) (The data were obtained from the National Health and Nutrition Survey Japan, 2012)

women from peak values in 2003–2005 to values measured in 2008 (Fig. 1.2). These trends also show that the number of steps/day has remained relatively stable in Japan over the past 5 years (Fig. 1.2).

According to the NHNS-J 2012, the most active prefectures include Hyogo for men (Fig. 1.3) and Chiba for women (Fig. 1.4). The prefectures with relatively low levels of physical activity include a group of prefectures in the northeast and west, for example, Aomori, Akita, and Nagasaki (Figs. 1.3 and 1.4), in which adults fall into the "low-active" category (i.e., 5,000–7,500 steps/day) using the step index of Tudor-Locke and Bassett (2004).

Results of a subjective self-reported exercise-habits questionnaire presented in the NHNS-J (2012) also revealed that the majority of Japanese adults perform inadequate amounts of exercise, and the percentage of regular exercisers who exercise at least 2 days a week, 30 min or more each time, and have continued doing so for at least 1 year, was 36.1 % of men and 28.2 % of women aged 20 years or older. This is an approximately 1.3 % increase in men and 0.3 % decline in women from 2010 (Fig. 1.5). Even though the percentage of regular exercisers continues to rise, the exercise rate is still far less than the target rate of a 10 % increase established by Healthy Japan 21 (2nd edition). Unlike steps/day, there is an age-related increase in the percentage of regular exercisers, especially beyond 60 years of age (Fig. 1.6). Those who are over 60 years old are likely to have higher health awareness and more time than younger people heavily involved in work activities.

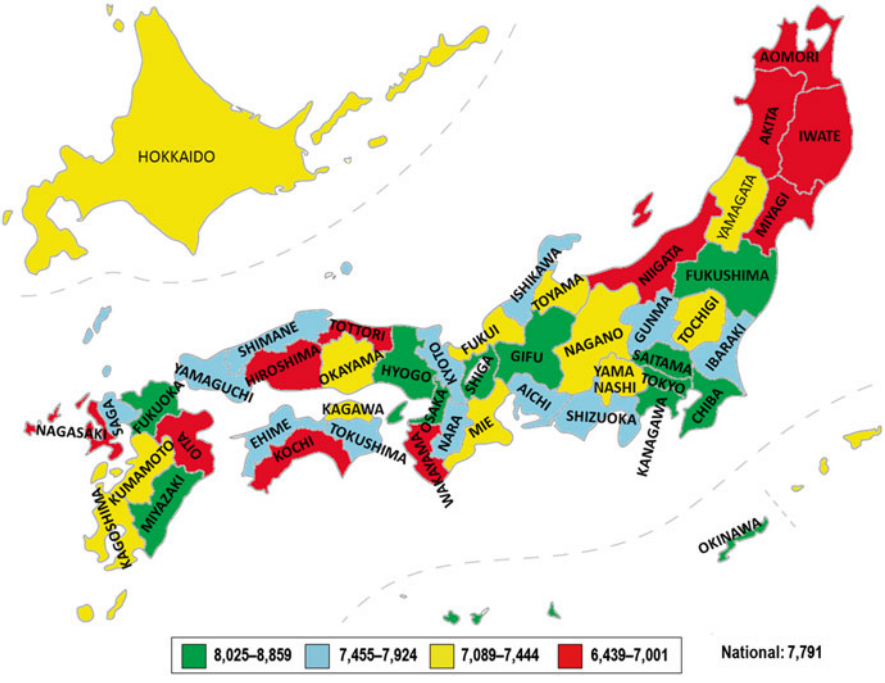

Fig. 1.3 Current physical activity levels (steps/day) of Japanese men (aged 20–64 yeras) in each prefecture (The data were obtained from the National Health and Nutrition Survey Japan, 2012)

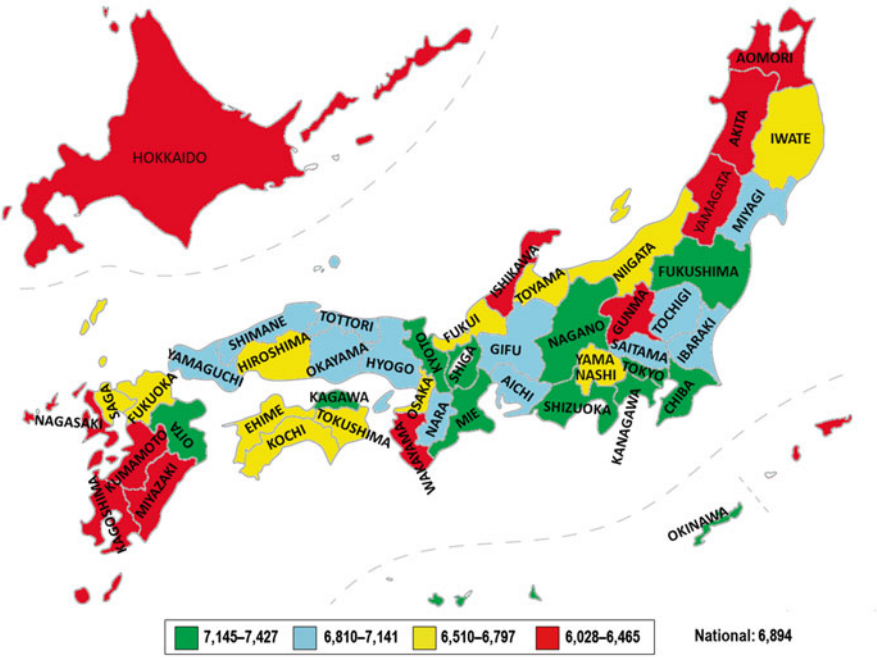

Fig. 1.4 Current physical activity levels (steps/day) of Japanese women (aged 20–64 years) in each prefecture (The data were obtained from the National Health and Nutrition Survey Japan, 2012)

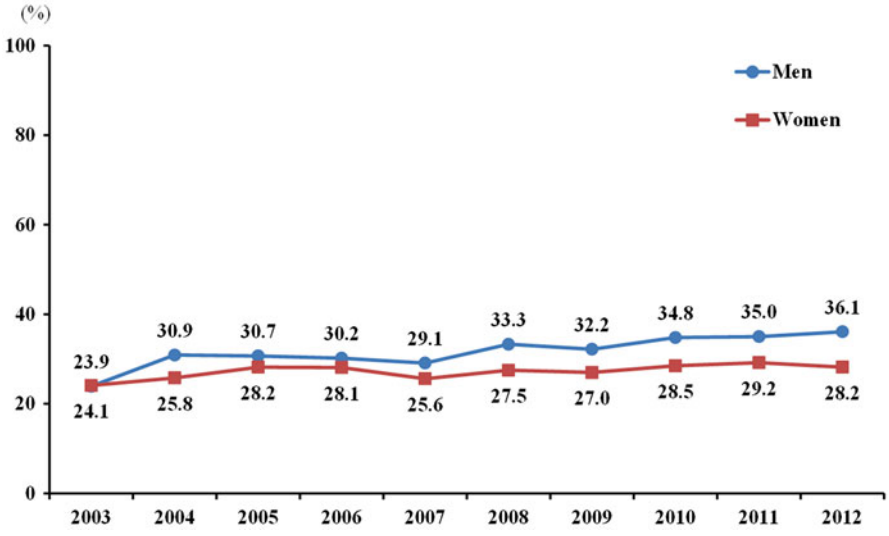

Fig. 1.5 Annual variation in the percentage of regular exercisers in Japan (aged 20 years or older, by gender categories) (The data were obtained from the National Health and Nutrition Survey Japan, 2012)

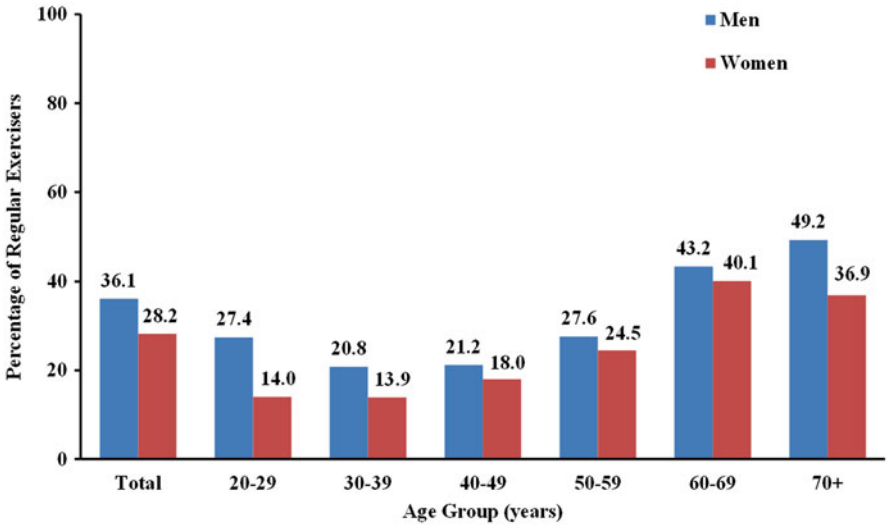

Fig. 1.6 The percentage of regular exercisers in Japan (aged 20 years or older, by gender/age categories) (The data were obtained from the National Health and Nutrition Survey Japan, 2012)

1.4 Summary

We have provided an overview of the current recommendations for physical activity in Japan and current information on the status of physical activity in Japanese adults. Some problems still exist in the physical activity guidelines and in the results of a survey on the status of physical activity in Japanese adults. The NHNS-J monitors levels of physical activity using spring-levered pedometers which are more affected by adiposity and less sensitive to low force accelerations (such as slow stepping) than accelerometer-based activity monitors, leading to underestimation of physical activity. Thus, caution should be applied when comparing NHNS-J with other cohort studies that use accelerometer-based activity monitors. The current recommendations of physical activity are mainly based on evidence in Western countries (e.g., Canada, the USA, Australia, and Europe) and on subjectively-assessed information about physical activity. Subjective measures of physical activity have been found to have several limitations, such as vulnerability to social pressure and recall bias. Technical development has offered some new, objective methods (e.g., accelerometers and pedometers) to monitor physical activity. Thus, further work is required to provide more evidence on the association between objectively-measured physical activity and health in Japan in order to improve the current physical activity guideline.

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Chapter 2
Population Strategy for Physical Activity Promotion in the Community

Takashi Arao

Abstract The importance of population-wide interventions for disease prevention and health promotion has been increasingly recognized among both researchers and health professionals. To stimulate and accelerate research on community-wide intervention for physical activity promotion, the strategies used for and scientific evidence of community-wide intervention program effectiveness were reviewed and the profile of our research, which is intended to promote physical activity in the whole population, of the community was described.

Keywords Population strategy • Physical activity • Community intervention • Health promotion

2.1 Introduction

The importance of health promotion has been growing in Japan as the society ages. In particular, the expectation of social benefits from reducing medical, health care, and long-term care expenses has been increasing, in addition to the personal benefits of disease prevention and health promotion. A number of recent reviews have suggested that a population strategy for community intervention seems to be the most successful way to achieve these public health benefits (Baker et al. 2011; Heath et al. 2012; Kahn et al. 2002; Sallis et al. 1998). This intervention strategy utilizes a multi-component approach, including educational, informational, political, and environmental aspects. Therefore, the population strategy for health promotion is complex; different sectors will be required to participate and collaborate if it is to be successful. In the past two decades, physical inactivity or a sedentary lifestyle has been recognised as a significant public health issue that needs to be addressed (Blair and Brodney 1999; Booth et al. 2012; Lancet 2012). Political approaches to promote physical activity at the national, regional, and local levels have been tried in Japan and in many other developed countries (Belanger and

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_2

Foster 2011; Kohl et al. 2012; Rutten et al. 2013). However, the effect of community-wide intervention upon physical activity has not been clearly identified.

In this chapter, to encourage research on community-wide intervention to promote physical activity, the strategies used for and scientific evidence underlying community-wide interventions are reviewed and our research, which was intended to promote physical activity at the level of the whole population of the community, is described.

2.2 Review of a Population Strategy for Physical Activity Promotion

It is well recognised that physical activity behaviors are affected by personal, social, and environmental factors (Baker et al. 2011; Kahn et al. 2002; Sallis et al. 1998). Therefore, a population strategy to promote increased physical activity should be implemented using diverse approaches, including community-based informational, behavioural, social, political, and environmental approaches. A model that incorporates comprehensive factors associated with the promotion of physical activity was used to implement an intervention and to asses the effectiveness of the population strategy.

2.2.1 Model of the Population Strategy for Physical Activity Promotion

Since the US Surgeon General's report on physical activity in 1996, public health agencies have focused on how to promote physical activity in communities, particularly in sedentary groups. In 1996, the Premier of New South Whales (NSW) in Australia established the NSW Physical Activity Task Force to develop a comprehensive strategic plan for promoting physical activity in NSW. This Task Force developed an integrated intersectoral strategic framework for physical activity promotion and a joint action plan for achieving the targets (New South Wales Physical Activity Task Force 1997). This framework for physical activity promotion consisted of three strategic goals:

- to increase safe and ongoing participation in physical activity, particularly among less active people;
- to develop quality infrastructure, opportunities, programs, and services to support participation;
- to realise the social, health, environmental, and economic benefits of participation.

These goals accompanied four strategic themes (program development and implementation, education and information, policy and guideline development, and monitoring and evaluation) and three focus areas (people, organizations, and environments).

Sallis et al. (1998) proposed a conceptual model for developing and implementing environmental and policy interventions to promote physical activity based on a ecological model of behavior. This model was adapted from the work of the NSW Physical Activity Task Force and emphasized the creation of supportive policies and environments. In this model, complex programs are planned and implemented by interdisciplinary teams such as advocacy or planning groups which include representatives of several agencies or organizations within a community. Sallis et al. (1998) also proposed identifying potential environmental and policy influences on four domains of active living: recreation, transportation, occupation, and household activities.

In 2011, the Cochrane Public Health Group published a review of community-wide interventions for increasing physical activity. In this review, (Baker et al. 2011) developed a logic model to evaluate the effects of community-wide interventions upon population levels of physical activity. The framework of this model divides actions into two phases, a community strategy development phase and an implementation phase. The community strategy development phase consists of community intervention actions to identify target groups, populations, the delivery setting, stakeholders, and intervention options. The implementation phase consists of actions taken to promote physical activity behavior change. Actions include mass media campaigns, community participation or educational events, advocacy, and environmental changes. In this model, variables that could be used to assess impacts and outcomes from short- to long-term were proposed. Short-term impacts include awareness of the physical activity message, improvements in physical activity-related knowledge, improvements to infrastructure that supports physical activity, legislation, and fiscal and policy changes. Medium-term impacts include improvement of physical-activity-related attitudes and beliefs, intention by the members of the targeted community to increase physical activity, increased levels of physical activity/decreased sedentary behaviour or physical inactivity, and improved access to physical activity opportunities. Long-term outcomes include reduced morbidity and mortality due to increased physical activity.

2.2.2 Intervention Components and Theoretical Approaches of a Population Strategy for Promoting Physical Activity

Baker et al. (2011) systematically reviewed community-wide intervention studies of physical activity promotion (Baker et al. 2011). They used a multi-level screening process to narrow the field to 25 papers for their review, and reported the intervention components used in the included studies. In almost all (22) of these studies,

partnerships were first built with local governments or non-governmental organizations. The next most common strategy was individual counseling by health professionals (19 studies), followed by communication strategies using posters, flyers, information booklets, web sites, and maps (18 studies), social marketing through local mass media such as television, radio, newspaper (15 studies), working with specific setting such as workplace, school, community (11 studies), and environmental change strategies (7 studies). Baker et al. (2011) also reported the theoretical perspectives used for developing the intervention strategies in the included studies. Six studies developed an intervention strategy using an ecological approach, 4 studies used a stage-of-change model for choosing the intervention framework, 4 studies based their approach on the social learning model, and 2 studies were founded on the community empowerment model. Other theoretical approaches such as behavioral change due to individual self efficacy, persuasive communications theory, and community organisation principles were used.

2.2.3 Effects of a Population Intervention Strategy for Promoting Physical Activity

Baker et al. (2011) reported the effects of a community-wide intervention strategy on physical activity at a population level as quantified by dichotomous and continuous numbers (Baker et al. 2011).

Eight studies out of 25 included in the review reported the change in physical activity using the proportion of participants who attained a level of recommended physical activity or who were physically inactive. Among these eight studies, only one study showed a significant regular physical activity increase in areas where an intervention took place (Jiang et al. 2008). Intervention in this study was conducted in multiple regions of Beijing, China, using strong regional government intervention strategies such as quarterly 'door-to-door' distribution of handouts, counselling by health practitioners, and identifying people with high risk factors through an intensive individual screening campaign. As a result, the percentage of active people in the intervention areas significantly increased as compared to non-intervention areas. The relative risk (RR) of the percentage of active people adjusted for the difference in baseline values was 1.20 (95 % CI:1.09 ~ 1.31). In other studies, however, no significant effects of community-wide intervention on physical activity at the population level were reported. Although no significant increase in the percentage of active people in the whole population was observed, the subgroup analysis of gender showed a significant increase in the percentage of active men (Lupton 2003) and women (Brown et al. 2006) at the population level. (Lupton et al. 2003) conducted a community intervention based on community empowerment for 6 years in a fishing area in Norway. Men in the intervention area showed an 8.6 % increase over pre-intervention baseline in moderate physical activity for a minimum of four hours per week during the last year of the study; no significant change (0.6 %) was

observed in the control (non-intervention) area. As a result, a significant difference ($P<0.047$) was observed between the two areas. Physical activity increases were also observed among women in both the intervention area (7.9 %) and the control area (2.1 %), but the difference in change between the two areas did not reach statistical significance. Brown et al. (2006), conversely, reported a significant positive effect of community intervention on the proportion of Australian women who achieved 150 min of total activity in at least five separate sessions during the week. In this study, however, a significant decrease of 6.4 % in active women was found in the control community, but no significant change (0.9 %) in the intervention community. The remaining five studies reported no significant effect of community intervention.

Four studies using the assessment criterion of "non-active person who does not meet physical activity recommendations" did not report any significant change in the percentage of inactive people in the whole community. A 3-year strategic multidisciplinary intervention study (Jenum et al. 2006) showed a significant decrease in the percentage of inactive people compared to the control area (unadjusted risk difference: 8.1 %, 95 % CI: 2.4–13.8 %). This difference, however, disappeared when results were adjusted for the difference in the baseline proportion of inactive people in intervention vs. control areas (adjusted RR: 0.8, 95 % CI: 0.59–1.08). Another three studies measuring leisure time physical inactivity reported no significant difference in the proportion of inactive people in the intervention area vs. the control area.

Using continuous physical activity data, 6 studies reported the results of community intervention (Table 2.1). De Cocker et al. (2007) implemented a multistrategy community-based intervention to promote physical activity to adults. The intervention program was constructed based on the social-ecological model including a local media campaign, website, environmental approaches, the sale and loan of pedometers, workplace projects, efforts focused on the elderly, and dissemination of information. De Cocker et al. (2007) assessed the effect of intervention by using pedometer-measured physical activity (steps/day) and by determining physical activity in different domains, including work, transportation, domestic and gardening, and leisure time in a typical week, using the long form of the International Physical Activity Questionnaire (IPAQ) submitted by randomly-selected subjects. After 1 year of intervention, average daily step counts increased significantly in both men and women and in every age group by 896 steps/day (95 % CI:599–1192) in the intervention area, but decreased by 135 steps/day in the comparison area. As a result, significant differences in interaction between time and area and adjusted mean difference were observed. The same significant differences were found in reported time spent in walking, moderate physical activity, leisure-time physical activity, and work-related physical activity between the intervention and comparison areas. The within-group change in the intervention area was bigger (1,586 steps/day) in the subjects who were not already at the 10,000 steps/day target at baseline than in all respondents. These results revealed that the proportion of subjects reaching the 10,000 steps/day target increased by 8 % from the baseline value (42 %) to values measured at the end of the intervention (50 %) in the intervention area.

Table 2.1 Effects of population intervention for physical activity promotion (continuous outcomes)

Study	Measure	Subjects	Post-baseline mean difference	Adjusted mean difference[#]	Adjusted % change relative to the control mean	Intervention period	Assessment samples
Wendel-Vos et al. (2009)	Total Leisure time PA (h/week)	Men	−0.4	−0.6	−2.06	5 years	Cohort
		Women	2.2	2.1[a]	14.01[a]		
	Walking time (h/week)	Men	1.1	0.9	15.94		
		Women	2.0	2.2[a]	29.41[a]		
De Cocker et al. (2007)	Pedometer-determined PA (steps/day)	Adults (25–75 years)	Control: −135	10.0[c]	10.80[c]	1 year	Cohort
			Intervention: 896				
	Leisure time PA (min/week)		Control: −47	32.0[a]	25.60[a]		
			Intervention: −15				
	Walking time (min/week)		Control: −30	47.0[c]	17.34[c]		
			Intervention: 17				
Brownson et al. (2004)	7 day total walking (mean min/week)	Adults (≥18 years)	NA	−1.4	−1.38	2 years	Cross-sectional
	7 day total walking for exercise (mean min/week)		NA	−5.6	−17.61		
Brownson et al. (2005)	Walking (mean min/week)	Adults (≥18 years)	NA	5.2	4.75	1 year	Cross-sectional
Kloek et al. (2006)	METs/week	Deprived adults (18–65 years)	NA	−241.0	−3.54	2 years	Cohort
Sarrafzadegan et al. (2009)	Total daily PA (MET-min/week)	Intervention (38.6 ± 14.7 years) Control (39.1 ± 15.1 years)	Control: −114	46[a]	9.09[a]	3 years	Cross-sectional
			Intervention: −68				
	Leisure time PA (MET-min/week)		Control: 22	13[b]	12.26[b]		
			Intervention: 35				

Table is partly adopted from the review of Baker et al. (2011)
PA physical activity, *MET* metabolic equivalent
#: Adjusted for age, gender, race, and educational attainment. [a]: $P<0.05$, [b]: $P<0.01$, [c]: $P<0.001$

Wendel-Vos et al. (2009) conducted a 5-year lifestyle modification community intervention and investigated the net effects of the intervention using cohort samples. Men did not show a significant within-group or between-group change in any physical activity behaviors. Among the women, however, the mean changes in total time spent on leisure-time physical activity (2.1 h/week) and walking (2.2 h/week), adjusted for age, educational level, and the mean of baseline and follow-up, were significantly different between intervention and control areas. Additionally, among those with a low educational level, significant differences in adjusted mean change in walking (2.3 h/week) and bicycling (0.6 h/week) were observed between the two areas. Based on these findings, (Wendel-Vos et al. 2009) concluded that the community intervention program in this study was effective for promoting daily physical activity among women and people with a low educational level. In this study significant within-group decreases in physical activity behaviors at the end of the follow-up period were observed in the control area, but no significant change was seen in the intervention area. Therefore, we cannot conclude that the community intervention program implemented in this study effectively promotes daily physical activity in women and in people with a low educational level.

Similar results to the abovementioned study were reported by (Sarrafzadegan et al. 2009). They examined the effects of a comprehensive, integrated community-based lifestyle intervention on diet, physical activity, and smoking in Iranian communities. Along with physical activity, they assessed energy expenditure expressed as metabolic equivalent of task (MET) minutes per week for total daily physical activity and leisure time physical activity. MET was calculated based on data which were obtained through an oral questionnaire that asked about four activity domains: physical activities related to job, transportation, housework and house maintenance, and leisure time. Energy expenditure for total daily physical activities showed a significant decreasing trend over 3 years in both intervention and control areas, but the mean drop from baseline was significantly ($P<0.05$) smaller in the intervention areas (−68 MET min/ week) than in the control area (−114 MET min/ week). On the other hand, leisure time physical activities showed a significant increasing trend over 3 years in both areas, but the mean increase from the baseline was significantly ($P<0.01$) larger in the intervention area (35 MET-min/week) than in the control area (22 MET-min/week).

However, Brownson et al. (2004, 2005), and Kloek et al. (2006) did not report any significant increase in walking time or total energy expenditure in physical activity in a study of the effects of an integrated community-based intervention for physical activity promotion in different communities.

The abovementioned results of a systematic review suggest that the efficacy of collective strategic community intervention based on different approaches to promote physical activity remains unclear, due to large differences in research results. The main reasons for such large discrepancies in research results seem to be differences in the strength of intervention, strategy and method of intervention, evaluation indicators and experimental design, and target area. Also, different potential bias, such as differences in age and sex, socio-economical status, race and ethnicity of the targeted subjects in the research might affect the results.

2.3 Our Challenge to Promote Physical Activity in the Community

In this section, the profile of our projected research for promoting physical activity in an entire local community will be described. Our research started in 2013 and will continue for 5 years.

2.3.1 Objectives

The objectives of this research are to evaluate the effectiveness of population intervention on promoting physical activity (primary outcome) and affecting medical expenses and long-term care cost (secondary outcomes) in an entire community.

2.3.2 Method

We designed a cluster non-randomized control trial in the intervention area (Nagaizumi, Sizuoka, Japan) and control area (Oiso, Kanagawa, Japan). These two areas are separated by about 40 km and have similar populations of 32,000. A baseline survey using the IPAQ-short form (SF) was conducted in both areas from April to May 2013. The subjects of the survey were 3,200 randomly-chosen residents aged 30–74 years in each area who responded to the questionnaire in the mail. Measurement items are physical activity, intermediate factors affecting physical activity, information about amount of physical activity, opportunity to perform physical activity and exercise, the perceived physical activity environment (convenience, safety, etc.), motivation for doing physical activity, and the characteristics of the subjects (sex, age, educational level). The health-care and long-term-care expenses are recorded annually by the local government in each area.

2.3.3 Intervention Program

The intervention program in this study was constructed based on an ecological model (Sallis et al. 1998) and a logic framework (Kahn et al. 2002). The logic framework showing the intervention strategy and assessment measures used in our study is shown in Fig. 2.1. The main strategies of the intervention are political, environmental, social, and informational approaches to promoting physical activity in the whole population. The political approaches consist of creating a 5-year health-promotion community plan with partnership between citizens and local government, and providing Community Healthy Mileage which is an incentive program

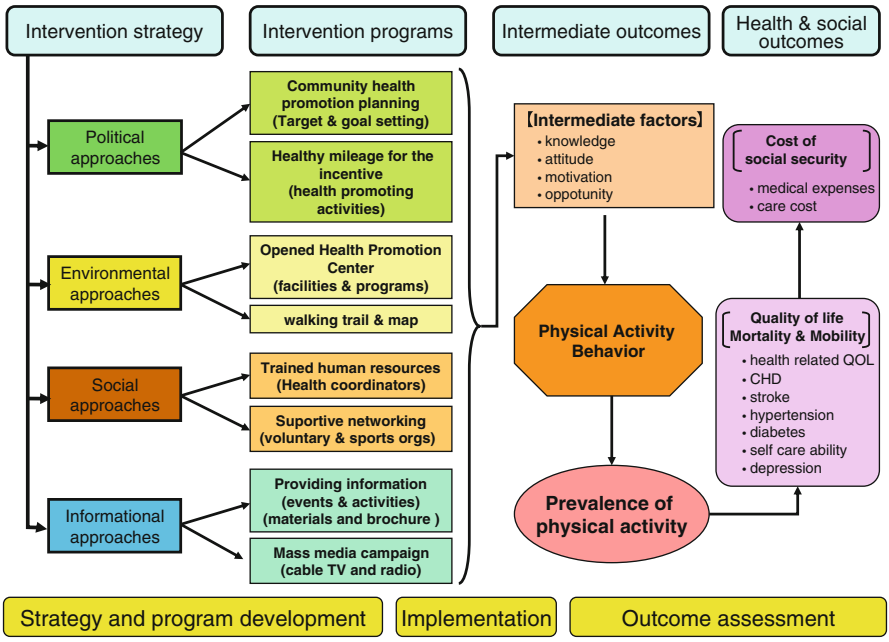

Fig. 2.1 Logic framework showing the intervention strategies and assessment measures in our study. *QOL* quality of life, *CHD* coronary heart disease

that motivates people to increase physical activity and health behaviors with family, friends, neighbors, co-workers, community group members, etc. The environmental approaches include constructing a new Health Promotion Center consisting of various sports and exercise facilities, including a walking trail and health care and health promotion offices. In this Center, various sports and exercise programs are provided to the users; classrooms are available for health promotion lectures which are planned and implemented by the citizens. Supportive social approaches consist of health coördinators who are trained and work as volunteers to promote physical activity in the community. A support network will be constructed, consisting of various health-promoting volunteers and community sports organizations. Informational approaches will include health-promotion events and activities, and materials and brochures advertising Community Healthy Mileage program are distributed to every household. A mass media campaign via cable TV and radio is being carried out, and a walking map has been created and is distributed by volunteers.

Data from a baseline survey of 842 subjects in the intervention area and 863 subjects in the control area were analyzed to examine the equity of the baseline values between the study communities. The results showed that Nagaizumi offered more opportunities for physical activity than did Oiso. Fewer people in Nagaizumi, however, met the guideline values for physical activity than did people in Oiso. A cross-sectional assessment survey is planned for 1 year, 3 years, and 5 years after the baseline survey.

The evidence from our research on the effects of community intervention for promoting physical activity in a population will contribute to making local and national government policies that promote physical activity.

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Chapter 3
Promotion of Strength Training

Yoshio Nakamura and Kazuhiro Harada

Abstract The health benefits of strength training have been well established by numerous intervention studies. Based on such studies, current physical activity guidelines recommend strength training to improve public health. However, previous reviews have not focused on the behavioral aspects of strength training. Thus, this chapter briefly reviews research trends in the prevalence and correlates of strength training, and interventions to promote strength-training behavior. Previous studies have reported 3.9–21 % of the populations in each country engage in strength-training behavior. Recent studies have begun to reveal the environmental correlates of strength-training behavior (e.g., access to strength-training facilities), as well as socio-demographic and psychosocial correlates (e.g., age, perceived health benefits, and barriers to participation). Although a community-wide campaign has been reported, intervention studies to promote strength-training behavior are limited. Further well-designed observational studies examining correlates of strength-training behavior and large-scale intervention trials are warranted to confirm effective strategies to promote strength-training behavior.

Keywords Strength training • Behavioral research • Behavior mechanisms • Environment design • Health promotion

3.1 Introduction

An increasing number of studies have shown that strength training (generally described as exercises designed to enhance muscle strength and endurance) provides numerous health benefits. Based on such studies, meta-analyses have revealed that strength training is an effective way to reduce blood pressure (Cornelissen et al.

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_3

2011), lipids and lipoproteins (Kelley and Kelley 2009), metabolic syndrome (Strasser et al. 2010), postmenopausal bone loss (James and Carroll 2006), and physical disability (Liu and Latham 2011). Thus, in addition to aerobic activities, current physical activity guidelines and national policies recommend strength training for public health. Table 3.1 presents a summary of strength-training recommendations. Each country represented in this table (the United States [US Department of Health and Human Services 2008, 2009], Australia [Brown et al. 2005], Canada [Public Health Agency of Canada 1998], the United Kingdom [O'Donovan et al. 2010]), and the World Health Organization (2010) recommend strength training (at least twice a week) to improve the health of populations around the globe.

While the health benefits of strength training are well established and strength training is recommended for public health, strategies that can be used to successfully promote strength training have not been clarified in previous studies. To elucidate them, behavioral epidemiology is a useful framework (Sallis et al. 2000). A behavioral epidemiology framework (Sallis et al. 2000) discriminates health promotion studies into five phases. Phase 1 establishes links between behaviors and health outcomes, phase 2 develops measures of the behavior and examines prevalence of the behavior, phase 3 identifies correlates of the behavior, phase 4 develops and evaluates interventions to change the behavior, and phase 5 translates research into practice. Following this framework (Sallis et al. 2000), some review articles

Table 3.1 Strength training recommendations for public health

Name and year	Title	Target population
Public Health Agency of Canada (1998)	Handbook for Canada's Physical Activity Guide to Healthy Active Living & Handbook to the Guide for Older adults	Adults (<65 years) and older adults (≥65 years)
Australian Government Department of Health and Aging (Brown et al. 2005)	Choose Health: Be Active	Older adults
American College of Sport Medicine/American Heart Association (Haskell et al. 2007 and Nelson et al. 2007)	Physical Activity and Public Health: Updated Recommendation	Adults and older adults
US Department of Health and Human Services (2008)	2008 Physical Activity Guide for Americans	Adults and older adults
American College of Sport Medicine (Chodzko-Zajko et al. 2009)	Exercise and Physical Activity for Older Adults: Position Stand	Older adults
US Department of Health and Human Services (2009)	Healthy People 2020	Adults
British Association of Sport and Exercise Sciences (O'Donovan et al. 2010)	The ABCs of Physical Activity for Health	Adults and older adults
World Health Organization (2010)	Global Recommendations on Physical Activity for Health	Adults and older adults

(Cornelissen et al. 2011; Kelley and Kelley 2009; Strasser et al. 2010; James and Carroll 2006; Liu and Latham 2011) are now available describing phase 1 studies of strength training (i.e., the relationships between strength-training behavior and health outcomes). However, no previous reviews have described the trends in the studies of prevalence, correlates, and intervention strategies of strength-training behavior, which correspond to phases 2, 3, and 4. Review articles have been published for walking behaviors and bicycling (Ogilvie et al. 2007; Panter and Jones 2010; Saelens et al. 2003; Saelens and Handy 2008; Yang et al. 2010); such reviews will be essential to guide research about and the promotion of healthy strength training.

Thus, this section briefly reviews research trends in (1) prevalence of strength-training behavior, (2) correlates of strength-training behavior, and (3) interventions to promote strength-training behavior.

3.2 Prevalence of Strength-Training Behavior

Table 3.2 presents the prevalence of strength-training behavior reported in previous studies. As shown in Table 3.2, the definitions of strength training and target populations varied by studies. However, previous studies have reported the prevalence of strength-training behavior as being from 3.9 % to 21 % of the populations in each country (Chevan 2008; Galuska et al. 2002; Harada et al. 2008a, b; Humphries et al. 2010; Kruger et al. 2004, 2006; Morrow et al. 2011). Healthy People 2020, a health promotion plan in the United States, set a goal of elevating the percentage of those who perform regular strength training to 30 % of the entire population by 2020 (US Department of Health and Human Services 2009).

We reported the prevalence of strength-training behavior in Japan in 2 studies (Harada et al. 2008a, b). The first study (Harada et al. 2008a) was a secondary analysis of the 2006 SSF National Sports-Life Survey (Sasakawa Sport Foundation 2006). This survey is a high-quality cross-sectional survey assessing participation in sports, exercises, and physical activities in Japan. The analysis revealed that the prevalence of strength training on 2 days or more per week was 3.9 %, and that the prevalence was lower in older individuals (2.5 % for those 60–69 years old, 0.6 % for those over 70 years old). However, the 2006 SSF National Sports-Life Survey did not give a specific definition for strength training.

We defined strength training as all exercises intended to enhance muscle strength and endurance, and conducted a web-based questionnaire survey of 5,177 people (Harada et al. 2008b). We found that 14.4 % of respondents engaged in strength training on 2 or more days per week, while 39.5 % of them did not intend to engage in any strength training at all. Furthermore, Harada et al. (2008b) also revealed that the most common types of strength training were done at home (74.3 %), used the participant's own body weight (60.4 %), and were done without special lectures (85.1 %).

Table 3.2 Prevalence of strength training

Study	Target population	Term and definition	Prevalence
Chevan (2008)	American adults (≥18 years, *n* = 29,783)	Strength training: physical activities specifically designed to strengthen muscles, such as lifting weights or doing calisthenics	21 % (≥2 days/week)
Galuska et al. (2002)	American adults (≥18 years, *n* = 16,697)	Resistance training: lifting weight	13.4 % (≥1 day/month) 8.7 % (≥2 days/week)
Harada et al. (2008a)	Japanese Adults (≥20 years, *n* = 1,867)	Strength training: no definitions	3.9 % (≥2 days/week)
Harada et al. (2008b)	Japanese Adults (≥20 years, *n* = 5,177)	Strength training: all exercises intended for enhancing muscle strength and endurance	14.4 % (≥2 days/week)
Humphries et al. (2010)	Australian adults (≥18 years, *n* = 1,230)	Resistance training: gym-based resistance training	13.7 % (≥1 day/week)
Kruger et al. (2004)	American older adults (≥65 years, *n* = 5,537)	Strength training: physical activities specifically designed to strengthen muscles, such as lifting weights or doing calisthenics	11 % (≥2 days/week)
Kruger et al. (2006)	American adults (≥18 years, *n* = 30,801 to 33,326)	Strength training: physical activities specifically designed to strengthen muscles, such as lifting weights or doing calisthenics	17.7–19.6 % (≥2 days/week)
Morrow et al. (2011)	American women adults (unavailable for age range, *n* = 918)	Muscle strengthening activity: activities to increase muscle strength or tone, such as lifting weights, using weight machines, using exercise bands or doing pull-ups or sit-ups	15 % (≥2 days/week)

3.3 Correlates of Strength-Training Behavior

3.3.1 Socio-demographic Correlates of Strength-Training Behavior

Information about socio-demographic correlates of physical activity is necessary to enable us to decide who should be targeted for promotions of physical activity. Table 3.3 presents socio-demographic correlates reported in previous studies (Chevan 2008; Galuska et al. 2002; Harada et al. 2008a, b; Humphries et al. 2010; Kruger et al. 2004, 2006). Overall, 11 factors are reported as socio-demographic correlates of strength-training behavior; gender, age, educational level, self-rated

Table 3.3 Socio-demographic correlates of strength training

Factor	Significant association	Non-significant association
Gender (male)	Chevan (2008), Galuska et al. (2002), Harada et al. (2008a, b), Kruger et al. (2004, 2006)	Humphries et al. (2010)
Age (younger)	Chevan (2008), Galuska et al. (2002), Harada et al. (2008a, b), Humphries et al. (2010), Kruger et al. (2006)	Kruger et al. (2004)
Educational level (high)	Chevan (2008), Galuska et al. (2002), Harada et al. (2008b), Kruger et al. (2006)	Humphries et al. (2010)
Self-rated health (good)	Galuska et al. (2002), Humphries et al. (2010), Kruger et al. (2004)	Harada et al. (2008a)
Marital status (single)	Chevan (2008), Harada et al. (2008b)	Harada et al. (2008a), Kruger et al. (2004)
Body mass index (normal)	Galuska et al. (2002), Kruger et al. (2006)	Harada et al. (2008b)
Ethnicity (white)	Kruger et al. (2004, 2006)	Chevan (2008), Galuska et al. (2002)
Income level (high)	Harada et al. (2008b)	Humphries et al. (2010)
Full-time job (yes)	Harada et al. (2008b)	
Smoking status (no)	Harada et al. (2008a)	
Self-rated fitness (good)	Harada et al. (2008a)	
Sedentary Behavior		Harada et al. (2008b)

health, marital status, body mass index, ethnicity, income level, full-time job, smoking status, and self-rated fitness. Among them, gender, age, and educational level have been repeatedly indicated as the correlates of strength training in previous studies.

In Japan, our two studies (Harada et al. 2008a, b) examined socio-demographic correlates of strength-training behavior. Harada et al. (2008a) revealed that gender, age, smoking status, and self-rated fitness are associated with strength training, but self-rated health and marital status are not significantly associated with strength training in the Japanese population. Furthermore, Harada et al. (2008a) indicated that age is the socio-demographic correlate most strongly associated with strength training. Thus, Harada et al. (2008a) suggest that strength-training promotions targeting older people might be needed.

In Harada et al. (2008b), six factors (gender, age, educational level, marital status, income level, and full-time job) were identified as socio-demographic correlates of strength training behavior. Although the influence of marital status differs from that found in Harada et al. (2008a), Harada et al. (2008b) also suggested the importance of strength-training promotions targeting older people.

3.3.2 *Psychosocial Correlates of Strength-Training Behavior*

The identification of modifiable factors associated with physical activity is recognized as an essential phase in the development of effective promotion strategies. Numerous studies have examined psychosocial correlates of physical activity. Furthermore, as shown in Table 3.4, recent studies have begun to reveal psychosocial factors associated with strength-training behavior. Six studies showed that the self-efficacy/perceived behavioral control (one's beliefs about their capabilities to maintain strength-training behavior) is positively correlated with strength-training behavior (Bopp et al. 2006; Bryan and Rocheleau 2002; Cardinal and Kosma 2004;

Table 3.4 Psychosocial correlates of strength training

Factor	Significant association	Non-significant association
Self-efficacy/perceived behavioral control	Bopp et al. (2006), Bryan and Rocheleau (2002), Cardinal and Kosma (2004), Cardinal et al. (2006), Harada et al. (2008b), Rhodes et al. (2007)	Dean et al. (2007), Plotnikoff et al. (2008)
Behavioral intention	Bryan and Rocheleau (2002), Dean et al. (2007), Rhodes et al. (2007)	Plotnikoff et al. (2008)
Perceived benefits/pros	Bopp et al. (2004), Cardinal et al. (2006), Harada et al. (2014b)	
Perceived barriers/cons	Bopp et al. (2004), Cardinal et al. (2006), Harada et al. (2014b)	
Attitude		Dean et al. (2007), Plotnikoff et al. (2008), Rhodes et al. (2007)
Subjective norm		Dean et al. (2007), Plotnikoff et al. (2008), Rhodes et al. (2007)
Social support	Bopp et al. (2004)	Bopp et al. (2006)
Enjoyment	Bopp et al. (2006)	
Process of change	Cardinal and Kosma (2004)	
Information from interpersonal channels (friends, health care provider)	Harada et al. (in press)	
Information from the Internet	Harada et al. (in press)	
Information from print media (book)	Harada et al. (in press)	
Information from mass media		Harada et al. (in press)
Depression		Bopp et al. (2004)
Perceived stress		Bopp et al. (2004)
Personality (extroversion)		Bryan and Rocheleau (2002)

Cardinal et al. 2006; Harada et al. 2008b; Rhodes et al. 2007). Moreover, behavioral intention (Bryan and Rocheleau 2002; Dean et al. 2007; Rhodes et al. 2007), social support (Bopp et al. 2004), enjoyment (Bopp et al. 2006), and the processes of change (a concept of the transtheoretical model [Prochaska and DiClemente 1983]: Cardinal and Kosma 2004) are reported as psychosocial correlates of strength-training behavior.

We have reported the results of two studies about psychosocial correlates of strength-training behavior (Harada et al. 2014b; Harada et al. in press). Although previous studies have examined associations between perceived benefits of and barriers to strength training (Bopp et al. 2004; Cardinal et al. 2006), they have not focused on using these associations to create strength-training recommendations for older people. Thus, Harada et al. (2014b) developed perceived health benefit-and-barrier scales based on current strength-training recommendations for older people, and examined associations of perceived health benefits and barriers to strength training with the stages of change for strength-training behavior (a concept of the transtheoretical model [Prochaska and DiClemente 1983]: precontemplation, contemplation, preparation, action, and maintenance stages) among older Japanese people. A cross-sectional questionnaire was distributed through the mail to 2,092 individuals aged 60–74 years living in Tokorozawa city, and 1,244 of them returned questionnaires. The results, after adjusting for demographic variables, showed that both the perceived health-benefit and the barrier scores were significantly associated with the stages of change for strength-training behavior described above. Based on these findings, Harada et al. (2014b) suggest that information about the health benefits of strength training for older adults and about the recommended type of strength training for this population might help to develop strategies to promote strength training among older people.

Our second study (Harada et al. in submission) explored what makes a communication channel an effective way to provide strength-training information. To develop successful communication strategies promoting strength-training behavior among older people, identification of effective communication channels for providing information is necessary. However, no studies have examined associations of information sources with strength-training behavior. Thus Harada et al. (in press) examined which information sources about strength training are associated with strength-training behavior among older Japanese adults. In this study, we analyzed the same data as Harada et al. (2014b). The results showed that strength-training information from healthcare providers, friends, books, and the Internet were positively correlated with regular strength-training behavior. This result suggests that providing strength-training information from these sources would be an effective way to promote strength-training behaviors among older adults. In contrast, this study did not find significant relationships between information from mass media and strength-training behavior. According to our result, providing information by mass media is an ineffective way to change strength-training behavior at the population level.

3.3.3 *Environmental Correlates of Strength-Training Behavior*

In terms of an ecological model (Sallis et al. 2006), environmental attributes, which can have long-term effects on large populations, represent an emerging area of research into physical activity and public health. However, except for our studies, only two studies (Bopp et al. 2006; Sallis et al. 1997) have examined environmental correlates of strength-training behavior, and Bopp et al. (2006) did not find significant associations (Table 3.5). A further examination of the relationship between strength-training behavior and environmental factors would provide information useful for exploring the effectiveness of environmental intervention to promote strength training.

Therefore, we investigated the relationship between strength-training behavior and the perceived environment in older Japanese people aged 65–75 (Harada et al. 2011). An Internet-based survey was conducted of 293 older adults. In this survey, we measured two types of environmental factors: environmental factors for general physical activity (11 items, the international physical activity questionnaire environmental module: Inoue et al. 2009), and environmental factors specific to strength training (access to facilities for strength training and home equipment for strength training). In results, regarding the specific environmental factors, both home equipment for strength training and access to facilities for strength training were positively correlated with strength-training behavior. In contrast, only 1 of the 11 general environmental factors was significantly correlated with strength-training behavior. Thus, these results indicate that specific environmental factors will be associated with strength training behavior more strongly than general environmental factors.

Table 3.5 Environmental correlates of strength training

Factor	Significant association	Non-significant association
Home equipment	Harada et al. (2011), Sallis et al. (1997)	
Perceived access to strength-training facilities	Harada et al. (2011, 2014a)	
Seeing active people	Harada et al. (2011)	
Objective access to strength-training facilities		Harada et al. (2014a)
Perceived access to exercise/ recreational facilities		Sallis et al. (1997), Harada et al. (2011)
Environmental barriers		Bopp et al. (2006)
Residential density		Harada et al. (2011)
Presence of sidewalks/bike lanes		Harada et al. (2011)
Perceived access to public transport		Harada et al. (2011)
Perceived access to shops		Harada et al. (2011)
Neighborhood safety (crime, traffic)		Harada et al. (2011)
Aesthetics		Harada et al. (2011)
Household motor vehicles		Harada et al. (2011)

Next, we examined the associations of perceived and objectively-measured access to strength-training facilities with strength-training behavior (Harada et al. 2014a). Because the importance of employing objective assessments (e.g., the use of a geographic information system; see below) has been highlighted in other physical activity studies, employing both self-reported and objective assessments of environmental factors is appropriate if we aim to better understand environmental influences on strength-training behavior. A cross-sectional questionnaire survey targeted 3,000 Japanese adults and 1,051 answered it. Objective access to strength-training facilities (number of facilities within a radius of 1,500 m from the respondent's home) was calculated for each respondent using a geographic information system. Our results showed that perceived good access to exercise facilities, but not objective access to facilities, was significantly associated with strength-training behavior. Thus, Harada et al. (2014a) concluded that perceived access to strength-training facilities may be a stronger predictor of strength-training behavior than objective access to the facilities.

3.4 Interventions to Promote Strength-Training Behavior

Table 3.6 presents summaries of intervention studies designed to promote strength-training behavior. Compared with observational studies (i.e., studies about prevalence and correlates of strength-training behavior), a fewer number of intervention studies have been conducted.

Ferherman et al. (2011) and Shirazi et al. (2007) developed intervention programs based on the transtheoretical model (Prochaska and DiClemente 1983). This model is a commonly-used psychological model of health behaviors and consists of four concepts: stages of change, processes of change, decisional balance, and self-efficacy. Intervention programs were provided to women volunteers recruited from local centers. Ferherman et al. (2011) and Shirazi et al. (2007) showed that intervention groups significantly improved psychological variables (e.g., stages of change and decisional balance) and muscle strength.

Katula et al. (2006) reported the effects of a group-based counseling program. The program was developed based on the empowerment theory (Zimmerman 1995) and the self-efficacy theory (Bandura 1997). Each group consisted of two participants (total $n = 22$ at baseline), and they were educated to provide social support and to enhance each other's self-efficacy. The results showed that the intervention group improved the desire for body strength and the self-efficacy for strength-training.

In Japan, Kamada et al. (2013) reported the effects of a community-wide campaign by a cluster randomized control trial. While three other studies (Fetherman et al. 2011; Katula et al. 2006; Shirazi et al. 2007) targeted voluntary participants and analyzed smaller samples, Kamada et al. (2013) targeted all middle-aged and older people living in Unnan city. Unnan city consists of 32 communities defined by the city government. From the 32 communities, 12 communities were randomly selected and allocated to 1 of 4 groups: control, aerobic activity, flexibility and

Table 3.6 Intervention to promote strength-training behavior

Study	Target population	Allocation of group	Intervention strategy	Duration	Main results
Ferherman et al. (2011)	Older women (≥55 years) recruited from senior centers	Based on access to two local senior centers, participants were allocated into strength training only group ($n=14$) or strength training plus behavior change group ($n=13$)	Counseling using goal-setting worksheet developed by the transtheoretical model constructs (2 times)	12 weeks	Intervention group progressed the stages of change and improved perceived pros, body strength, and body flexibility.
Kamada et al. (2013)	All middle-aged and older adults (40–79 years)	12 communities (randomly sampled from Unnan city) were randomly allocated four groups: control group; aerobic activity group; flexibility and muscle-strengthening activities group; and aerobic, flexibility, and muscle-strengthening activities group	Combination of information, education, and support deliveries developed by social marketing principles	1 year	Intervention group did not show significant improvement in level of physical activity
Katula et al. (2006)	Older adults (≥60 years) recruited by advertisement	Participants were randomly allocated into traditional strength training group ($n=18$) or strength training plus empowerment group ($n=20$)	Group-based counseling (1 time) and pair supports based on empowerment theory and self-efficacy theory (biweekly)	6 weeks	Intervention group improved the desire for body strength and the self-efficacy for strength-training
Shirazi et al. (2007)	Middle-aged women (40–65 years) randomly sampled from the District Health Center	A trial and control center were randomly selected from 39 centers ($n=61$ in the trial center, $n=55$ in the control center)	Education program based on the stages of change and processes of change (2 instructional sessions & print delivery every 2 weeks)	12 weeks	Intervention group progressed stages of change, and improved total physical activity level, muscle strength, and balance ability

muscle-strengthening activities, and aerobic, flexibility, and muscle-strengthening activities. The campaign consisted of three components: information delivery (e.g., flyers, leaflets, community newsletters), education delivery (e.g., education and encouragement by professionals during medical check-ups and community events), and support delivery (e.g., development of social support, and providing pedometers). This program was developed using social-marketing principles (analyzing the situation, segmenting and targeting the market, setting objectives, and developing a marketing strategy). However, although awareness and knowledge levels were significantly higher in the intervention group, the intervention group did not show a significant improvement in the level of physical activity including engagements in strength training.

3.5 Conclusions

In conclusion we briefly review research trends in prevalence, correlates, and intervention strategies of strength-training behavior. Key points of this review include:

1. Previous studies have reported the prevalence of strength-training behavior as 3.9–21 % of the populations in each country.
2. Among socio-demographic factors, gender, age, and educational level have repeatedly been indicated as the correlates of strength training in previous studies.
3. The self-efficacy, behavioral intention, social support, enjoyment, the process of change, perceived benefits and barriers, and sources of strength-training information have been reported as psychosocial correlates of strength-training behavior.
4. Recent studies have begun to reveal environmental correlates of strength-training behavior (e.g., access to strength-training facilities).
5. Although results of a community-wide campaign were reported, intervention studies to promote strength-training behavior are limited.

Compared with studies of walking and bicycling behavior (Ogilvie et al. 2007; Panter and Jones 2010; Saelens et al. 2003; Saelens and Handy 2008; Yang et al. 2010), fewer studies have been conducted to elucidate how to promote the health benefits of strength training. Further well-designed observational studies (e.g., longitudinal examinations measuring both the objective environment and psychosocial factors) designed to examine the correlates of strength-training behavior and large-scale intervention trials are warranted to confirm effective strategies to promote strength-training behavior.

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Chapter 4
Does Newspaper Coverage Promote Cancer Prevention?

Rina Miyawaki, Ai Shibata, Kaori Ishii, and Koichiro Oka

Abstract The newspaper is a primary source of cancer information for the public, and newspaper articles could provide effective and comprehensible information about cancer prevention. Content analyses of cancer news coverage contribute to understanding the effect of newspaper coverage on public knowledge and behavior. The current study reviewed previous comprehensive content analyses. The news coverage was not balanced with regard to the population incidence and mortality of each cancer. Lack of balance may contribute to distortion in readers' perceptions of cancer risk. In addition, newspaper articles rarely mentioned cancer prevention behaviors, although there was a positive association between news coverage and individuals knowledge of cancer prevention. The cancer stories in newspapers are affected by the social, existential, and religious characteristics of a country; the themes of cancer stories differ according to country. However, no study has used comprehensive content analysis to investigate cancer news coverage in Japan. Thus, comprehensive analysis of cancer story content in Japanese newspapers should be conducted to assess the value these stories have in delivering accurate information to the public.

Keywords Cancer prevention • Newspaper • Content analysis • Health communication

4.1 Importance of Cancer Prevention

Cancer is one of the most common diseases among the Japanese. Since 1981, the mortality and incidence rate of cancer have been continuously increasing in Japan. It is estimated that over 360,000 Japanese died of cancer in 2012, accounting for

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_4

28.7 % of the total number of deaths (Ministry of Health, Labour and Welfare 2013). In 2008, nearly 750,000 new cancer cases were diagnosed; up to 50 % of the Japanese population is diagnosed with cancer during their lifetime (Foundation for Promotion of Cancer Research 2013). Both incidence and mortality rates of lung, colon, and breast cancer have been increasing in particular.

It is estimated that 45 % of cancer incidence and mortality in Japan is potentially preventable (Inoue et al. 2012). A number of studies have confirmed that cancer can largely be averted through lifestyle choice and behavior change (World Health Organization 2003; World Cancer Research Fund/American Institute for Cancer Research 2007). For example, tobacco smoking moderately increases the risk of all cancers (Ezzati and Lopez 2003; Inoue et al. 2005). Alcohol drinking increases the risk of some types of cancer, including breast and colon cancer (WCRF/AICR 2007; Inoue et al. 2007). In addition, physical activity decreases the risk of all cancers (Inoue et al. 2008), more specifically colon (Wolin et al. 2011; Pham et al. 2012) and particularly breast cancer risk (Monninkhof et al. 2007).

Despite considerable evidence that cancer can be prevented, Japanese general awareness of the attributable fraction of cancer causes by major lifestyle factors is lower than their awareness of cancer-causing infections, air pollution, occupational exposure and food additives (Inoue et al. 2006). Those who recognized methods of preventing cancer were significantly more likely to engage in preventive behaviors than those who did not recognize such methods (Hawkins et al. 2010). Therefore, it is necessary to inform individuals about the effect of lifestyle modification and behavior change on cancer prevention as indicated in the Cancer Control Act (Ministry of Health, Labour and Welfare, Japan 2007).

4.2 Role of the Mass Media in Cancer Prevention

Recently, much attention has been devoted to the use of health communication. Health communication encompasses the study and use of communication strategies to inform and influence individual and community decisions that enhance health (U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion 2010). Health communication was adopted in “Healthy People 2020” which provided national objectives and an agenda for improving health and preventing disease (U.S. Department of Health and Human Services). Furthermore, the Institute of Medicine has stressed that mass media are critical to health communication across the cancer continuum. Although previous studies reported that most trusted source of health information is physicians (Hasse et al. 2005; Oh et al. 2010), interactions with physicians are infrequent or of limited duration (Meissner et al. 1992). In contrast, people are routinely exposed to news coverage of health issues, and mass media coverage (e.g., television, radio, magazines, and internet) is an important source of cancer information for the public. The prior study indicated that mass media had a pronounced impact on public awareness, knowledge, and understanding of health and cancer (Jorgensen et al. 2000). Stephenson and Southwell (2006) also noted that mass media had a great influence on cancer

communications and were able to attract and hold the attention of people at risk for cancers. Thus, it is important to effectively use mass media to increase awareness of and knowledge about cancer prevention in the population.

4.3 Effects of Newspaper Coverage on Cancer Prevention

Mass media are cited as one of the key sources of cancer information. Newspapers tend to allow more space for information about health topics, including cancer, than television news broadcasts do. Additionally, television news often provides content that is similar to that of newspapers (Fishman et al. 2010). Contemporary research has shown that newspapers are regarded as more credible than the internet and television (Spiro 2001). In Japan, newspaper readership remains strong; the circulation of the five major newspapers is more than 27 million in Japan (Kishi et al. 2008). This suggests that newspapers are a primary source of trusted health information.

Stryker et al. (2008) explored the effects of newspaper coverage on public knowledge about cancer prevention by examining the associations between the contents and the volume of cancer news coverage, self-reported attention to health news in newspapers, and knowledge of cancer risks. Content analysis of stories about specific cancer prevention behaviors revealed that newspapers paid greater attention to tobacco and diet than to exercise, sun, and alcohol. Attention to health news in newspapers was significantly associated with knowledge of factors that influence cancer prevention, especially about smoking and dietary factors. These findings suggested that there was a positive association between frequency and quality of cancer news coverage and individuals' knowledge of cancer prevention. Thus, researchers have conducted content analyses of newspaper coverage about cancer to understand the potential influence of news stories about cancer on public health beliefs and behaviors.

4.4 Prior Content Analyses of Cancer News Coverage

Comprehensive content analyses of cancer coverage in newspapers have been rare. Only a few studies have been conducted in the U.S. In the 1980s, an early content analysis study was conducted by the National Cancer Institute, which analyzed the top 49 circulating U.S. newspapers. The study analyzed 2,138 cancer news articles published in 1977 and 1,466 cancer news articles published in 1980 (Freimuth et al. 1984). In both time periods, cancer news stories tended to focus on causes of cancer, famous people with cancer, and treatment. Prevention was rarely the primary topic and occupied the attention of fewer than 5 % of all stories. The most frequently covered types of cancer were breast and lung. However, more than half of the cancer stories were general or nonspecific. This finding suggests that American newspapers paid close attention to only a few topics and types of cancer at that time.

Because cancer occurs more frequently now than in the past, cancer stories have become an increasingly popular topic in the news media (Viswanath et al. 2006). Recently, more comprehensive content analysis quantified news stories of cancer, and the results were compared with those of the earliest analyses (Jensen et al. 2010). A total of 5,327 articles about cancer were published in the top 50 circulating U.S. newspapers in 2003. Breast cancer was found to be the most covered topic; leukemia was found to be over-reported in relation to its incidence rates. Colon cancer coverage also increased in comparison with the past study (Freimuth et al. 1984). However, coverage of other types of common cancers remained infrequent, which was consistent with the previous study. The quantity of coverage about breast cancer and leukemia is important. However, other cancers also warrant an increase in coverage. Another consistent finding was that cancer stories have focused heavily on cancer treatment rather than prevention, detection, or coping strategies. Treatment-focused stories have received a large volume of coverage because these stories are dramatic, and journalists may well favor them. Regrettably, because few stories mentioned cancer risk factors and prevention, news consumers could easily miss this important information.

Several studies have investigated the coverage of cancer in Canadian newspapers (Musso and Wakefield 2009; Henry et al. 2012). These studies indicate that breast cancer, the most commonly-diagnosed cancer among Canadian women (Canadian Cancer Society 2009), was covered most frequently. This finding is consistent with the previous studies analyzing American newspapers (Freimuth et al. 1984; Jensen et al. 2010). However, lung cancer received only half the coverage of breast cancer, although the leading cause of cancer death in Canada is lung cancer (Canadian Cancer Society 2009). The large number of breast cancer stories could be related to issues of gender in newspapers which preferred stories of women with cancer rather than stories of men with cancer. For example, one previous study mentioned that stories of self-transformation through cancer in women were much more common than similar stories about men (Seale 2002). Moreover, leukemia, which makes up a low percentage of cancer among adults, was often represented because it is the most common cancer among children. Stories about childhood cancer have more pathos and add to the drama and human interest of an illness story.

The results obtained from the analysis of themes in Canadian newspapers are characteristic of newspaper coverage generally. In 2008, common cancer-related themes were research (26.7 %), risk factors (26.0 %), and treatment (24.3 %) (Henry et al. 2012). The results suggested that Canadian newspapers tended to focus on cancer risks. Specifically, content analysis of cancer risk factors revealed that lifestyle cancer risks were more frequently mentioned than social, environmental, or biological cancer risks in Canadian print media (Musso and Wakefield 2009). This finding was consistent with other analyses (Jensen et al. 2010). Additionally, Canadian newspapers emphasized risk management through individual choice and lifestyle change. Conversely, environmental and social risks related to cancer were minimized. The findings reflect the premise in Canadian social policy that responsibility for health risk management lies with the individual.

Finally, in Japanese newspapers, trends in cancer coverage were revealed by keyword analysis using stories published from 1992 to 2007 (Kishi et al. 2008). The study showed that articles about lung, breast, and stomach cancer were more frequently presented in Japanese newspapers than articles about other cancers. This result reflects the high morbidity and mortality caused by these cancers in Japan.

Keyword analysis in the same study indicated that there were a number of articles on diagnosis and therapy. The findings suggested that cancer articles in Japanese newspapers were influenced by the development of new cancer therapies. Other trends include the effect of contemporary politics, legal proceedings, and particular case studies on cancer information in newspapers. The study also revealed that Japanese newspapers did not focus on reports of celebrities with cancer whereas such profiles were commonly mentioned in the mass media of Western countries (Jensen et al. 2010; Chapman et al. 2005; Jones et al. 2012).

4.5 Suggestions for Future Research on Newspaper Coverage of Cancer News

Newspaper could provide effective and comprehensible information about cancer to the public. Content analyses of cancer news coverage contribute to understanding the effect of newspaper coverage on public knowledge and behavior. Previous comprehensive content analyses indicated that news coverage was not balanced with regard to the population incidence and mortality of each cancer. Most previous studies indicated that cancer news coverage focused heavily on breast cancer and leukemia, but paid little attention to other common cancers (colon, lung, prostate, cervical). Lack of balance may contribute to distortion in readers' perceptions of cancer risk. If so, an important improvement would be to increase newspaper articles about other common cancers. In addition, several studies have indicated that the themes of cancer stories in newspapers differ according to country. The social, existential, and religious characteristics of a country affect the cancer stories in its newspapers.

Some research has further explored cancer news coverage in Western countries. Recently, investigation has focused on news coverage of specific types of cancer (Stryker et al. 2005; Cokkinides et al. 2012). Moreover, some thematic analyses of cancer news examined how cancer prevention and screening efficacy messages were presented in news coverage (Moriarty and Stryker 2008). Despite the self-efficacy of practicing cancer-preventive behaviors (Egbert and Parrott, 2001; Ishii et al. 2013; de Nooijer et al. 2004), it was found that cancer stories rarely mentioned cancer prevention or detection behaviors. Overall, they contained few efficacy messages. These findings indicate it is important to encourage health journalists to include more efficacy statements.

Another study focused on the impact of narrative on readers' ways of relating to cancer (e.g., perceptions, motivation for information seeking, and preventive behaviors)

by classifying news stories as positive, negative, or neutral (Henry et al. 2012). This study found that positive representations outnumbered negative representations, reflecting improvements in cancer treatments. Positive articles were thought to instill readers with hope, whereas negative articles might encourage hopelessness in readers. However, overly positive portrayals could lead to overly optimistic expectations of a cure or to a delay in seeking treatment. The study suggested that newspapers could help people by increasing their coverage of both positive and negative aspects, with emphasis on the psychosocial dimensions.

The relationship between news consumption and cancer-prevention knowledge in U.S. was examined by Stryker et al. (2008). Their findings contribute to understanding how the public learns about cancer from news coverage. In contrast, in Japan, Kishi et al. (2008) revealed the trends in newspaper coverage about cancer by keyword analysis (2008). However, no study has used comprehensive content analysis to investigate news coverage in Japan. The distinctive characteristics of Japanese newspaper cancer coverage are not well understood, especially with regard to articles about prevention. Thus, comprehensive cancer story content in Japanese newspapers should be conducted to assess the value these stories have in delivering accurate information to the public. Additional research is needed to determine whether cancer information in newspapers influences cancer prevention behaviors among the Japanese population. If the typical characteristics of newspaper coverage were better understood, more effective and accurate information could be provided to the public.

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Chapter 5
Health Impact of Light-Intensity Physical Activity and Exercise

Yuko Gando and Isao Muraoka

Abstract Physical inactivity is an independent risk factor for cardiovascular disease and diabetes. High levels of moderate/vigorous physical activity are associated with better health outcomes. However, there is currently a limited understanding about the relationship between light-intensity physical activity and health benefits. In this chapter, we summarize the available literature pertaining to the health impacts of light-intensity physical activity and exercise. Arterial stiffening and insulin resistance are significantly related to the daily time spent in light physical activity, especially for older people, and independent of moderate/vigorous physical activity. The effectiveness of light-intensity exercise such as yoga or stretching for improving vascular functions remains uncertain. However, yoga practice may be helpful in reducing risk factors for type 2 diabetes.

Keywords Vascular function • Glycemic control • Physical activity benefit

5.1 Introduction

Cardiovascular disease accounts for the majority of premature morbidity and mortality in the developed world. In Japan, nearly 320,000 patients die of heart and cerebrovascular diseases each year (approximately 255 per 100,000 person-years in 2011) (Ministry of Health, Labour and Welfare 2011). The prevalence of and death rate from cardiovascular disease have been rapidly increasing in Japan owing to population aging, physical inactivity, and obesity. It has now been more than 60 years since the introduction of the hypothesis on the relationship between physical activity and cardiovascular disease proposed by Morris et al. (1953) based upon

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their pioneering study on London bus drivers; rates of cardiovascular disease were much lower in physically active London double-decker bus conductors than in sedentary bus drivers. Since then, physical inactivity has been documented as an established risk factor for cardiovascular disease. With increasing rates of urbanization and other major changes in work and transportation methods, the prevalence of the sedentary lifestyle has increased further. A sedentary lifestyle resulting from low physical activity levels both at work and during leisure time is associated with a significant increase in cardiovascular disease and mortality, and these associations are independent of other major risk factors.

Physical inactivity is an independent risk factor for cardiovascular disease and diabetes. Therefore, physical inactivity is a key factor in the etiology and progression of chronic disease, including cardiovascular and metabolic disease. High levels of moderate/vigorous physical activity are associated with better health outcomes. However, there is currently a limited understanding about the relationship between light-intensity physical activity (<3 Metabolic Equivalents) and health benefits. In this chapter, we summarize the available literature on the health impacts of light-intensity physical activity and exercise.

5.2 Definition of Physical Activity Intensity

Physical activity is defined as any bodily movement produced by the contraction of skeletal muscles that results in a substantial increase over resting energy expenditure (Caspersen et al. 1985). Exercise is a type of physical activity consisting of planned, structured, and repetitive bodily movements done to improve or maintain one or more components of physical fitness (Caspersen et al. 1985). It is important to define the range of intensities associated with physical activity. The concept of Metabolic Equivalents (METs) is a useful and convenient way to describe the intensity of a variety of physical activities. In a recent update to a joint American College of Sports Medicine and Centers for Disease Control and Prevention publication, light physical activity was defined as requiring <3 METs, moderate activity 3–6 METs, and vigorous activity >6 METs (Haskell et al. 2007).

5.3 Light-Intensity Physical Activity and Health Impacts

Previous studies using uniaxial accelerometers and heart rate monitoring have measured the impact of physical activity on health outcomes (Assah et al. 2008; Ekelund et al. 2009; Kozakova et al. 2007; Sugawara et al. 2006). They reported that moderate/vigorous-intensity physical activities have favorable effects on arterial stiffness and insulin resistance, although light-intensity physical activities had no such effect. However, uniaxial accelerometry does not detect horizontal movements and may underestimate the amount of light physical activity accomplished. Objective evidence now demonstrates that the light-intensity physical activities of daily living

have relatively high energy costs (Hendelman et al. 2000). Therefore, we previously investigated the relationships between light-intensity physical activity and its health impacts using triaxial accelerometry. Our previous study suggested that longer times spent in light-intensity physical activity are associated with the attenuation of arterial stiffening (Gando et al. 2010). Central arterial stiffness increases with age in adults. The most frequently reported assessment methods used are pulse wave velocity, pulse wave analysis, and distensibility/compliance (change in diameter/change in pressure). Aortic pulse wave velocity, a clinically important measure of central arterial stiffness, progressively increases with age in adults without clinical cardiovascular disease. Age-related arterial stiffening is associated with higher incidences of cardiovascular mortality and cardiovascular events. Figure 5.1 shows the effects of age and the amount of light physical activity on arterial stiffening. In an older group, arterial stiffness, measured using carotid-femoral pulse wave velocity (cfPWV), was higher in the low than in the high light-physical-activity-level group. The differences in cfPWV between the high and low light-physical-activity-level groups remained significant after normalizing for amount of moderate and vigorous physical activities. We also analyzed the correlations between the daily time spent in light, moderate, and vigorous physical activities and arterial stiffness in each age category (Fig. 5.2). In the middle-aged group, cfPWV was significantly related to the daily time spent in moderate and vigorous physical activities. In the older group, cfPWV was significantly related to the daily time spent in light and moderate physical activities but not in vigorous physical activity.

Moreover, our previous study also suggested that light physical activity is beneficially associated with insulin resistance (Gando et al. 2013). Insulin resistance is a precursor of type 2 diabetes. Figure 5.3 shows the age, sex, and fitness-specific

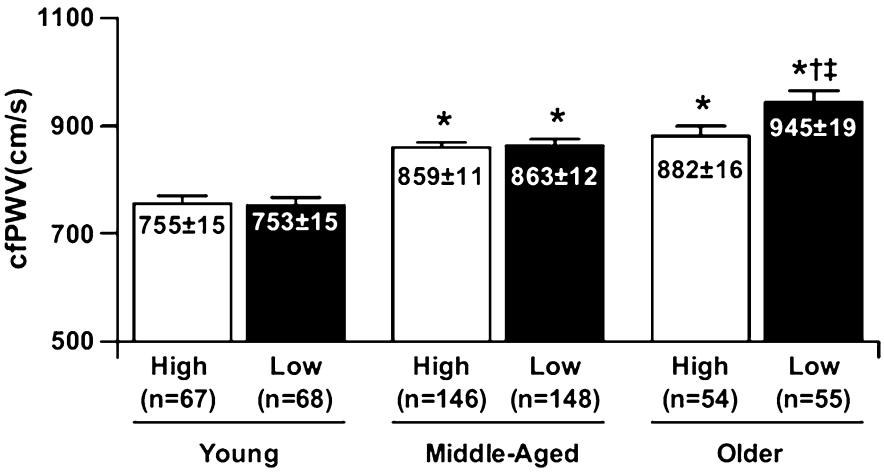

Fig. 5.1 Arterial stiffness in the high and low light physical activity level groups. In the older subjects, carotid-femoral pulse wave velocity (cfPWV) was higher in the low than in the high light physical activity level group. *$p < 0.05$ versus young; †$p < 0.05$ versus middle-aged; ‡$p < 0.05$ versus high in the same age group (Gando et al. 2010)

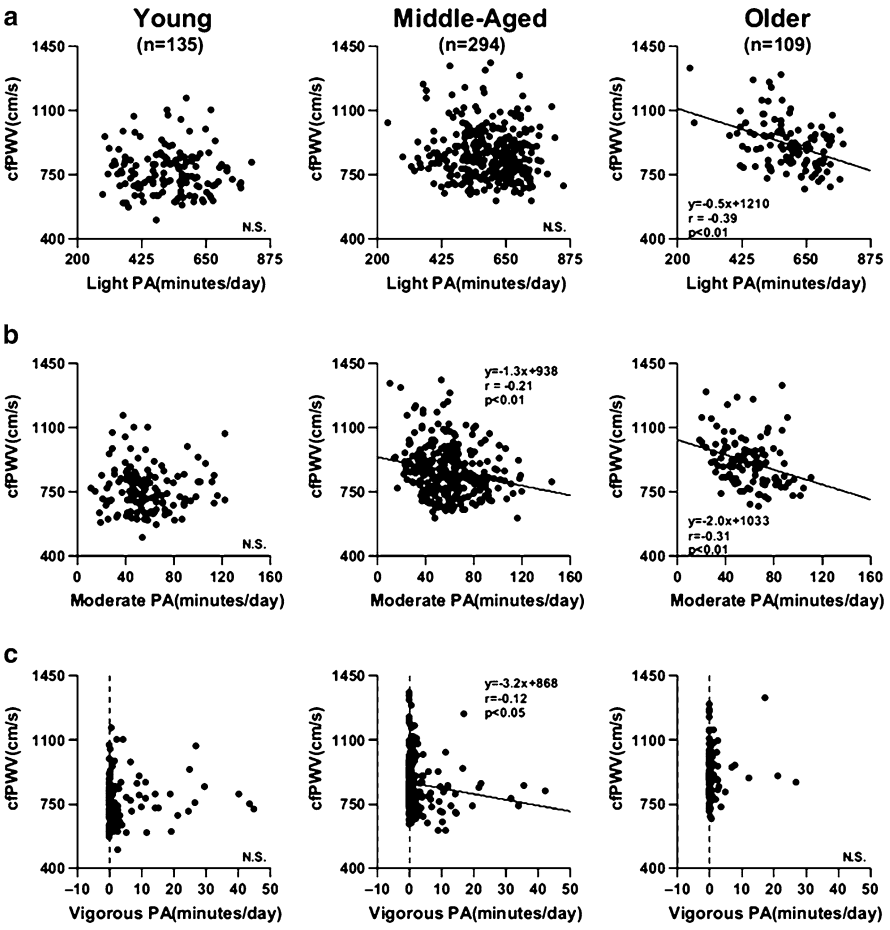

Fig. 5.2 Relationships between daily times spent in each physical activity intensity and carotid-femoral pulse wave velocity (cfPWV). In the older group, cfPWV was significantly related to the daily time spent in light and moderate physical activity (Gando et al. 2010)

associations between light physical activity and indicators of insulin resistance (based on the homeostasis model assessment of insulin resistance [HOMA_R]). An inverse association was observed between light physical activity and HOMA_R in elderly subjects, women, and unfit individuals. These associations were independent of moderate/vigorous physical activity. Healy et al. (2007) also reported that light-intensity physical activity is associated with 2-h plasma glucose level independent of moderate/vigorous physical activity.

Increasing the amount of light physical activity for older people may be easy to achieve as compared to moderate/vigorous physical activity. Moreover, people typically spend only a small proportion of time doing moderate/vigorous physical activities. Most times in a day could be broadly categorized into two distinct modes as

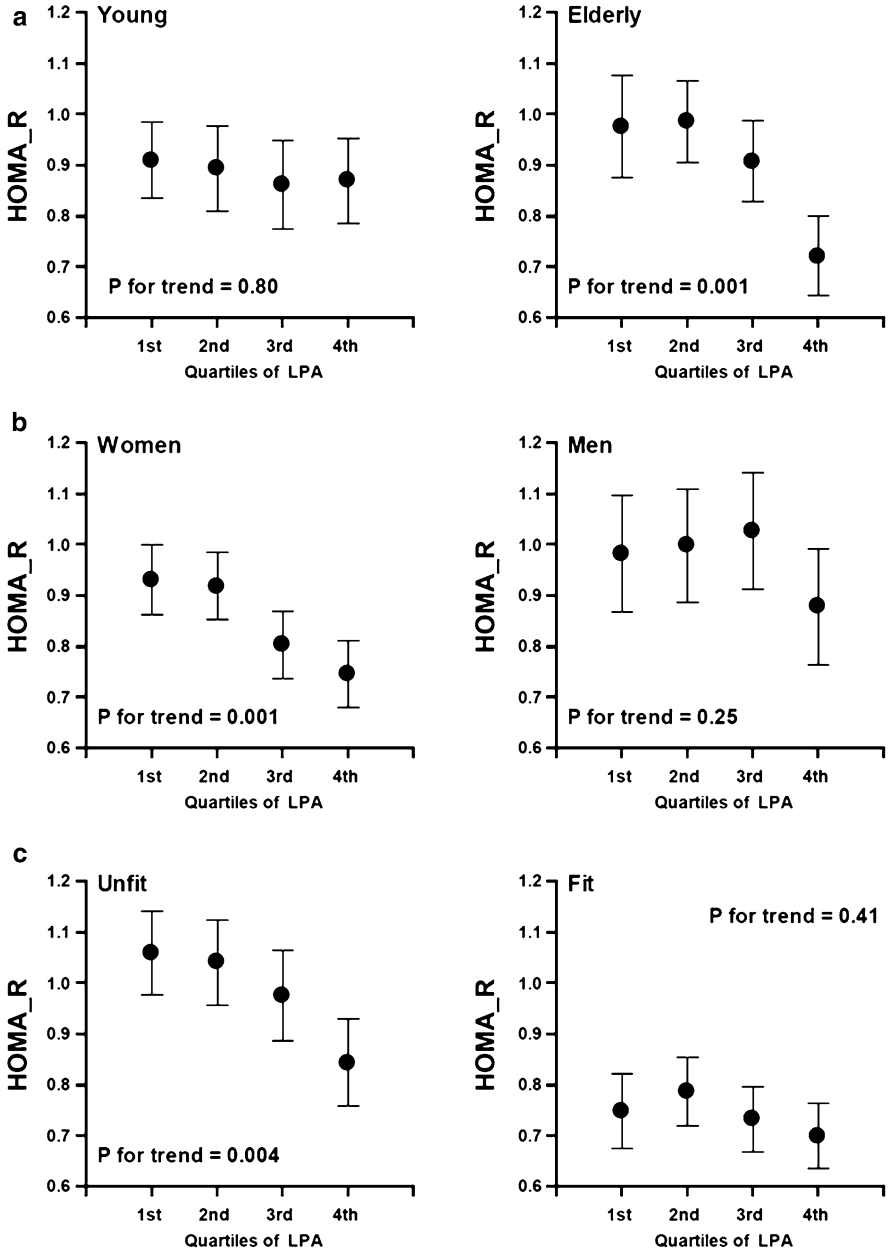

Fig. 5.3 Marginal means (95 % confidence interval [CI]) of indicators of insulin resistance (based on the homeostasis model assessment of insulin resistance, HOMA_R) stratified by quartiles of light physical activity (LPA) in the young and elderly, women and men, and unfit and fit groups (prepublication version reprinted with permission from Gando et al. (2013))

follows: light physical activity and inactivity (mostly sedentary and sleeping time). Therefore, the individuals who spend more time in light physical activity must have spent less time in sedentary behaviors. Light-intensity physical activity is particularly important for older adults; substituting light physical activity for sedentary behavior may be a practical and achievable disease preventive strategy in older people.

5.4 Light-Intensity Exercise and Health Impacts

Regular aerobic exercise and high levels of cardiorespiratory fitness are associated with a reduced risk of cardiovascular disease and diabetes. The mode and intensity of the exercise are important factors for achieving health benefits. However, it is not clear if light-intensity exercise influences vascular function and glycemic control. Generally, yoga or other types of stretching exercises are considered to be light-intensity exercises. These exercises can easily be practiced at home. Previous studies demonstrated that subjects who regularly practiced yoga had higher vascular function (carotid artery distensibility). There were negative correlations between trunk flexibility and arterial stiffness (Yamamoto et al. 2009). We identified six prospective trials investigating the effects of yoga or stretching exercise training on vascular functions (Table 5.1). These studies involved individuals who were healthy

Table 5.1 Prospective studies examining the effects of light-intensity exercise on vascular function

Reference	Year	n	Subjects' condition	Intervention	Major findings
Hunter et al. (2013b)	2013	Ex young: 24 Ex older: 18	Healthy	3×/week; 8 weeks	↑ Carotid artery compliance, ↓ β-stiffness – Carotid artery compliance, – β-stiffness
Hunter et al. (2013c)	2013	Ex: 13	Healthy	3×/week; 12 weeks	– Carotid artery compliance – FMD
Wong and Figueroa (2013)	2013	Ex: 14 Con: 14	Obese	3×/week; 8 weeks	– baPWV, – cfPWV, ↑ AI
Kim et al. (2012)	2012	Ex: 16 Con: 18	Healthy	2×/week; 8 months	– Arterial compliance
Cortez-Cooper et al. (2008)	2008	Ex: 12	Healthy	3×/week; 13 weeks	↑ Arterial compliance
Sivasankaran et al. (2006)	2006	Ex: 10	Coronary artery disease	3×/week; 6 weeks	– Endothelial function

FMD brachial artery flow-mediated dilation, *baPWV* brachial-ankle pulse wave velocity, *cfPWV* carotid-femoral pulse wave velocity, *AI* aortic augmentation index, ↑ indicates increase, ↓ indicates decrease, – indicates no change

or obese, and also patients with coronary artery disease. The Bikram yoga intervention improved carotid artery compliance and β-stiffness in the young healthy adults but not in older adults (Hunter et al. 2013b). The regular practice of Hatha yoga is not associated with improvements in carotid artery compliance and brachial artery flow-meditated dilation. Brachial artery flow-mediated dilation, a noninvasive measure of endothelial function, has been shown to correlate with measures of coronary artery function and independently predicts cardiovascular events. Arterial compliance of the large and small arteries was not affected by Ashtanga yoga (Kim et al. 2012). In another study, there was no change in endothelium-dependent vasodilation after Hatha yoga in all subject samples reported (Sivasankaran et al. 2006). However, when a subgroup analysis was performed, there was a tendency ($p = 0.09$) for vascular reactivity to increase in patients with coronary artery disease. There were no significant effects on brachial-ankle pulse wave velocity and cfPWV, but significant decreases in augmentation index after stretching exercises were accomplished (Wong and Figueroa 2013). Stretching exercise programs significantly increased carotid arterial compliance (Cortez-Cooper et al. 2008). Based on these results, the effectiveness of yoga or stretching exercise for vascular functions remains uncertain. There are many different types of yoga, all with variations in breathing exercises, postures, and spirituality levels. Moreover, exercise intensities are dependent on the individual's flexibility level. Therefore, large randomized controlled trials of higher quality are needed to better quantify results.

Studies have been carried out to evaluate the effect of yoga on glycemic parameters. We identified 15 prospective trials investigating the effects of yoga on glycemic controls (Table 5.2). These studies involved individuals who were healthy, obese, hypertensive, had type 2 diabetes mellitus, and had coronary artery disease. Mizuno and Monteiro (2013) observed a significant reduction of blood glucose levels with yoga intervention. Hatha yoga intervention produced reduction in HbA1c levels (Hunter et al. 2013c), and Bikram yoga intervention improved glucose tolerance in older and obese adults, but not in young and lean adults (Hunter et al. 2013a). In a randomized controlled trial study by Hegde et al. (2013), a significant improvement in fasting glucose levels was found during follow-up. Significant decreases in HbA1c and fasting glucose levels were observed after yoga practice in a large-sample-size intervention study (Beena and Sreekumaran 2013). There were also significant decreases found in fasting and postprandial blood glucose levels (Madanmohan et al. 2012). In obese postmenopausal women, yoga exercise decreased blood insulin levels, glucose levels, and HOMA_R (Lee et al. 2012). In type 2 diabetic patients, yoga practitioners achieved significant improvements in fasting glucose, postprandial glucose, insulin, or HbA1c with short- and long-term interventions (40 days to 6 months) (Gordon et al. 2008; Hegde et al. 2011; Malhotra et al. 2005; Singh et al. 2008). On the other hand, some studies have reported that there were no significant effects on glycemic control after yoga intervention (Agte et al. 2011; Cade et al. 2010; Vizcaino 2013). Based on these results, it can be postulated that the effect of yoga on glycemic control is limited to type 2 diabetic patients and obese populations. Therefore, yoga intervention may be helpful in reducing risk factors for type 2 diabetes.

Table 5.2 Prospective studies examining the effects of light-intensity exercise on glycemic parameters

Reference	Year	n	Subjects' condition	Intervention	Major findings
Vizcaino (2013)	2013	Ex: 10	Type 2 diabetes mellitus	3×/week; 6 weeks	– Glucose control
Mizuno and Monteiro (2013)	2013	Ex: 17 Con: 16	Hypertension	3×/week; 4 months	↓ Fasting glucose
Hunter et al. (2013b)	2013	Ex young: 24 Ex older: 18	Healthy	3×/week; 8 weeks	– Insulin resistance ↓ Insulin resistance
Hunter et al. (2013a)	2013	Ex young: 14 Ex older: 14	Lean Obese	3×/week; 8 weeks	– Glucose tolerance ↑ Glucose tolerance
Hegde et al. (2013)	2013	Ex: 14 Con: 15	Prediabetes	3×/week; 4 months	↓ Fasting glucose, – HbA_1c
Beena and Sreekumaran (2013)	2013	Ex: 73 Con: 70	Type 2 diabetes mellitus	6×/week; 3 months	↓ HbA_1c, ↓ fasting glucose
Madanmohan et al. (2012)	2012	Ex: 15	Type 2 diabetes mellitus	3×/week; 6 weeks	↓ Glucose
Lee et al. (2012)	2012	Ex: 8 Con: 8	Obese postmenopausal women	4 months	↓ Insulin, ↓ glucose, ↓ HOMA_R
Hegde et al. (2011)	2011	Ex: 60 Con: 63	Type 2 diabetes mellitus	3×/week; 3 months	↑ Glycemic control
Agte et al. (2011)	2010	Ex: 26 Ex: 26	Mild hypertensive healthy	2 months	– Glucose – Glucose
Cade et al. (2010)	2009	Ex: 29 Con: 21	HIV-infected	2 ~ 3×/week; 20 weeks	– Glucose tolerance
Singh et al. (2008)	2008	Ex: 30 Con: 30	Type 2 diabetes mellitus	7×/week; 45 days	↓ Glucose, ↓ insulin
Gordon et al. (2008)	2008	Ex: 77 Con: 77	Type 2 diabetes mellitus	6 months	↓ Fasting glucose
Malhotra et al. (2005)	2005	Ex: 20	Type 2 diabetes mellitus	40 days	↓ Fasting glucose
Damodaran et al. (2002)	2002	Ex: 20	Mild hypertension	7×/week; 3 months	↓ Glucose

HOMA_R, homeostasis model assessment of insulin resistance, *Ex* exercise, *Con* control, ↑ indicates increase, ↓ indicates decrease, – indicates no change

5.5 Conclusion

Populations in Japan and other modern societies are aging. Human aging is associated with vascular dysfunction, poor glycemic control, and an increased risk of clinical cardiovascular disease and diabetes. Therefore, the prevalence of cardiovascular disease and type 2 diabetes will rapidly increase in the few next decades in many industrialized countries. Greater resources will be required to meet increased health-care needs; these increased needs and the associated costs will pose a threat to our health-care systems. A key strategy will be to delay the onset and development of age-associated physiological dysfunction and disease. Habitual physical activity is one of the most powerful tools that can be used to achieve this goal and light physical activity and exercise may be a practical and achievable disease preventive strategy for older people. Light-intensity physical activity and exercise goals can be achieved through household tasks and other non-exercise activities; these activities need not be fitness-enhancing. The modes of physical activity that are common at the population level are primarily unstructured forms, and collated study data demonstrate that elevated energy expenditure through less-defined modes of physical activity is likely to be important in the primary prevention of arterial stiffening and insulin resistance. On the other hand, it should be emphasized that structured exercise training at moderate/vigorous intensity is an important way to prevent arterial stiffening and insulin resistance. Habitual physical activity can play a key role in healthy aging.

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Chapter 6
Evaluation of Physical Activity and Sedentary Behavior

Shigeho Tanaka

Abstract Physical activity (PA) is defined as any bodily movement produced by skeletal muscles that results in energy expenditure (EE) above the resting level. PA consists of exercise and non-exercise PA, also termed non-exercise activity thermogenesis (NEAT). NEAT is much larger than that of exercise-induced EE, and varies substantially between individuals. Questionnaires can provide qualitative information, such as type and purpose of PA, that differs from that provided by objective methods. However, the accuracy of questionnaires to measure PA intensity and EE is not sufficient. On the other hand, accelerometers are objective, small, non-invasive tools for measuring PA intensity and EE. Most NEAT is non-locomotive activities, and NEAT, especially NEAT due to non-locomotive activity, is difficult to measure under free-living conditions. Therefore, accurate metabolic equivalents (METs) estimation for non-locomotive and sedentary activities is required in addition to estimates of locomotive activity. Accelerometers can be used to study patterns of activity across time. A new generation of accelerometers will provide information on body posture and activity recognition to allow objective assessment of subjects' habitual activities. Step counts mainly reflect moderate intensity PA, rather than total PA or physical activity level (PAL). The relationship between step counts and total PA depends on sex, age, and occupation. Accurate estimation of sedentary activities is important, because many people spend almost 10 h/day in sedentary behavior. The prediction accuracy of lower-intensity PA is generally poor. One possible reason is the low sensitivity of accelerometers. Predictive equations for sedentary behavior with high accelerometer sensitivity may improve the prediction accuracy.

Keywords Physical activity • Non-exercise activity thermogenesis • Non-locomotive activity • Accelerometer • Sedentary behavior

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_6

6.1 Introduction

Total energy expenditure (TEE) comprises basal metabolic rate (BMR), diet-induced thermogenesis (DIT), and physical activity (PA) energy expenditure (PAEE). BMR is the largest component of total daily EE (TDEE) in most individuals. If PA level, defined as TEE divided by BMR, is normal (1.75) (Black et al. 1996; Tabata et al. 2013), BMR, DIT, and PAEE account for approximately 60 %, 10 %, and 30 %, respectively, of TEE. PAEE is the most variable component of TEE, and each component's proportion of TEE depends mainly on PAEE.

PA is defined as any bodily movement produced by skeletal muscles that results in EE above the resting level (Caspersen et al. 1985). PA consists of exercise and non-exercise PA, also termed non-exercise activity thermogenesis (NEAT) (Levine 2007), such as activities of daily living, small muscle movements, spontaneous muscle contractions, and postural maintenance (e.g., work, commuting, performing yard work, and household activities such as typing, vacuuming, dishwashing, and fidgeting). The magnitude of exercise-induced EE depends on the type of exercise and subject characteristics. For example, 30 min of brisk walking would require less than 100 kcal. Thus, exercise-induced thermogenesis is not large in general. On the other hand, NEAT varies by at least 800 kcal/day among individuals with normal body weight (60 kg), while the PA level varies from 1.4 to 2.2 or more (Tabata et al. 2013). NEAT is much larger than exercise-induced EE, and varies substantially between individuals. Regarding PA intensity, physical activity level (PAL) may depend on the duration of moderate-intensity PA (Westerterp 2001; Thompson and Batterham 2013), although more studies to determine this are necessary.

6.2 Methods for Evaluating Physical Activity

6.2.1 Overview

The doubly labeled water (DLW) method is an excellent method to use for measuring TEE in unrestrained humans under free-living conditions over about 2 weeks, with relatively high accuracy and precision (Speakman 1998). However, this method can only evaluate TEE and cannot provide day-to-day or minute-by-minute variations.

At present, several methods are used to measure EE in a field setting, i.e., behavioral observation, questionnaires (including diaries, recall questionnaires, and interviews), and physiological markers such as heart rate and motion sensors or activity monitors. Questionnaires can provide qualitative information that differs from the information provided by objective methods, such as the type and purpose of PA.

However, the accuracy of questionnaires to measure PA intensity and EE is not sufficient (Neilson et al. 2008). For Japanese adults, two questionnaires, the International Physical Activity Questionnaire (IPAQ) and the Japan Arteriosclerosis Longitudinal Study Physical Activity Questionnaire (JALSPAQ), have been validated using the DLW method (Ishikawa-Takata et al. 2008, 2011). However, neither questionnaire can differentiate sedentary from moderately-active individuals. Thus, the ability to predict PAL values in less-active individuals needs improvement (Tanaka 2012).

6.2.2 Accelerometer-Based Activity Monitor

Accelerometers are objective, small, non-invasive tools for measuring PA intensity and EE (Chen et al. 2012; Plasqui et al. 2013). Most algorithms supplied with uniaxial and triaxial accelerometers can accurately estimate the intensity of locomotive activities. However, most of NEAT is non-locomotive activities. A human calorimetry study (Ohkawara et al. 2011a) showed that to increase PAEE from "low" to "active" levels through brisk walking, an additional 165 min of walking time at 5.6 km/h (more than an additional 25,000 steps/day) was needed in subjects with a 65 kg body weight. These findings suggest that an enormous number of steps are needed to achieve an active level of PAL if individuals extend PAEE by locomotive activity only. Therefore, non-locomotive activity, a component of NEAT, may also play a significant role in increasing PAL under free-living conditions. The intensities of non-locomotive activities such as vacuuming and sweeping cannot be accurately estimated by most accelerometer algorithms leading to underestimation of total EE by algorithms based on locomotive activities (Matthews 2005; Hikihara et al. 2012), because different relationships between counts per minute and METs were observed for locomotive and non-locomotive activities (Fig. 6.1). Time spent in sedentary and light activities is also underestimated by locomotion-based equations. Therefore, an accurate MET estimation for non-locomotive and sedentary activities is required in addition to an estimation of locomotive activity. In Japan, two types of algorithms are utilized to classify locomotive and non-locomotive activities; one uses the ratio of vertical to horizontal acceleration (Tanaka et al. 2007; Midorikawa et al. 2007) and the other uses the ratio of unfiltered to filtered synthetic acceleration (Oshima et al. 2010). These algorithms were developed and have been proven to contribute to more accurate prediction of EE for both locomotive and non-locomotive activities (Fig. 6.2).

Accelerometers can be used to study patterns of activity over time. A new generation of accelerometers will provide information on body posture and will recognize and thus allow objective assessment of subjects' habitual activities (Chen et al. 2012; Bonomi and Westerterp 2012).

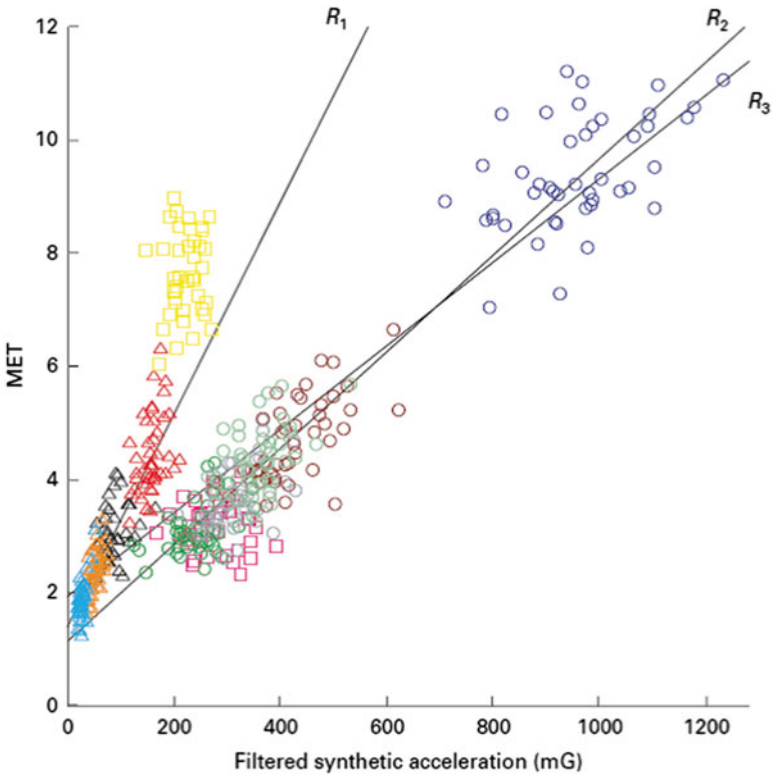

Fig. 6.1 Relationships between measured metabolic equivalents (METs) and filtered synthetic accelerations during locomotive and non-locomotive activities in the validation group (n = 44). R1 (r = 0.907), regression line for non-locomotive activities only; R2 (r = 0.930), regression line for combined non-locomotive and locomotive activities; R3 (r = 0.961), regression line for locomotive activities only. Ascending and descending stairs were removed from the regression analyses for R1, R2, and R3 (Adapted from Ohkawara et al. 2011b)

6.2.3 Pedometer

Pedometers can be used as an objective and convenient method for evaluating PA. Step counts mainly reflect moderate intensity PA, rather than total PA or PAL. The relationship between step counts and total PA depends on sex, age, and occupation (Oshima et al. 2012; Tanaka and Tanaka 2012; Tanaka et al. 2013). In addition, it should be noted that different pedometers may provide different step counts (Schneider et al. 2004; Silcott et al. 2011). Silcott et al. (2011) reported that a difference of more than 30 % was observed in step counts measured by different pedometers under free-living conditions.

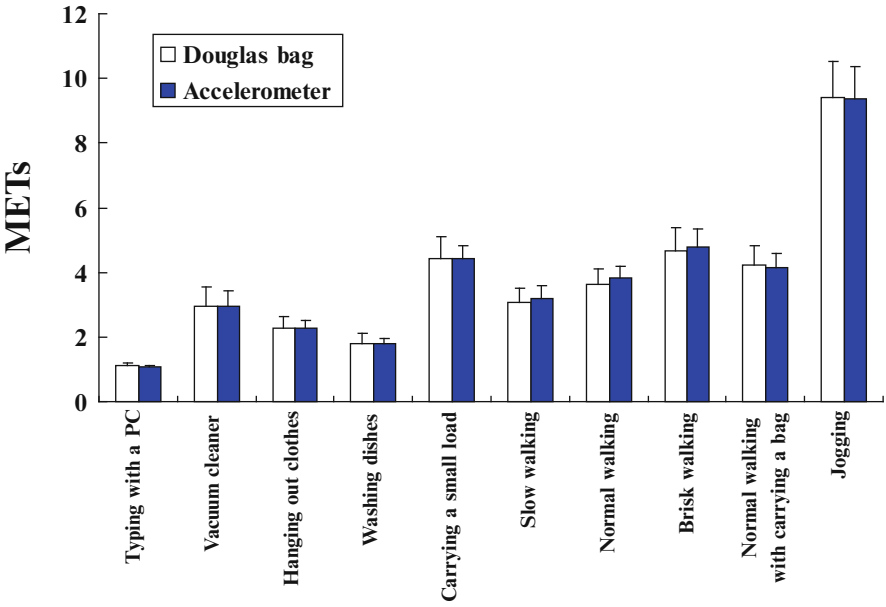

Fig. 6.2 Measured and estimated physical activity intensity (METs) in the cross-validation group, except for going up and down stairs, using an Omron HealthCare, Active style Pro HJA-350IT (Ohkawara et al. 2011b) accelerometer

6.3 Evaluation of Sedentary Behavior

Accurate estimation of sedentary activities is important, as many people perform sedentary behavior for almost 10 h/day (Owen et al. 2010). Sedentary behavior is defined as any waking behavior characterized by an EE $\leq$1.5 METs while in a sitting or reclining posture (Sedentary Behaviour Research Network 2012). The accuracy with which devices measure lower-intensity PA is not good in general, even for accelerometers. One possible reason is the low sensitivity of accelerometers. Equations that predict sedentary behavior measured by highly sensitive accelerometers may improve the prediction accuracy (Fig. 6.3) (Ohkawara et al. 2011b).

6.4 Conclusion

NEAT comprises most PA and its inter-individual variability is large. Moreover, most NEAT consists of non-locomotive activities. Now we can accurately estimate MET even for some non-locomotive and sedentary activities. Novel approaches have recently been developed to provide information on body posture and activity recognition. Therefore, a new generation of accelerometers will provide a greater

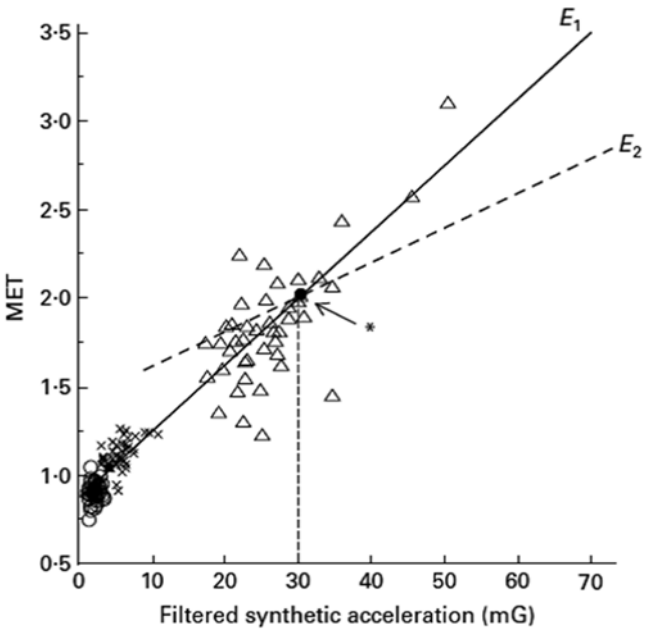

Fig. 6.3 Relationship between measured metabolic equivalents (METs) and filtered synthetic accelerations during sedentary activities in the validation group (n = 44). E1 (r = 0.942, P < 0·001, standard error of estimate 0.151 MET), regression line for sedentary activities; E2, regression line for non-locomotive activities. *Threshold point for the classifying sedentary vs. non-locomotive activities (29.9 milligauss, mG). Dishwashing was included in both E1 and E2 (Adapted from Ohkawara et al. 2011b)

variety of more accurate information on human activity/behavior continuously and objectively, including sedentary behavior and light activities and the context of those behaviors. Such development will contribute to better personalized lifestyle interventions for health promotion and will facilitate a higher quality of research on PA and sedentary behavior.

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Chapter 7
Sedentary Behaviour: Applying the Behavioural Epidemiological Framework

Stuart J.H. Biddle

Abstract Sedentary behaviour – sitting time – has become a popular area of research to compliment that on moderate-to-vigorous physical activity. In this chapter, the behavioural epidemiology framework will be used to structure discussion concerning the measurement of sedentary behaviour, health outcomes, and interventions. Sedentary behaviour is an important area worthy of study.

Keywords Sedentary behaviour • Behavioural epidemiology • Sitting time

7.1 Introduction

For many people, the following sequence of behaviours comprises a typical day:

- Sit in the car while driving to work
- Sit at work for most of the day
- Sit in the car while driving home
- Sit and watch TV with dinner
- Go to bed.

If you are thinking that a 30 min run might make up for all of the sitting, then you will need to think again! Almost the whole day can be comprised of 'sedentary' (sitting) behaviour.

The sport and exercise sciences have seen many developments over the years, including the burgeoning of health-related issues. For psychologists, for example, this has involved the study and application of psychological factors associated with participation in moderate-to-vigorous physical activity (MVPA) for improved health, including behaviour change, as well as the psychological outcomes of physical activity. Behavioural and biological health scientists are now showing great

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_7

interest in 'sedentary behaviour' (sitting time) mainly because technology-driven behaviours that are largely sedentary and are thought to have links to adverse health outcomes are increasingly common.

7.2 The 'Behavioural Epidemiology Framework' Applied to Sedentary Behaviour

The 'Behavioural Epidemiology Framework' has been adopted as a guide for the study of health behaviours, including physical activity (Sallis and Owen 1999). Behavioural epidemiology is concerned with the distribution and origins of behaviours thought to be associated with disease outcomes as well as the relationship between these behaviours and disease outcomes in the population. In relation to sedentary behaviour, this framework is concerned with answering five basic questions:

1. How do we measure sedentary behaviour?
2. What is the association between sedentary behaviour and health outcomes?
3. What are the main correlates of sedentary behaviour?
4. What interventions can successfully change sedentary behaviours?
5. How can we translate findings from research into practice?

Questions 1, 2, and 4 will be addressed in this chapter. Question 3 is addressed elsewhere in this book (see the chapter by Clarke & Sugiyama).

7.2.1 How Do We Assess Different Sedentary Behaviours?

The measurement of sedentary behaviour is challenging because of the variety of behaviours involved and the often intermittent and incidental nature of these behaviours. Currently, there is a lack of consensus on the most appropriate methods of assessing sedentary behaviour. Assessing different sedentary behaviours may require self-report checklists and questionnaires. However, self-report methods often lack validity (Atkin et al. 2012). In addition, self-report methods have predominantly focussed on TV viewing or other screen-based behaviours and this could be considered a rather narrow approach. People find many ways to be sedentary and TV viewing time does not appear to be a good marker of overall sedentary behaviour (Biddle et al. 2009a; Sugiyama et al. 2008). Recent work has attempted to develop more refined self-report measures that assess multiple sedentary behaviours (e.g., TV viewing, reading, socialising) and /or domain-specific behaviours (e.g., sitting at work or at home, motorised travel) (Clark et al. 2009; Hardy et al. 2007; Marshall et al. 2010). An advantage of self-report over other methods is that self-report allows behaviour type (e.g., watching TV vs. sitting and reading) and

context (e.g., alone, with family members, etc.) to be assessed. This additional information may be particularly useful for intervention design.

Objective assessment of sedentary behaviour can be undertaken using either a movement sensor (accelerometer) or a body posture monitor (inclinometer), and these are increasingly being used. This approach overcomes the recall limitations of self-report methods and can provide an objective assessment of overall levels of sedentary behaviour, and also patterns of sedentary behaviour across a day. Accelerometers are now being used to assess sedentary time in large-scale surveillance studies (Colley et al. 2011; Matthews et al. 2008). Extensive discussion on the measurement of sedentary behaviour can be found in Atkin et al. (2012).

7.2.2 *What Is the Association Between Sedentary Behaviour and Health Outcomes?*

A recent systematic review provided a comprehensive examination of the relationship between sedentary behaviour and six health indicators in young people aged 5–17 years (Tremblay et al. 2011). The authors reported that sedentary behaviour (primarily assessed as TV viewing) was associated with unfavourable body composition, decreased fitness, lowered scores for self-esteem and pro-social behaviour, and decreased academic achievement. The findings also suggested that increased sedentary time was associated with increased metabolic and cardiovascular disease (CVD) risk factors, although the evidence was less strong for these. The authors concluded that the findings showed consistent evidence for an inverse relationship between sedentary behaviour and positive health outcomes in young people.

A systematic review by Chinapaw et al. (2011) only included prospective studies that examined the relationship between childhood sedentary behaviour and health indicators. They found insufficient evidence for a longitudinal relationship between 'sedentary time' (usually TV time) and body mass index (BMI), blood pressure, blood lipids, or bone mass. However, moderate evidence was found for an inverse longitudinal relationship between 'sedentary time' and aerobic fitness. These authors concluded that the possible detrimental health effects of prolonged or excessive sitting on health indicators in young people need further study, with stronger designs.

Wilmot et al. (2012), in a meta-analysis, showed that when combining quite large epidemiological studies, those in the highest duration sitting group in comparison to those in the lowest had increased risk of all-cause mortality, cardiovascular mortality and disease, and diabetes. Results for all-cause mortality were confirmed by Chau et al. (2013). In a review of prospective studies with adults, Proper et al. (2011) concluded that there was moderate evidence for a positive relationship between sitting time and the risk for type two diabetes and strong evidence for associations with all-cause and CVD mortality. Edwardson et al.'s (2012) meta-analysis showed that those in the most sedentary group had a 73 % increased risk of metabolic

syndrome compared with those in the least sedentary group. This remained unchanged when accounting for physical activity, thus suggesting that sedentary behaviour is an independent risk factor.

In summary, there is growing evidence for the deleterious health effects of higher levels of sitting, although at what level sitting becomes unhealthy is not known. This evidence is stronger for adults than for young people, which is not surprising given the essentially healthy profile of many young people and lack of hard endpoints by which to judge health.

7.2.3 What Are the Main Correlates of Sedentary Behaviour?

These are covered in the chapter by Clarke and Sugiyama and will not be covered here.

7.2.4 What Interventions Are Successful for Changing Sedentary Behaviours?

The majority of interventions to reduce sedentary behaviour have been made with young people, and mainly children rather than adolescents. Interventions are now emerging with adults.

The main focus of the literature has been on reducing TV viewing or screen media use in 8–11 year old children. The interventions have taken place in schools, homes, community settings, and clinics. We have recently reviewed ten systematic reviews on this topic (Biddle et al. 2014) and found that effect sizes and narrative summaries showed a small effect. Where data were meta-analysed, the largest effect size was −0.29. Interventions that focussed on reducing sedentary behaviour had a small but statistically significant effect when measured after the intervention and a larger statistically significant effect when measured during the intervention. The small intervention effect may be due to several factors. Essentially, sedentary behaviours may be difficult to change. This could be due to their strong habitual nature. We know that health behaviour change can take place via either a ‘deliberative route’, with conscious decision-making and considerable conscious processing and planning, or a more ‘automatic route’, where there is less conscious processing and more reliance on habit (Michie et al. 2011). Habit itself reflects behavioural patterns that are learned through context-dependent repetition. This repetition of behaviour then reinforces context-behaviour associations (Gardner et al. 2011). Therefore, encountering the context is sufficient to automatically cue the habitual response. For example, a child may return from school and simply sit in front of the TV. This behaviour may be much more automatic than conscious if it has been developed in that context over time.

Sedentary behaviours could also be more reinforcing than some physical activities. When coupled with little or no effort being required, this could explain their appeal. Young people are more likely to choose sedentary behaviours even when physically active alternatives are freely available (Epstein and Roemmich 2001).

Sedentary behaviour was defined differently among the studies included in the reviews we synthesised (Biddle et al. 2014). Often, interventions examined one or two aspects of sedentary behaviour (e.g., TV or media use only). These behaviours do not fully represent the sedentary opportunities available to children and more activities should be included such as car travel, talking, or playing quiet indoor games where sitting is the main physical feature. It has been reported that only one third of the total sedentary time in youth consists of TV viewing (Biddle et al. 2009b) and youth can find many other ways to be sedentary.

Interventions to reduce sedentary behaviours have been underpinned by a number of theoretical perspectives, most commonly social cognitive theory and behavioural choice theory (Steeves et al. 2012). However, given the likely strong habitual element of sedentary behaviours, as discussed, theoretical perspectives that directly address the automatic nature of habit may be required (Biddle et al. 2012).

The reviews of Schmidt et al. (2012) and Steeves et al. (2012) focused on the strategies employed within interventions to reduce screen time among children. Effective interventions employed multiple behaviour modification strategies with the most common being goal setting and self-monitoring, followed by pre-planning, problem solving, and positive reinforcement (Steeves et al. 2012). However, interventions that also included electronic monitoring devices or contingent TV devices to assist behaviour change were the most effective according to these authors (Schmidt et al. 2012; Steeves et al. 2012). Electronic monitoring devices allow participants to set a time goal or budget for viewing after which point the television will automatically turn off. Contingent TV devices may be open loop or closed loop. In a closed-loop system TV viewing is made contingent on a concurrent behaviour such as stationary cycling. In an open-loop system TV viewing is made contingent on physical activity accumulated at other times, allowing participants to choose when they use the TV time they have earned. While the inclusion of these devices effectively reduces TV viewing time (estimated reductions of between 30 % and 90 % (Steeves et al. 2012)) little is known about the long-term effectiveness and sustainability of using these devices. In addition, there are questions about acceptability within families and there is little information on how long the reduction in TV viewing would remain once the devices are removed.

Interventions with adults are currently scarce but growing. In a review of adult studies purporting to analyse interventions for reducing sitting in the workplace, Chau et al. (2010) located six studies; all were designed to increase physical activity rather than to decrease time spent in sedentary behaviours. This may have accounted for the lack of intervention effectiveness as far as sitting was concerned.

A recent feasibility trial with Australian adults aged 60 years and over used a 45 min face-to-face meeting to assist participants to reduce sitting time and to increase breaks in sitting (Gardiner et al. 2011). Various strategies were offered,

including goal setting and self-monitoring. The intervention was successful with a small reduction in sedentary time of 3.2 % and an increase in the number of breaks from sedentary time. Pronk et al. (2012) introduced sit-to-stand work stations into offices which resulted in increased time spent standing. In addition, beneficial changes were noted for upper back and neck pain as well as mood states.

Interventions with adults are still in their infancy. Strategies may need to involve a mixture of individual (goal-setting, self-monitoring, prompts), social (targeted social support), and environmental actions (e.g., modified office design such as standing desks and walking meetings).

7.3 Conclusions

Sedentary behaviour research has grown considerably in recent years and is a serious topic for health and physical activity scientists. Given the large amount of sitting people engage in, and the nature of the environment that typically encourages high amounts of sitting and little physical activity, the priority is to identify strategies for behaviour change that people will find acceptable. Some of these may need to involve less conscious models of behaviour change, such as nudging or 'stealth' (Marteau et al. 2011).

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Chapter 8
Prevalence, Trends, and Correlates of Sedentary Behavior

Bronwyn Clark and Takemi Sugiyama

Abstract Sedentary behavior is a growing public health concern. Engaging in sedentary behavior is detrimentally associated with a number of health risks and higher mortality. On average, adults spend over half of their waking hours sedentary while engaged in leisure, transport, and work. Over the past 50 years, sedentary time appears to have increased particularly through television viewing, travel by car, and use of technology; however, recent trends in car use may be stable or reversing in some developed countries. Segments of the population that engage in more sedentary leisure pursuits include older adults, non-workers, and those with lower educational attainment. In transport-related and occupational sitting, office workers who commute by car are more sedentary. The environments in which people live (their neighborhoods) and the work they do (desk bound or not) affect the amount of time people spend in sedentary behavior. Light-intensity physical activity seems to be a key behavioral determinant of sedentary time. Initiatives or settings that encourage light-intensity activity may help to reduce sedentary behavior. Further research examining prevalence, trends, and correlates of specific sedentary behaviors is needed in a wide range of countries to inform interventions aimed at reducing sedentary time.

Keywords Sitting • Leisure • Transport • Workplace

8.1 Introduction

Engaging in moderate-to-vigorous intensity physical activity (MVPA) has a well-established preventive role for common 'lifestyle' diseases such as cardiovascular disease and type 2 diabetes (Kesaniemi et al. 2001). Research on physical activity

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_8

and health has led to the establishment of guidelines for the recommended level of physical activity for preventive health benefits (Haskell et al. 2007). In addition to lack of MVPA, research has begun to examine the health impact of sedentary behavior, or prolonged sitting time. Sedentary behaviors are those that involve low energy expenditure and are undertaken in a seated or recumbent position during waking hours. Strong scientific evidence indicates that time spent in sedentary behaviors, independent of meeting the recommended level of physical activity during leisure, is associated with poor health outcomes, including obesity, the metabolic syndrome, type 2 diabetes, cardiovascular disease, and premature mortality (Chau et al. 2013; Thorp et al. 2011; Williams et al. 2008).

This chapter will discuss the prevalence, trends, and correlates of sedentary behavior (overall sitting and sitting for specific purposes) in adults, who spend more time sedentary than do children or adolescents (Matthews et al. 2008). Findings on prevalence and trends of sedentary behavior provide a basis for gauging the magnitude of the problem and whether it is increasing over time. Identifying demographic correlates of the behaviors helps to determine population subgroups that are most at risk for engaging in sedentary behavior. Understanding psychosocial and environmental factors associated with sitting will help to develop initiatives to reduce sedentary behavior. Together, understanding these aspects of sedentary behavior is essential for developing and improving public health interventions. Examining domain-specific sitting is relevant in this context, as sedentary behaviors for different purposes are known to be associated with different factors, thus requiring different intervention strategies.

8.2 Prevalence: How Sedentary Are We and in What Domains?

Sedentary behavior takes up a significant proportion of the average adult's day. Studies using accelerometers to measure sedentary behavior have shown that adults are sedentary, on average, for around 9 h/day in 16 h of awake time (Healy et al. 2007); thus, sedentary behavior is the predominant activity during waking hours (Healy et al. 2008; Hagstromer et al. 2007; Matthews et al. 2008). For older adults (60+ years), the amount of sedentary time is greater, at around 10 h/day, and sedentary time continues to increase as people age into their 70s and 80s (Evenson et al. 2012; Matthews et al. 2008).

Sedentary behavior is prevalent around the world, including in both developed and developing nations, although there may be disparities among different cultures and countries. A recent study of sitting time in 20 diverse countries showed that people report spending an average of around 5 h a day sitting down; however, this ranged between 3 h/day in Portugal and 7 h/day in Japan and Saudi Arabia (Bauman et al. 2011) (Fig. 8.1). Reported sitting time is less than accelerometer-derived sedentary time as people tend to report less sitting time than objectively-measured sedentary time (Healy et al. 2011).

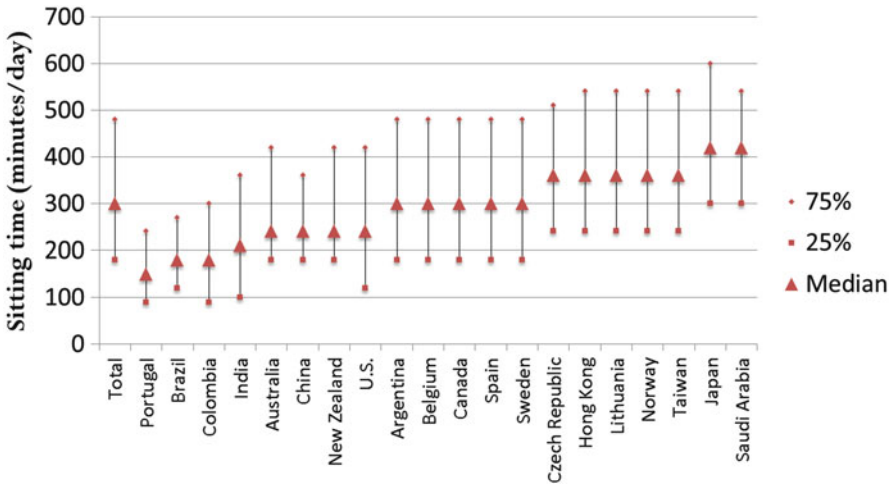

Fig. 8.1 Total self-reported sitting time on week days (minutes/day) across 20 countries. Data collected using the International Physical Activity Questionnaire (Bauman et al. 2011)

There are several behavioral domains in which sedentary behavior occurs. They include leisure (e.g., television [TV] viewing, computer use, reading, talking, and socializing), transport (e.g., sitting in a car), and workplace (e.g., desk work, meetings). In the following, we discuss the prevalence of sitting in each domain.

8.2.1 Leisure-Time Sedentary Behavior

On average, Australian adults spend over 4 h/day in sedentary leisure pursuits, which represents around 90 % of their leisure time (Chau et al. 2012). This is similar to levels reported in the Netherlands (van der Ploeg et al. 2013). TV viewing has been identified as the most common leisure-time sedentary behavior (Australian Bureau of Statistics 2006; Bureau Labor Statistics 2009; Chau et al. 2012; van der Ploeg et al. 2013) and takes up about half of Australian adults' sedentary leisure time (Fig. 8.2). People report watching TV for 2–3 h/day on weekdays and for more than 3 h/day on the weekends (Bureau Labor Statistics 2009; Clark et al. 2010; Craig et al. 2009). TV viewing appears to be particularly prevalent among older adults. The proportion of time spent watching TV has been shown to increase linearly from age 35 to 75 years (10 % and 35 % of waking hours respectively) (Depp et al. 2010).

The prevalence of other leisure time sedentary behaviors has been less well reported. Other pursuits include sitting while socializing, reading, and using a computer, as shown in Fig. 8.2 (Chau et al. 2012). While computers are becoming a more frequent household fixture, time spent using computers for leisure still does not equal the amount of time spent watching TV. In recent time-use surveys (2005

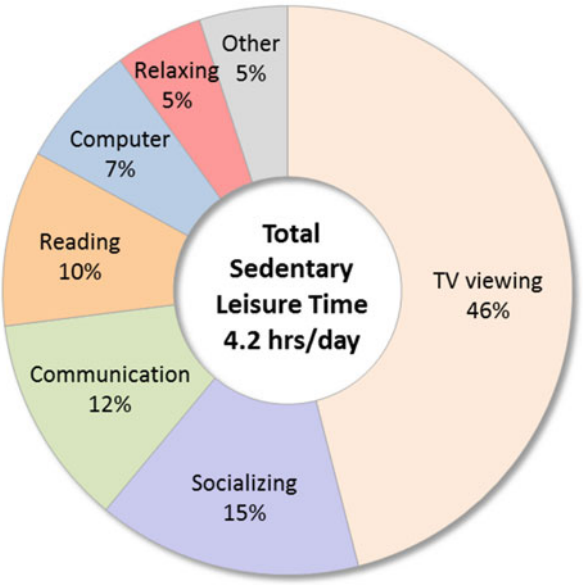

Fig. 8.2 Purpose of sedentary time spent in leisure as reported by Australian adults (20 years and older, n = 5,505) in the Australian Time Use Survey 2006 (Chau et al. 2012)
Note. "Other" includes listening to music and hobbies

and 2006), leisure-time computer use was reported as less than half an hour per day (Chau et al. 2012; van der Ploeg et al. 2013).

8.2.2 Transport-Related Sedentary Behavior

Sitting in a car (as a driver or a passenger) is a typical sedentary behavior. In many western countries, the primary mode of transport is the car (Brownson et al. 2005). For instance, 86 % of people in the U.S.A. (McKenzie and Rapino 2011) and 78 % in Australia (Australian Bureau of Statistics 2012) use a car as the main form of transportation to work or school. According to the 2009 National Household Travel Survey in the U.S., American adults drive a car on average for 56 min/day (U.S. Department of Transportation 2009). Prolonged car use is observed in a portion of the population. In the 2006–08 household travel surveys in the greater Sydney area, Australia, 18 % of men and 11 % of women used a car for more than 2 h/day (Sugiyama et al. 2012). People who live in countries with higher population density may spend less time in cars. For instance, the national travel surveys in Britain and Sweden (both conducted in 2012) reported that people (including children) spend, on average, 35 min/day and 37 min/day sitting in a car, respectively (Department of Transport 2013; Transport Analysis 2012).

8.2.3 Occupational Sedentary Behavior

For working adults the workplace presents a considerable opportunity for sitting, especially with increased use of technology. In office workers, 77 % of working hours are spent sedentary (Thorp et al. 2012). This means that typical office workers spend more than 6 h/day sedentary in their office, which is potentially the largest contributor to daily sedentary behavior for those working adults. Certain employment groups, such as office-based workers, sit at work more than others (Thorp et al. 2012; van Uffelen et al. 2012). However, there is little information about how long people performing different jobs sit at work.

8.3 Trends: Are We Becoming More Sedentary?

Time spent in several domain-specific sedentary behaviors appears to be increasing over the long term (Brownson et al. 2005; Ng and Popkin 2012). However, overall trends are not clear because trends in total sedentary time have not been investigated, except for a few studies on non-occupational sedentary time. In the Netherlands, non-occupational sedentary time decreased from 8.2 h/day in 1975 to 7.6 h/day in 2005, although the proportion of non-occupational time that was classed as sedentary remained relatively constant, at about 60 % (van der Ploeg et al. 2013). However, in Australia, total non-occupational sedentary time was stable at around 7.5 h/day between 1997 and 2006 (Chau et al. 2012). Monitoring of sedentary time at a population level is needed to determine if sedentary behavior is increasing, and if so, in which domains.

8.3.1 Leisure-Time Sedentary Behavior

Although spare time available for leisure has been decreasing in the last 30 years (van der Ploeg et al. 2013), screen time appears to be increasing with differing contributions from TV viewing and computer use. In Australia, TV viewing time did not change between 1997 and 2006 (about 2 h/day), but leisure time spent using the computer increased from 6 min/day in 1997 to 19 min/day in 2006 (Chau et al. 2012). Over the same period, TV viewing decreased in Canada and the Netherlands while computer time increased, suggesting that leisure-time computer use may be replacing TV viewing time to some extent (Shields and Tremblay 2008; van der Ploeg et al. 2013) and may keep increasing in the future. Other leisure-time sedentary behaviors such as reading, socializing, listening to music, and enjoying hobbies and crafts appear to be decreasing, possibly due to reduced spare time (Chau et al. 2012; van der Ploeg et al. 2013).

8.3.2 Transport-Related Sedentary Behavior

In the last half of the twenty-first century, the use of cars increased (Brownson et al. 2005), as this method of transport became available to more people. However, recent trends (over the last 10 years) appear to show a decrease in vehicle use in some countries. For instance, the U.S. travel survey data show that average time spent driving increased from 49 min/day in 1990 to 62 min/day in 2001, then decreased to 56 min/day in 2009 (U.S. Department of Transportation 2009). Similarly, the average time spent in cars in the U.K. peaked in 2005 (at about 40 min/day) and has gradually decreased since then (Department of Transport 2013). Increased use of public transport due to the rising cost of driving (gasoline, parking) and improvement in public transport may be factors involved in the decreasing trends of car use in some developed countries (Buehler et al. 2011).

8.3.3 Occupational Sedentary Behavior

While there is evidence that total occupational time is increasing (van der Ploeg et al. 2013), there is limited information on trends in occupational sitting time. Over the past few decades, more and more jobs have required sitting at a computer. According to the Australian Bureau of Statistics, the proportion of Australian businesses with internet access increased from 29 % in 1997–98 to 90 % in 2009 (Australian Bureau of Statistics 2011). The increase in time spent in front of the computer and the availability of email means that office-based tasks can mostly be completed without leaving the chair. Technology (automation) has also transformed some jobs into seated tasks. However, a recent trend of office design generally points to "collaborative environments", in which workers can work and communicate with colleagues easily (Myerson 2008). This trend encourages more movement and less sitting in the workplace. Such changes in workplace design may counteract the increase in sitting brought about by increased use of technology.

8.4 Correlates: What Factors Influence Sedentary Behavior?

As shown above, adults in many countries tend to spend a lot of time sitting (typically 9 h/day), and a long-term trend of increasing sedentary time in some domains has been seen. How to reduce sedentary time is therefore an important public health issue that research needs to address. Identifying correlates of sedentary behavior is relevant in this context, as they can inform effective intervention strategies to reduce sitting.

Several studies have examined correlates of overall sedentary time, and many of them have consistently shown that older adults, men, and those with higher education tend to be more sedentary overall (Bennie et al. 2013; Kozo et al. 2012; Matthews et al. 2008; Van Dyck et al. 2010). However, in order to inform the development of initiatives to reduce sitting time, correlates of specific sedentary behaviors (leisure-time, transport, and workplace) need to be identified, since different types of sedentary behavior are likely to be influenced by varied sets of factors (Owen et al. 2011; Rhodes et al. 2012). There is increasing, yet still modest evidence on correlates of specific sedentary behaviors. The following sections summarize individual, social, and environmental attributes associated with each domain-specific sedentary behavior.

8.4.1 Leisure-Time Sedentary Behavior

The majority of studies examining correlates of sedentary behavior focus on TV viewing time. Individual demographic factors found to be associated with longer TV time include older age, non-working status, and lower education (Clark et al. 2010; Kikuchi et al. 2013; King et al. 2010; Shields and Tremblay 2008; Van Dyck et al. 2011). These findings suggest that the availability of discretionary time for leisure (more is available for non-workers and older adults) is likely to be a main factor influencing TV viewing time. Lack of other leisure options may also be involved in the amount of TV viewing time. On the relationships between psychological factors and TV viewing, many psychosocial attributes associated with physical activity were found not relevant to TV viewing time (Williams et al. 1999). This may be because, unlike physical activity, TV viewing may be a "default" behavior that can be carried out without a conscious decision. It appears that little has been studied about the social characteristics (e.g., social interaction, social norms) relevant to TV viewing time. Several studies have examined how neighborhood environments are related to residents' TV time. A particular focus is on walkability, a composite environmental measure known to be related to residents' walking. Highly-walkable areas tend to have higher residential density and diverse land use, which leads to better access to shops and services. A study in the U.S. has shown low walkability to be associated with high TV viewing time (Kozo et al. 2012). The same association was reported for women only in an Australian study (Sugiyama et al. 2007), but another American study found no association between walkability and women's prolonged TV viewing time (Coogan et al. 2012). However, longer TV time was found to be associated with living in outside major cities (Clark et al. 2010; Kikuchi et al. 2013) and with a lack of places to shop (Strong et al. 2013). The current evidence seems to suggest that access to shops and other destinations in local areas is related to residents' TV viewing time.

8.4.2 Transport-Related Sedentary Behavior

Studies on correlates of car use focus mainly on environmental factors rather than on individual or social factors, since time spent in cars is obviously influenced by where people live. On a larger scale, those living in suburbs, compared to those living in urban areas, tend to spend longer time in cars for commuting and shopping (Sugiyama et al. 2012). Within a local area, studies have shown consistently that components of walkability (residential density, land use mix, street connectivity, ratio of retail floor area to retail land area) are associated with time spent in the car (Frank et al. 2004; Koohsari et al. 2014; Kozo et al. 2012; Van Dyck et al. 2012). These studies suggest that car use is likely to be less in highly-walkable, compact neighborhoods with accessible shops, services, and public transport stops. It is possible that car use is replaced by active modes of travel (walking, cycling) in such neighborhoods. Taking into account the correlates of active travel may help develop strategies to reduce sitting time spent in cars.

8.4.3 Workplace Sedentary Behavior

Occupational sitting can be the largest component of sedentary behavior for working adults. However, only a few studies have examined correlates of occupational sitting. Occupation makes a difference in time spent sitting at work with office workers (managers, clerks, and scientific and artistic professions) shown to sit significantly longer than manual workers (agricultural, service, trade, industrial, transportation, and commercial) at work (Jans et al. 2007). Desk-bound work for professional occupations may be the driver behind higher education being associated with longer overall sedentary time, whereas leisure-time sedentary behaviors (mainly TV viewing) are associated with lower education. Type of work (desk-bound or not) is obviously a major determinant of how long people sit in their workplace (Thorp et al. 2012; van Uffelen et al. 2012). A few studies have examined the impact of office environments on workplace sitting. A quasi-experimental study found that an intervention group supplied with a height-adjustable workstation reduced their sitting time more than 2 h from the baseline measure of 5.5 h/day (Alkhajah et al. 2012). A natural experiment where participants moved from a conventional "closed-design" office building to a modern building fostering movement (height-adjustable workstations for some, standing-option meeting rooms and common areas, centralized supplies/printing, and vertically integrated office layout) found that sitting time (6 h/day before the move) was reduced by 20 min after the move (Gorman et al. 2013). These studies illustrate that spatial and functional aspects of office environments are likely to impact workers' behavior patterns. Currently, little is known about individual, social, and organizational correlates of workplace sitting. However, it is notable that workplace interventions aiming to increase physical activity failed to reduce sitting time (Chau et al. 2010).

8.4.4 Behavioral Correlates

Unlike physical activity, which is a relatively short event mostly done purposefully, sitting may be a default behavior that is shaped by the presence of other behaviors. In this sense, "behavioral" correlates can play an important role in determining sedentary behavior. Such correlates are rarely discussed for physical activity, but their presence is a particular feature of sedentary behavior. Several studies have examined relationships between sedentary behavior and physical activity. A study using accelerometers found, for instance, that sedentary behavior was strongly negatively associated with light-intensity physical activity, but its association with MVPA was weak (Healy et al. 2008). A strong negative association between sitting and light-intensity physical activity was also reported in a European study (Spittaels et al. 2012). These findings suggest that light-intensity physical activity is likely to be a key behavioral determinant of sedentary behavior. Light-intensity physical activity can include standing and moving around. The two studies on occupational sitting discussed above indeed showed that the reduction in sitting was replaced mostly by standing (Alkhajah et al. 2012; Gorman et al. 2013). An intervention study aiming to reduce older adults' sitting time also found that two thirds of the reduction in sedentary time was substituted for by an increase in light-intensity activity (Gardiner et al. 2011). It is possible to argue that approaches or settings that facilitate light-intensity activity may be effective as a strategy to reduce sedentary time.

8.5 Conclusion

Sedentary behavior is prevalent with over half of adults' waking hours spent sedentary. Common purposes for sedentary time include TV viewing, car use, and desk work. Increases in time spent sedentary have been noted over the past 50 years, largely driven by motor vehicle use, increasing access to technology, and screen-based leisure pursuits. In recent years, however, non-occupational sedentary time may have decreased in some countries due to less time available for leisure and a reduction in car use.

Research on correlates of sedentary behavior is still in its early stage, and studies have mainly been conducted in a few countries in North America, Australia, and Europe. However, emerging studies identify some attributes that are related to sedentary time. Demographically, population subgroups that are particularly sedentary during leisure time are people who are older, not working, and with lower education. However, for transport-related and occupational sitting, office workers who commute by car are highly sedentary. Modifiable factors that appear to be important for sedentary behavior are the place or setting where sitting takes place. In all the domains (leisure-time, transport, and workplace), environmental attributes in neighborhoods or in workplaces seem to have a bearing on sedentary behavior. In addition,

light-intensity physical activity (standing and moving) was identified as a strong behavioral factor shaping sedentary behavior. It can be argued that creating settings where light-intensity activity is easy to do has the potential to reduce sitting time.

There are a number of topics that warrant further exploration. Studies on sedentary behavior have been conducted mainly in Western countries, except for a few recent studies in Asia (Ding et al. 2011; Kikuchi et al. 2013) and in the Middle East (Mabry et al. 2013). Because lifestyle-related diseases such as diabetes and heart disease are increasing in developing countries, achieving a better understanding of prevalence, trends, and correlates of sedentary behavior is an important research agenda if we aim to enhance population health in a wide range of countries. Population monitoring of sedentary time that covers all aspects of time use is necessary to provide researchers with the target contexts in which sedentary behavior is most commonly occurring. Such monitoring may use emerging technologies such as mobile phones and non-health data sources including time use and transport surveys. Less is known about prevalence, variations, and trends of occupational sitting time. Since occupational sitting can be the largest contributor of daily sedentary time in the working population, more research is necessary to determine sedentary time accrued in various working environments. Factors influencing occupational sitting are also not well understood. Organizational factors (e.g., norms) may be important in influencing workers' behaviors at the office. Examining office environmental attributes relevant to workers' sitting time can inform the development of new office designs that facilitate more movement and consequently less sedentary time.

It is possible that more new technologies and assistive devices will further reduce the necessity for us to move in our daily life. In addition, the most sedentary segment of the population, older adults, is growing faster than any other age group in many countries. Thus, sedentary behavior may pose an even greater threat to society in the future. Longitudinal studies tracking sedentary behavior, new methodological developments, interdisciplinary collaboration (among occupational health, architecture, interior design, and urban/transport planning), and effective research translation are needed to address this significant public health problem.

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Part II
Effects of Physical Activity, Exercise, and Fitness on the Human Organism

Chapter 9
Responses of the Autonomic Nervous and Endocrine Systems to Exercise

Shizuo Sakamoto

Abstract Exercise is a stressor, and living organisms respond differently to various exercise patterns. This chapter describes one such biological response, the response patterns of the autonomic nervous and endocrine systems with a focus on stress hormones. Exercise-related accidents, especially in relation to the abnormal secretion of stress hormones that leads to chronic fatigue and sleep deprivation and which may cause sudden death, are also discussed.

Keywords Autonomic nervous system • Endocrine system • Stress hormone • Exercise pattern • Exercise intensity • Exercise-induced sudden death

9.1 Body Responses to Exercise as Described in Previous Papers

9.1.1 Differences in Hormonal Response According to Exercise Intensity, Time of Day of Exercise Exposure, and Exercise Pattern

Hackney (2006), in a discussion about exercise as a stressor on the neuroendocrine system, presented various perspectives. According to Hackney, a hormone secretory response occurs in the following three patterns, depending on the difference in relative exercise intensity. Pattern 1: hormone secretion increases gradually as exercise intensity increases to a moderate level; this level of secretion at a moderate level of exercise is maintained whether the intensity of exercise is moderate or high. Pattern 2: as exercise is intensified, secretion gradually increases up to a moderate level of exercise and rapidly increases further when the exercise intensity exceeds the moderate level. Pattern 3: as exercise is intensified, secretion gradually decreases. As shown in Fig. 9.1, neuroendocrine secretion differs depending on the exercise stage, as classified by Hackney (2006) as follows: initial stage of exposure to exercise

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_9

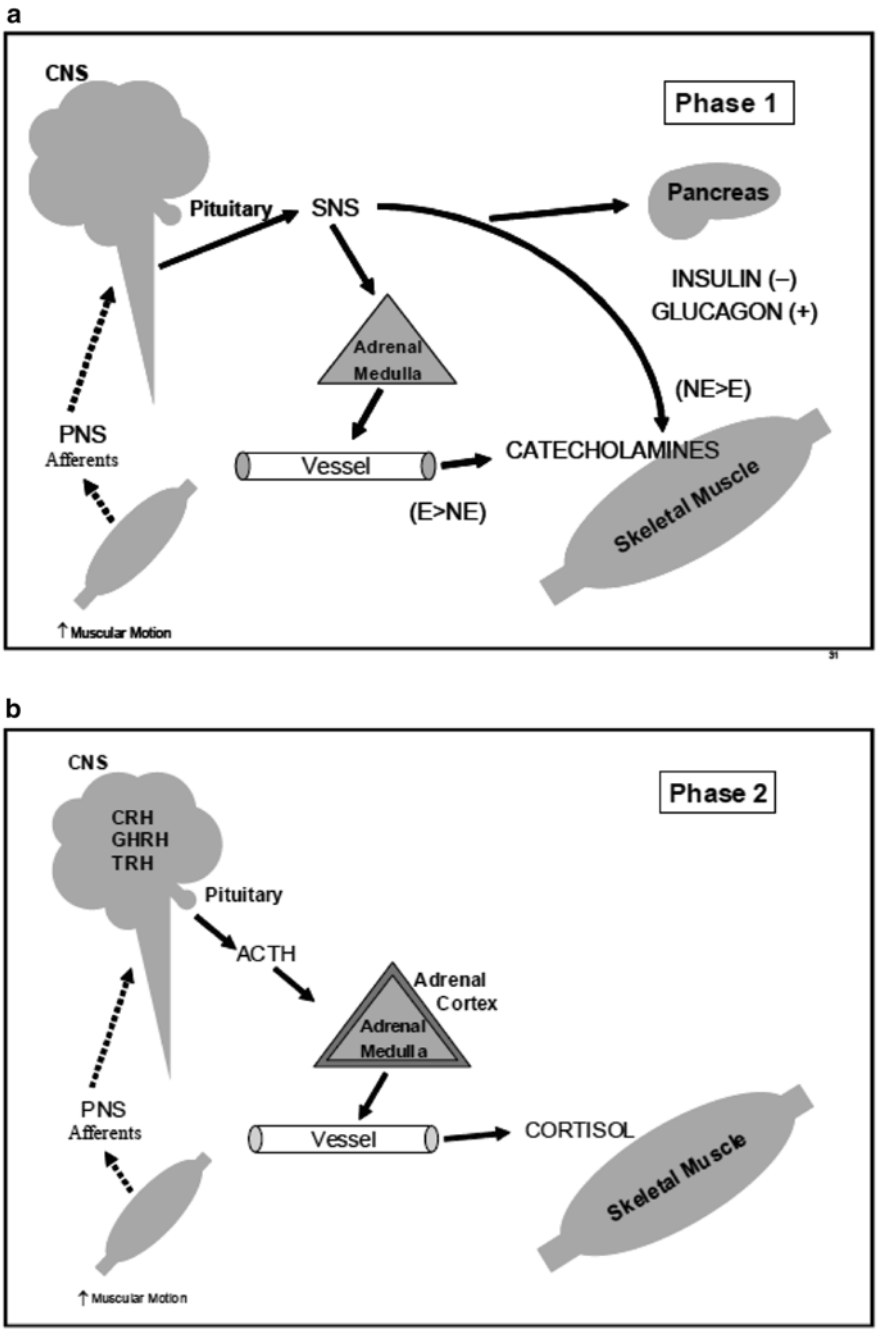

Fig. 9.1 Regulation of hormonal secretion by sympathetic nervous system, pituitary gland, subordinate glands and muscle tissues (Permitted by Hackney 2006). (**a**) Onset phase 1. (**b**) Intermediate phase 2. (**c**) Prolonged phase 3. *CNS* central nervous system, *SNS* sympathetic nervous system,

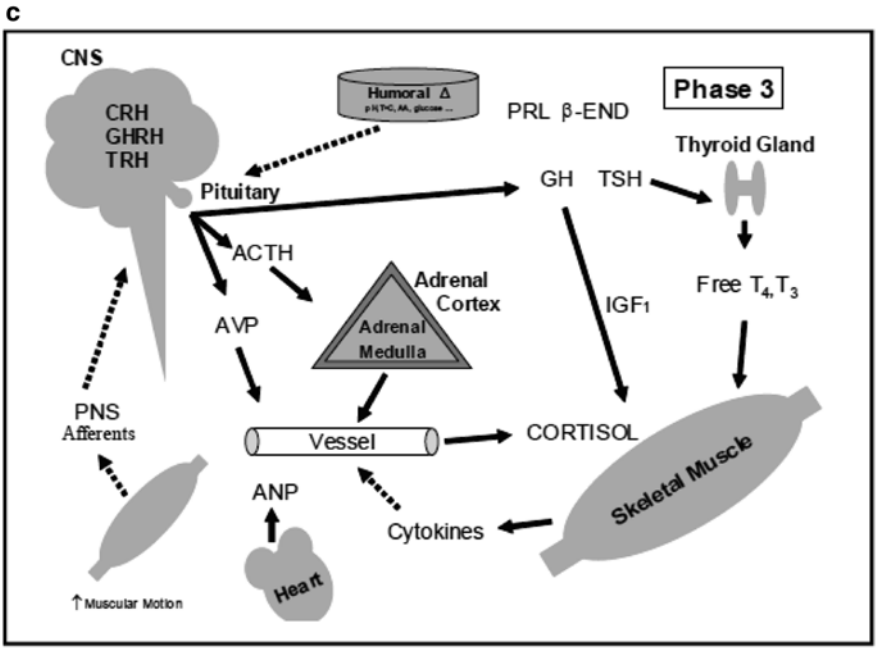

Fig. 9.1 (continued) *PNS* peripheral nervous system, *E* epinephrine, *NE* norepinephrine, *CRH* corticotropin releasing hormone, *GHRH* growth hormone releasing hormone, *TRH* thyrotropin-releasing hormone, *ACTH* adrenocorticotropic hormone, *AVP* arginine vasopressin, *ANP* atrial natriuretic peptide, *PRL* prolactin, *β-END* β-endorphin, *GH* growth hormone, *TSH* thyroid-stimulating hormone, *IGF-1* insulin-like growth factor-1, T_3 triiodothyronine, T_4 thyroxine. This example is for an exercise bout of moderate intensity and duration

(phase 1: onset), middle stage (phase 2: intermediate), and stage of prolonged exercise (phase 3: prolonged). During the initial exercise phase, musculoskeletal exercise stimulates the sympathetic nervous system via the afferent peripheral nervous system and the central nervous system. The sympathetic nervous system stimulates the adrenal medulla to induce the secretion of catecholamines (epinephrine > norepinephrine), while the secretion of catecholamines (norepinephrine > epinephrine) from the sympathetic nervous system itself is induced. The islets of Langerhans in the pancreas are also stimulated, promoting glucagon secretion and, conversely, inhibiting insulin secretion. These hormones act on the skeletal muscles. During the middle phase of exercise exposure, musculoskeletal exercise stimulates the central nervous system, particularly the hypothalamus, via the afferent peripheral nerves to induce secretion of corticotrophin-releasing hormone (CRH), which further stimulates the anterior pituitary gland, promoting the secretion of adrenocorticotropic hormone (ACTH). ACTH stimulates the adrenal cortex to promote cortisol secretion. Cortisol also acts on skeletal muscle. During the phase of prolonged exercise exposure, the hypothalamus is continuously stimulated to induce

Table 9.1 The secretary responses of various hormones to the pattern or intensity of exercise

Hormone	Exercise type – situation					
	Anticipation	Short-term sub maximal	High intensity	Prolonged exercise	Resistance exercise	Aerobic training
ACTH	+	+	++	++	++	–
Aldosterone	0	+	++	++	+	0
AVP	0	+	++	++	?	0
Catecholamine	+	+	++	++	++	–
Cortisol	+	+	++	++	++	–
β-Endorphin	0	+ or 0	++	++	+	0
Estrogens	0	+	+	?	?	– or 0
FSH	0	+	+ or 0	+, 0, –	++	–
Glucogon	0	+	+	++	?	–
Growth hormone	0	+	++	++	++	+
Insulin	0	–	–	–	–	–
Leptin	0	+ or 0	+ or 0	+ or 0	+ or 0	– or 0
LH	0	+	+, 0, –	+ or –	++	–
Progesterone	0	+	+	?	?	– or 0
Prolactin	+ or 0	+	++	+	+	– or +
T_3, T_4	0	0	0	+ or –	0	– or 0
Testosterone	0	+	+	+ or –	+	– or 0
TSH	0	+	+ or 0	+ or 0	?	0

Permitted by Hackney (2006)
"+" = increase; "++" = strong increase; "–" = decrease; 0 = no change; ? = unknown or unresolved
ACTH adrenocorticotropic hormone, *AVP* arginine vasopressin, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone, *T_3* triiodothyronine, *T_4* thyroxine, *TSH* thyroid-stimulating hormone

the secretion of not only CRH but also growth hormone-releasing hormone and thyrotropin-releasing hormone and to promote the secretion of ACTH, growth hormone (GH), thyroid-stimulating hormone (TSH), and arginine vasopressin (AVP). Among these hormones, GH stimulates insulin-like growth factor 1 (IGF-1), TSH stimulates the thyroid gland to secrete thyroid hormones (T_3 and T_4), and ACTH stimulates the adrenal cortex to secrete cortisol. Cortisol also acts on the skeletal muscle. Meanwhile, secretion of atrial natriuretic peptide (ANP) is also stimulated in the heart. As shown in Table 9.1 (Hackney 2006), the secretory responses of various hormones differ depending on the exercise pattern or intensity. Insulin secretion is reduced by exercise, regardless of the pattern or intensity of exercise. During short submaximal exercise, secretion of β-endorphin and leptin mildly increases or does not change, and that of thyroid hormones (T_3 and T_4) does not change. Meanwhile, secretion of other hormones, excluding insulin, mildly increases. During intense exercise, follicle-stimulating hormone (FSH), leptin, and TSH secretion is mildly increased or unchanged, whereas luteinizing hormone (LH) secretion varies (mild increase, no change, or decrease). Estrogen, progesterone,

testosterone, and glucagon secretion is mildly increased, whereas the secretion of other hormones, excluding insulin, substantially increases. During prolonged exercise, leptin and TSH secretion is mildly increased or unchanged; LH, thyroid hormone, and testosterone secretion is mildly increased or decreased; FSH secretion varies (mild increase, no change, or decrease); prolactin secretion is mildly increased; and secretion of other hormones, excluding insulin, is substantially increased. However, no data are available on estrogen or progesterone secretion. During resistance exercise, leptin secretion is mildly increased or unchanged; thyroid hormone secretion is unchanged; aldosterone, β-endorphin, prolactin, and testosterone secretion is mildly increased; and secretion of other hormones, excluding insulin, is substantially increased. However, no data are available on AVP, estrogen, progesterone, glucagon, or TSH secretion. During aerobic training, ACTH, catecholamine, cortisol, FSH, LH, glucagon, and insulin secretion is decreased; aldosterone, AVP, β-endorphin, and TSH secretion is unchanged; estrogen, progesterone, leptin, thyroid hormone, and testosterone secretion is decreased or unchanged; growth hormone secretion is mildly increased; and secretion of other hormones, including insulin, is decreased. Secretion of these hormones is considered to involve the sympathetic nervous system and hypothalamus- pituitary-target secretory gland axis.

Izawa and Ohno (1999) collated Japanese and overseas reports and described the differences in endocrine responses according to exercise conditions. They summarized different endocrine responses to endurance physical training as follows: (1) Secretion of ACTH, cortisol, and catecholamine is lower in athletes during submaximal exercise than in non-athletes at the same level of oxygen intake, whereas training does not influence hormone secretion in athletes compared to non-athletes for the same relative exercise intensity. During maximal exercise, secretion of ACTH and catecholamine is higher in athletes. (2) The increase in the secretory amount of glucagon due to exercise is lower in athletes. (3) The decrease in insulin secretion due to exercise is smaller in athletes. (4) The increase in the secretion of antidiuretic hormone due to exercise is smaller in athletes. (5) The effect of exercise on the secretion of testosterone is the same in athletes and non-athletes. (6) The increase in GH secretion due to exercise is either larger or smaller in athletes. (7) Changes in the secretion of TSH, FSH, LH, and prolactin due to exercise are unknown. (8) The plasma concentration of ANP is higher in athletes.

9.1.2 Differences According to Age

Kraemer et al. (1999) reported the differences in hormone secretion responses to high-intensity resistance training between young men (30 years at the time of starting training) and older men (62 years at the time of starting training). They compared total testosterone, free testosterone, cortisol, ACTH, IGF-1, and IGF-binding protein three levels in the blood before and after a 10-week training program.

Compared with the older men, the young men had significantly higher levels of total testosterone, free testosterone, and IGF-1; the training-induced increase in free testosterone during rest and exercise was significantly higher, as was the increase in the IGF-binding protein-three level at rest. In the older group, a significant increase in total testosterone and a significant decrease in resting cortisol were observed in response to the exercise stressor of training. The authors concluded that the hormone secretion response to resistance training increases even in older men, although the degree of increase was smaller than that in the younger men.

9.1.3 Differences According to Sex

Zouhal et al. (2008) reported no significant difference between men and women with regard to the catecholamine secretion response to exercise.

9.2 Evolution of Stress Hormones During Exercise in Athletes

9.2.1 General Evolutionary Pattern

Hyoudo et al. (1981, 1982) investigated the biological effects of a 20-km run in 20 male members of a university long-distance endurance running team. Blood samples were collected before, at the midway point, and immediately after the 20-km run to measure blood hormone levels. Hormone levels before running were compared with those immediately after running, yielding the following findings: (1) insulin activity significantly decreased; (2) GH levels, ACTH levels, cortisol levels, renin activity, and aldosterone levels significantly increased (abnormally high levels); (3) prolactin, thyroid hormone (T_3), catecholamine, and testosterone levels significantly increased (within the normal range); and (4) glucagon levels significantly increased (mild increase). The change in patterns observed before, at the midway point, and immediately after running were classified into four categories: (1) continuous increase in ACTH, cortisol, catecholamine, and aldosterone levels from the midway point to the end of the run compared to the pre-run levels (pre-run < midway < post-run); (2) marked increase in GH levels and renin activity at the midway point compared to pre-run levels, without a significant increase thereafter until the end of the run (pre-run < midway ≃ post-run); (3) negligible change in testosterone and thyroid hormone (free T_4) levels at the midway point or immediately after the run compared to pre-run levels (pre-run ≃ midway ≃ post-run); and (4) significant decrease in insulin activity at the midway point and immediately after the run compared to the pre-run level (pre-run > midway ≃ post-run). Hormones that show the first pattern are sometimes collectively called anti-stress hormones.

9.2.2 *Specific Pattern in Athletes Who Withdrew Halfway Through the Run*

In the 20-km-run study by Hyoudou et al. (1981, 1982) mentioned above, four team members dropped out of the run mid-way through it. Three of the four members withdrew because of poor physical condition, and one member experienced a pre-shock condition. The common feature among the first three members was the abnormal secretion of stress hormones. One of these three members had low ACTH and cortisol secretion, whereas another member had low ACTH, cortisol, and catecholamine secretion. The team member who dropped out because of a pre-shock condition had abnormally high ACTH secretion and abnormally low cortisol secretion.

9.3 Effects of Sleep Deprivation on Stress Hormone Secretion in the General Population

Konishi et al. (2009) examined eight young healthy men (mean age: 21.5 years) to determine how exercise tolerance and endocrine response would be influenced by acute sleep deprivation followed by a nap. After a 2-h nap, ACTH and cortisol secretion, in particular, showed a pattern of increased response to exercise stress similar to that observed after a regular night's sleep. In cases of a 20-min nap and no nap at all, ACTH secretion showed a decreasing trend and cortisol secretion showed only a minimally increasing trend compared to that observed after a regular night's sleep (no difference in exercise tolerance).

9.4 Secretion Pattern of Stress Hormones as a Trigger for Sport-Related Sudden Death

Considering the results described in Sects. 9.2.2 and 9.3 and the possible involvement of sleep deprivation and fatigue as a trigger for sudden death during exercise, abnormality in the secretion patterns of stress hormones may occur due to sleep deprivation or fatigue accumulation. Therefore, measuring autonomic nervous system and endocrine function and identifying secretion patterns are very important if we are to prevent exercise-related sudden death.

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Chapter 10
Exercise Modes and Vascular Functions

Hiroshi Kawano, Yuko Gando, and Mitsuru Higuchi

Abstract Most physical activities contribute to improvement of age-associated arterial stiffening resulting from reductions in arterial compliance or increases in arterial stiffness. From the viewpoint of exercise physiology, exercise can be divided into aerobic and resistance exercises. Although it is widely accepted that arterial compliance or stiffness is improved by habitual aerobic exercise, it has been reported that resistance training decreases arterial compliance and increases arterial stiffness. Interestingly, combined aerobic and resistance exercise did not affect arterial compliance, which suggests that simultaneously performed aerobic training may negate and prevent the reduction in arterial compliance induced by resistance exercise. It seems that not only moderate-to-high-intensity physical activity but also daily light physical activity, such as cooking, cleaning, washing clothes, or deskwork, decreases arterial stiffness. Arterial wall viscosity reflects dissipation of energy during conversion of cardiac pulsatile energy into arterial elastic energy, which is related to sympathoexcitation and intima-media thickening in the carotid artery. In addition, arterial wall viscosity increases with advancing age, and this age-associated increase in wall viscosity is attenuated in men with high cardiorespiratory fitness. A cross-sectional study found that endurance-trained athletes showed greater arterial wall viscosity compared with age-matched sedentary control men. In the future, the underlying physiological mechanisms and clinical implications of vascular function adaptations to various exercise training regimens warrant further investigation in people of various ages.

Keywords Arterial stiffness • Arterial compliance • Arterial wall viscosity • Aerobic exercise • Resistance exercise

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_10

10.1 Introduction

Arterial stiffness is increased and arterial compliance is decreased with advancing age. This age-associated arterial stiffening, called "arteriosclerosis", is attenuated by exercise training or high levels of physical activity. Exercise physiology mainly categorizes training type into endurance and resistance training. Many studies have indicated both favorable and unfavorable effects of various types of exercise on arterial compliance or stiffness. Recently, both targeted exercise and general physical activity have been the focus of attention, and the effects of various exercise training regimens on arterial mechanical characteristics have been reported. This review presents (1) a description of arterial functions based on mechanical characteristics such as pulse wave velocity or viscoelasticity, (2) findings regarding the effects of type and intensity of exercise and physical activity on arterial stiffness or compliance, and (3) a proposal for effective physical activity that may prevent and improve age-associated arterial stiffening.

10.2 Arterial Stiffening with Advancing Age

Osler said that "man is as old as his arteries." Many cross-sectional studies have demonstrated that large artery stiffness becomes progressively greater (compliance is lower) with aging, even in the healthy population and regardless of sex (Avolio et al. 1985; Tanaka et al. 1998; Valenti et al. 2010). The stiffness and compliance of large elastic arteries change by 40–50 % between 25 and 75 years of age in healthy adults without clinical disease or major coronary risk factors (Moreau et al. 2003; Tanaka et al. 2000). Moreover, lumen diameter and intima-media thickness in large elastic arteries increase with advancing age (Najjar et al. 2005) (Fig. 10.1). This morphological adaptation in large elastic arteries is thought to contribute to age-associated arterial stiffening. In contrast to large elastic arteries, peripheral arteries do not obviously stiffen with aging in healthy humans, because peripheral arteries have less elastin and more collagen than central arteries, leading to difficulty in changing the elastin-to-collagen ratio in peripheral arteries with advancing age.

It is believed that age-associated arterial stiffening is mainly affected by changes in the composition of the arterial wall, including fragmentation of elastin and increases in collagen deposition, collagen cross-linking, as well as vascular smooth muscle cell hypertrophy (Lakatta and Levy 2003; Nosaka et al. 2003). Functional changes that result in increased vascular smooth muscle tone, such as increased sympathetic nervous activity and bioactivity of locally-synthesized vasoconstrictor molecules (e.g. endothelin-1) and reduced endothelial dilator production (Tschudi et al. 1996), also likely contribute to arterial stiffening. It has been reported that the rural Chinese population has a low prevalence of atherosclerotic disease (Avolio et al. 1985) even though this population exhibits arteriosclerosis similar to that measured in other populations, which suggests that arterial stiffening with aging does not depend on atherosclerosis.

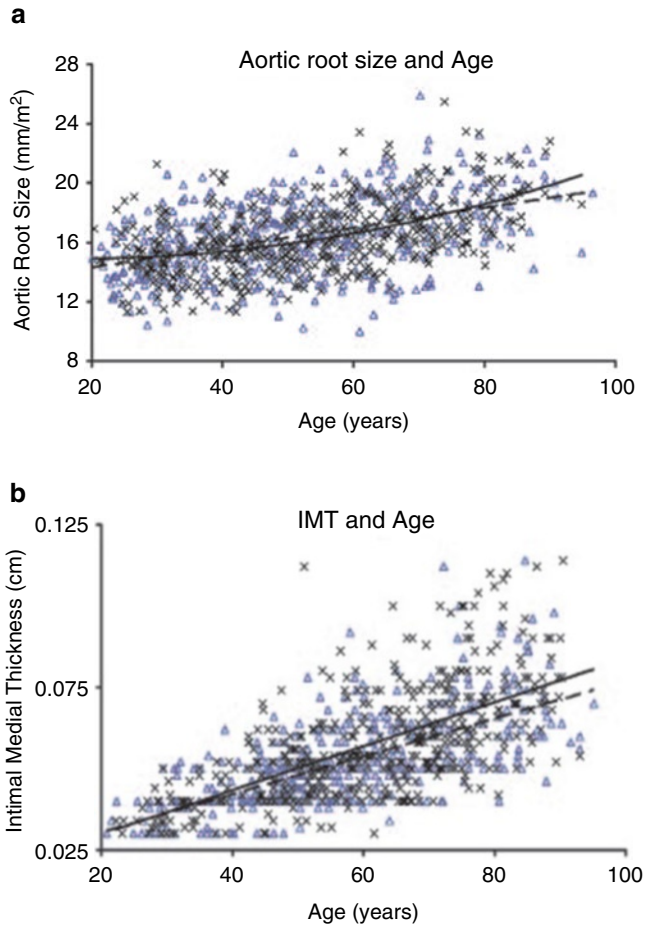

Fig. 10.1 Age-associated changes in vascular structure in men (×) and women (△). (**a**) Aortic root size measured by M-mode ultrasonography. (**b**) Common carotid intima-media thickness (IMT)

10.3 Assessments of Arterial Function

The large elastic arteries are viscoelastic tubes, the principal functions of which are to act as conduits and to buffer pulsatile flow energy generated by cardiac contractions. The buffering function permits the disappearance of pulsation in peripheral arteries (e.g. capillaries). Developing buffering dysfunction may induce coronary artery diseases or stroke through increased stress and blood pressure in peripheral arteries. The following methods have been established and are used to assess arterial stiffening.

Pulse wave velocity (PWV) was devised by Bramwell and Hill (Bramwell and Hill 1922) as an index of arterial stiffness; they received the Nobel Prize for this work. High distensibility in the artery can absorb amplified energy induced from

each pulsation, and thus decrease the energy propagating to the periphery, which results in a delayed pulse wave. In contrast to the situation in highly-distensible young arteries, the PWV in arteries with decreased distensibility due to advancing age is higher, because the arteries cannot buffer the pulsation energy. PWV is measured using applanation tonometry or the ultrasound Doppler technique. Generally, central arterial PWV is assessed between the common carotid and common femoral arteries (cfPWV), which independently predicts all-cause mortality, coronary artery diseases, and diabetes mellitus (Cruickshank et al. 2002; Laurent et al. 2001; van Popele et al. 2001). However, the cfPWV is limited to use in clinical sites, because technicians must have a high level of skill to use applanation tonometry or ultrasound. On the other hand, brachial-ankle PWV (baPWV) was devised in Japan as an index of systemic arterial stiffness. The baPWV measurement, which can be performed more easily than the cfPWV measurement, has become available as a means of measuring PWV (Kubo et al. 2002; Suzuki et al. 2001; Tomiyama et al. 2003; Yamashina et al. 2002). The baPWV can be obtained simply by wrapping the four extremities with blood pressure cuffs, and it serves as a simple marker of the severity of vascular damage (Yamashina et al. 2002). The baPWV is strongly correlated with cfPWV (r = 0.76) (Sugawara et al. 2005).

Dynamic arterial compliance and beta-stiffness index are measured by a combination of ultrasound imaging of the pulsatile common carotid artery and simultaneous applanation-tonometry-obtained arterial pressure from the contralateral carotid artery (Lage et al. 1993; Tanaka et al. 2000). The carotid artery diameter is measured from images obtained using an ultrasound machine equipped with a high-resolution linear-array transducer. A longitudinal image of the cephalic portion of the common carotid artery is acquired 1–2 cm distal to the carotid bulb. Pressure waveforms and amplitudes are obtained from the common carotid artery with a pencil-type probe that incorporates a high-fidelity strain-gauge transducer (Kelly et al. 1989; Tanaka et al. 2000). As baseline levels of blood pressure are subjected to hold-down force, the pressure signal obtained by tonometry is calibrated by equating the carotid mean arterial and diastolic blood pressure to the brachial artery value (Miyachi et al. 2004; Tanaka et al. 2000). Dynamic arterial compliance and the beta-stiffness index are calculated using the following equations (Parati and Bernardi 2006):

$$\text{dynamic arterial compliance} = \frac{\left(D_1 - D_0\right)/D_0}{2 \cdot \left(P_1 - P_0\right)} \cdot \pi \cdot D_0^{\,2}$$

and

$$\text{beta stiffness index} = \frac{\ln\left(P_1 / P_0\right)}{\left(D_1 - D_0\right)/D_0}$$

where D_1 and D_0 are maximal and minimal diameters, and P_1 and P_0 are the highest and lowest blood pressures. Although these parameters have been accurately

measured as optical arterial function (Parati and Bernardi 2006; Kawano et al. 2006, 2008; Miyachi et al. 2003, 2004; Tanaka et al. 2000), they are difficult for inexperienced technicians to measure accurately. This paper will present findings obtained by PWV and arterial compliance or the beta-stiffness index.

10.4 Effects of Different Modes of Exercise Training on Arterial Stiffness or Compliance

Exercise physiology divides exercise into aerobic and resistance exercises. Many studies have indicated that habitual aerobic exercise improves arterial stiffening. In a cross-sectional study, Tanaka et al. (2000) showed that endurance-trained individuals had the lowest value of beta-stiffness index and the highest value of dynamic arterial compliance compared to sedentary and recreationally-active groups (Fig. 10.2). This study also tried to verify the findings in a cross-sectional study using a 3-month intervention of aerobic exercise training (e.g. walking and jogging) in middle-aged and older women. The results indicated that, in both middle-aged and older women, dynamic arterial compliance and the beta-stiffness index increased and decreased by 25 % and 18 %, respectively, over a 3-month time period, comparable to the values of the recreationally-active group (Fig. 10.3). In another study, it was reported that 16 weeks of aerobic exercise (e.g. walking or jogging) improved cfPWV in middle-aged men (Sugawara et al. 2005). Thus, many studies have demonstrated the favorable effects of regular aerobic exercise on arterial compliance and arterial stiffness.

In contrast to the effects of aerobic exercise, it has been reported that resistance exercise may reduce dynamic arterial compliance and increase arterial stiffness. Miyachi et al. (2003) reported that resistance-trained men who performed weight training at heavy intensity for 2 years or more showed lower dynamic arterial compliance and a greater beta-stiffness index compared with age-matched sedentary healthy men (Fig. 10.4). We confirmed this result in a cross-sectional study, and showed that arterial compliance was reduced (beta-stiffness index was increased) by 4 months of resistance training in sedentary healthy young men (Miyachi et al. 2004) (Fig. 10.5). Moreover, other randomized control trials have also supported the finding that resistance training induces arterial stiffening (Collier et al. 2008; Kawano et al. 2006; Okamoto et al. 2006, 2009a, b). On the other hand, some studies have indicated no changes in arterial compliance and stiffness with chronic resistance training in young, middle-aged, and older populations (Cortez-Cooper et al. 2005; Maeda et al. 2006; Rakobowchuk et al. 2005; Yoshizawa et al. 2009). Recently, a meta-analysis by Miyachi (Miyachi 2012) examined the negative relationship between arterial compliance and habitual resistance training found in randomized control trial studies, and suggested that high-intensity resistance training is associated with increased arterial stiffness or decreased arterial compliance in young subjects with low baseline levels of arterial stiffness, but with no changes in older or low-intensity resistance training groups (Fig. 10.6).

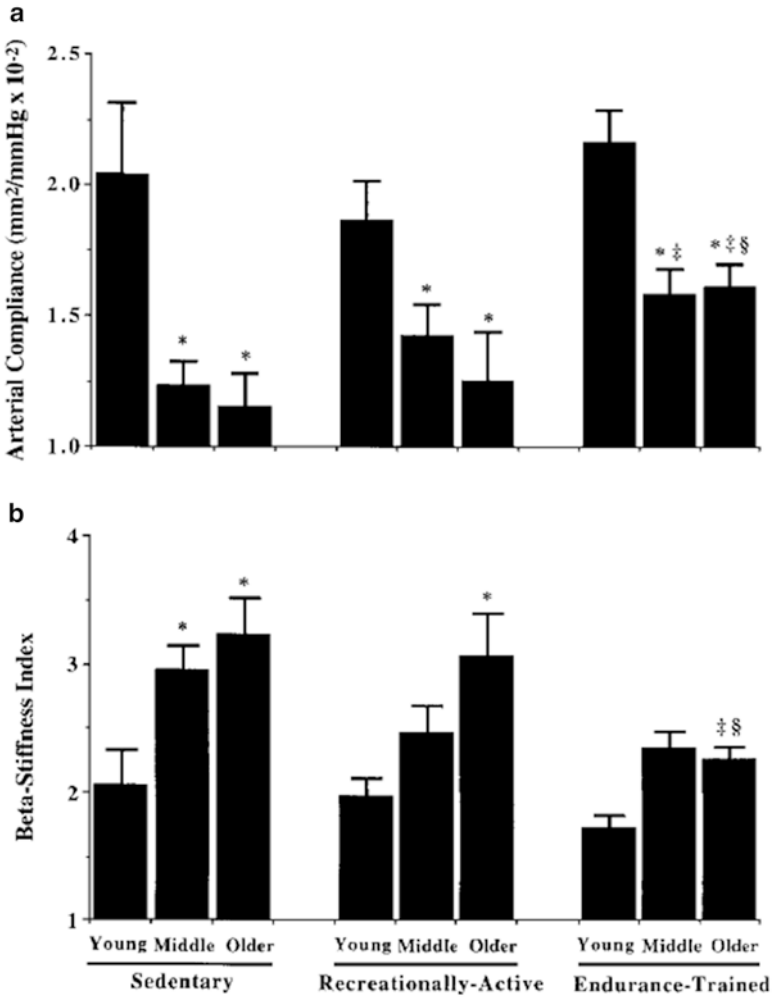

Fig. 10.2 Dynamic arterial compliance (**a**) and beta-stiffness index (**b**) of subjects in a cross-sectional study. *$P<0.05$ vs. young within the same activity group; ‡$P<0.05$ vs. sedentary of same age group; and §$P<0.05$ vs. recreationally active of same age group. Data are means ± SEM

10.5 Effects of Combined Aerobic and Resistance Training on Arterial Stiffness or Compliance

As described above, arterial stiffness is decreased with habitual aerobic exercise and is increased with resistance exercise. Both types of exercise have become popular modalities of exercise performed by most populations, and have become integral

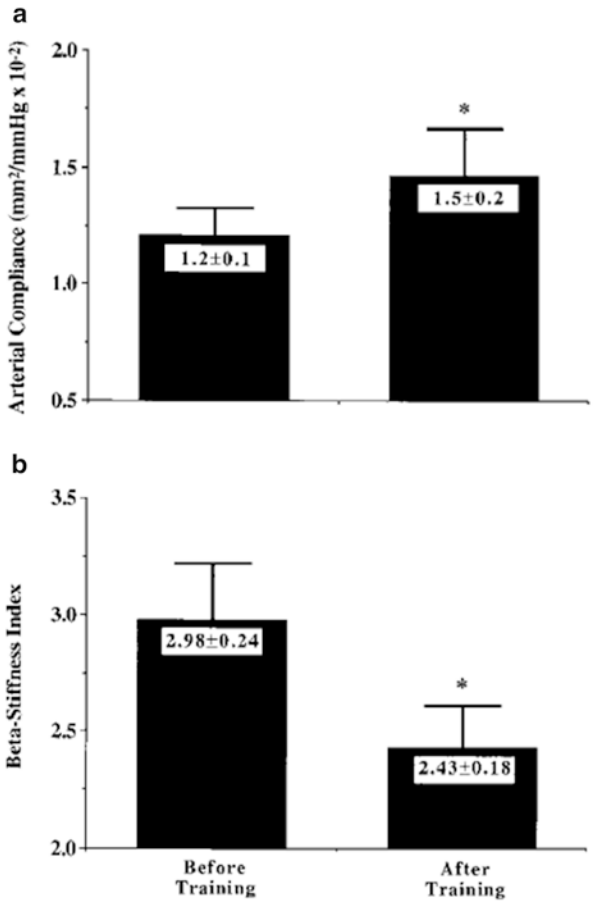

Fig. 10.3 Dynamic arterial compliance (**a**) and beta-stiffness index (**b**) before and after aerobic exercise intervention. *$P < 0.05$ vs. before training. Data are means ± SEM

components of exercise recommendations endorsed by a number of national health organizations (American College of Sports Medicine Position Stand. Exercise and physical activity for older adults 1998; Diabetes mellitus and exercise 2000; Williams et al. 2007). Many people perform a combination of aerobic and resistance exercises to maintain cardiorespiratory fitness and muscular strength and to prevent cardiovascular diseases. Therefore, we examined the effects of combined habitual aerobic and resistance exercise on arterial compliance and beta-stiffness index (Kawano et al. 2006). The combined aerobic and resistance training group showed no change in arterial compliance and beta-stiffness index over a 4-month training period (Fig. 10.7), which suggests that simultaneously performed aerobic training could negate and prevent the stiffening of carotid arteries caused by resistance

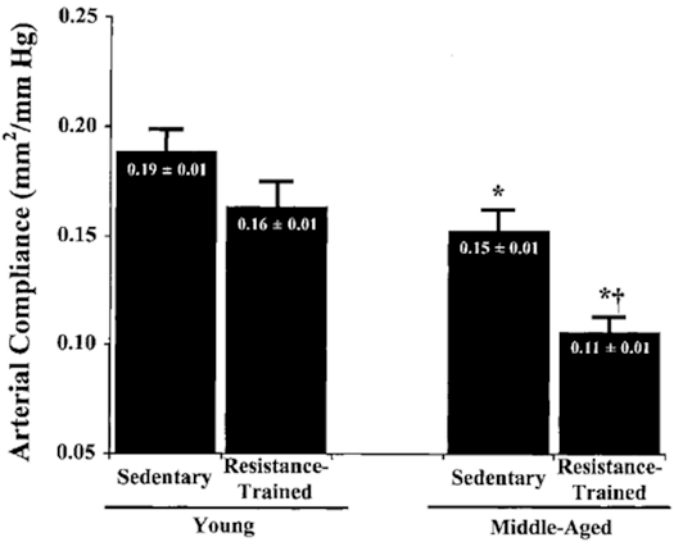

Fig. 10.4 Dynamic arterial compliance of sedentary and resistance-trained men. *$P<0.05$ vs. young of same activity group; †$P<0.05$ vs. sedentary of same age group. Data are means ± SEM

training. Moreover, Okamoto et al. (2007) investigated the effects of conducting aerobic exercise before vs. after resistance exercise on baPWV in healthy young adults. The study demonstrated that although baPWV was not improved if aerobic exercise occurred before resistance training, performing aerobic exercise afterwards can prevent the deterioration of baPWV (Fig. 10.8). These findings may have important clinical implications for exercise prescription.

10.6 Exercise Modes and Arterial Stiffness or Compliance

There are many modes of exercise involving combinations of various physical motions. Thus, it is difficult for exercise to be completely divided into aerobic and resistance exercise. Therefore, Table 10.1 shows the associations between arterial stiffness and mode of exercise or sports reported by original papers, excluding basic resistance and aerobic exercise (e.g. weight lifting, walking, or jogging) (Cook et al. 2006; Duren et al. 2008; Kawano et al. 2012; Nualnim et al. 2012; Petersen et al. 2006; Sanada et al. 2009). The association between arterial stiffness or compliance and rowing training was reported, followed by the effects of swimming and yoga. Most of these studies indicated favorable effects of these exercise modes on arterial compliance and stiffness. Future studies should determine the effects of sports that include many players (such as baseball or soccer) on arterial compliance and stiffness.

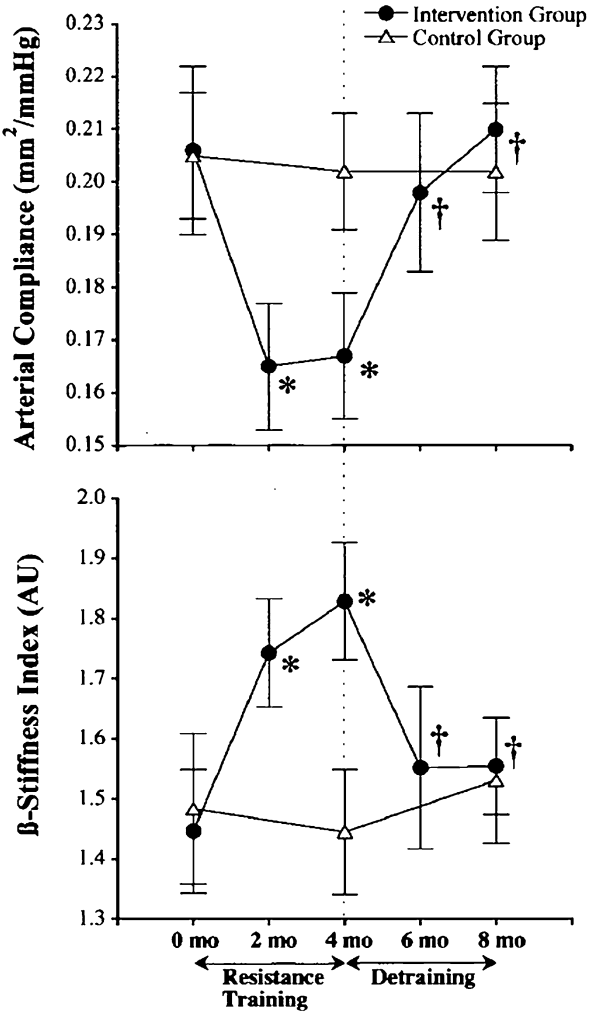

Fig. 10.5 Changes in dynamic arterial compliance (*top*) and beta-stiffness index (*bottom*) in the intervention group (*black circles*) and control group (*white triangles*). *$P<0.05$ vs. baseline; †$P<0.05$ vs. resistance training period (2- and 4-month values). Data are means ± SEM

10.7 Intensity of Physical Activity and Arterial Stiffness

Many studies have shown that high physical activity contributes to improvement of arterial stiffness. However, it is difficult to correctly determine the duration and intensity of physical activity, because most studies have used questionnaires, but self-reporting of activities is notoriously unreliable (Freedson et al. 1998). Therefore, it has remained unclear what kind of physical activity (e.g. duration and intensity)

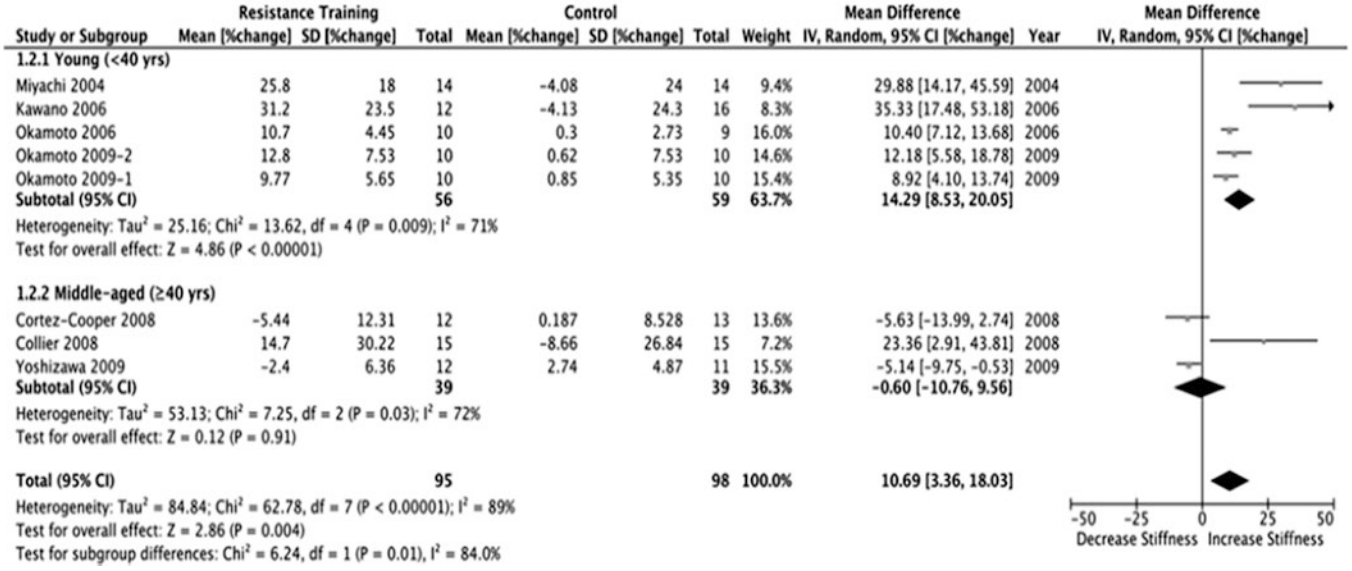

Fig. 10.6 Relative changes in arterial stiffness in individual studies of resistance training vs. no intervention. Relative changes in arterial stiffness index (%) of individual studies included in the meta-analysis of resistance exercise training vs. no intervention. Studies with young (<40 years old) or middle-aged (≥40 years old) participants were evaluated as separate observations. Weights are from random-effects analysis

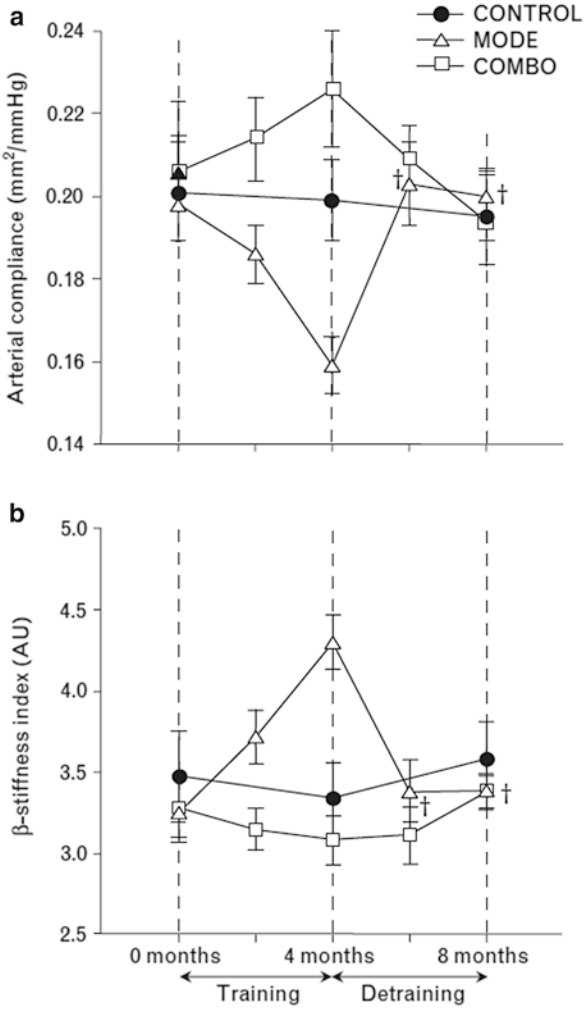

Fig. 10.7 Changes in (**a**) dynamic arterial compliance and (**b**) beta-stiffness index for the sedentary control group (CONTROL), the moderate-intensity strength training group (MODE), and the combined aerobic and strength training group (COMBO). *$P<0.05$ vs. baseline; †$P<0.05$ vs. 4 months. Data are means ± SEM

affects arterial stiffness or compliance. Recently, use of accelerometers has permitted estimation of physical activity volume from duration and intensity. Sugawara et al. (2006) examined the associations between the beta-stiffness index of the carotid artery and daily physical activity durations at different intensities (<4 METs = low intensity; 4 METs to <6 METs = moderate; ≥6 METs = vigorous) for 103 postmenopausal women. The beta-stiffness index was inversely related to the duration of physical activity at all intensities. The beta-stiffness index was significantly correlated with the duration of physical activity at moderate and vigorous

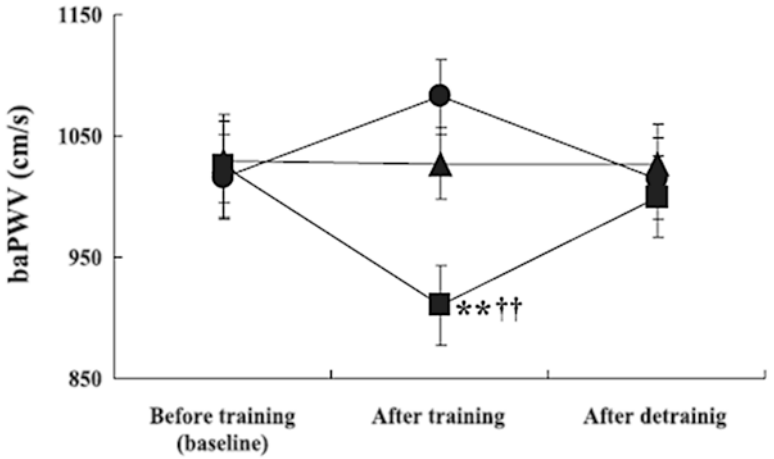

Fig. 10.8 Changes in baPWV in groups that ran before resistance training (BRT; *circles*), ran after resistance training (ART; *squares*), or remained sedentary (SED; *triangles*). *$P<0.05$; **$P<0.01$ vs. baseline; †$P<0.05$; ††$P<0.01$ vs. BRT group. Data are means ± SEM

intensity, but not at low intensity, even when adjustments were made for confounders (e.g. age, body mass index, blood pressure, etc.). In addition, the investigation also reported findings of exercise intervention for 17 menopausal women as follows: beta-stiffness indexes of both moderate (<4METs) and vigorous (<9 METs) intensity groups showed the same reduction (30–33 %) in beta-stiffness over 12 weeks. These cross-sectional and interventional results suggest that physical activity at moderate to vigorous intensity needs to be included in daily life to improve arterial stiffening.

10.8 Light Physical Activity and Arterial Stiffness

Generally, we perform physical activity at various intensities during our daily lives, ranging from 1 MET (e.g. sleeping) to 15 METs (e.g. climbing stairs). Although previous studies have applied uniaxial accelerometry to assess physical activity volume using duration and intensity, uniaxial accelerometry may be unsuitable for light (<3 METs) physical activity. However, most daily activities (e.g. cooking, cleaning, washing clothes, desk work, etc.) can be generally described as light physical activity (Fig. 10.9). This raises the question of whether light physical activity affects arterial stiffness. In recent years advances in triaxial accelerometry now permit this technique to adequately assess light physical activity of less than 3 METS. Gando et al. (2010) tested the effects of durations of light (≤2.9 METs), moderate (3.0–5.9 METs), and high (≥6.0 METs) physical activities on cfPWV for 538 healthy men and women. The results indicated that durations of not only moderate and high but also light physical activity were negatively correlated with

Table 10.1 The associations between arterial stiffness/compliance and modes of exercise/sport

Study design	Exercise mode	n	Sex	Mean age	Results
Cross-sectional	Yoga-trained	8	Male and female	48	Arterial stiffness in yoga-trained and endurance-trained groups was lower than in controls. (Duren et al. 2008)
	Endurance-trained	10	Male and female	52	
	Control	8	Male and female	51	
Cross-sectional	Swimmer	25	Male and female	56	Arterial stiffness in swimmers and runners was lower than in controls. (Nualnim et al. 2011)
	Runner	25	Male and female	52	
	Control	25	Male and female	54	
Cross-sectional	Rowing-trained	15	Male and female	50	Arterial stiffness in rowing-trained group was lower than in controls. (Cook et al. 2006)
	Control	15	Male and female	52	
Cross-sectional	Rowing-trained	28	Male and female	24	Arterial compliances of aorta, carotid and brachial arteries in rowing-trained group were similar to those in controls. (Petersen et al. 2006)
	Control	21	Male and female	28	
Cross-sectional	Young rowing-trained	26	Male	20	baPWV in middle-aged rowing-trained men was lower than in age-matched controls. (Sanada et al. 2009)
	Young control	23	Male	25	
	Middle-aged rowing-trained	24	Male	65	
	Middle-aged control	22	Male	65	
Cross-sectional	Rowing-trained	11	Male	68	Carotid arterial compliance and beta-stiffness index in rowing-trained men were similar to those in controls. (Kawano et al. 2012)
	Control	11	Male	65	

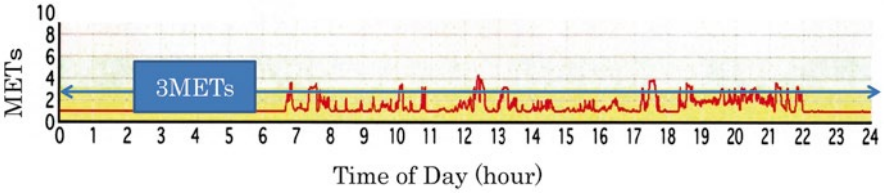

Fig. 10.9 Typical physical activity of one reference subject for one day

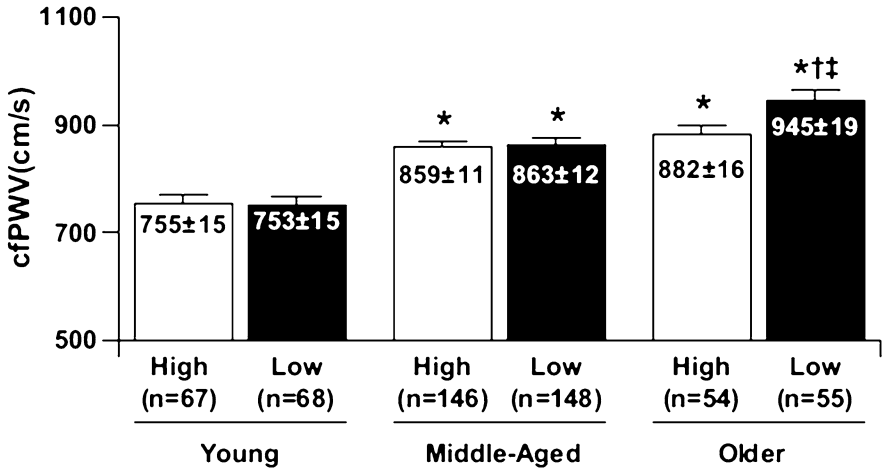

Fig. 10.10 cfPWV in high-light physical activity and low-light physical activity groups. *$P<0.05$ vs. young; †$P<0.05$ vs. middle-aged; ‡$P<0.05$ vs. high in the same age group. Data are means ± SEM

cfPWV. Furthermore, in the older subjects, cfPWV was greater in the high-duration light-physical-activity group than in the low-duration light-physical-activity group, and the differences remained significant after normalizing cfPWV for sex and durations of moderate and high physical activities (Fig. 10.10). These results suggest that performing light physical activity may prevent age-associated arterial stiffening. Moreover, older adults in the study showed a correlation between cfPWV and duration of light physical activity ($r=-0.39$) similar to the relationship between cfPWV and duration of moderate physical activity ($r=-0.31$), suggesting that light as well as moderate physical activity plays an important role in preventing and improving arterial stiffening.

10.9 Light-Intensity Exercise and Arterial Stiffness

Generally, because it is often defined as moving the body vigorously, we imagine exercise to entail physical activity of three or more METs, such as walking or running. However, there is also lighter intensity exercise, such as stretching, which is categorized as a form of exercise of less than three METs. Yamamoto et al. (2009) examined the relationship between flexibility and cfPWV in a cross-sectional study. Flexibility is increased by performing stretching exercise. In addition, both arterial stiffness and muscle flexibility are determined by the elastin-collagen composition of smooth muscle and/or connective tissue and skeletal muscle and/or tendons, respectively, and age-related alterations in the muscles or connective tissues in the arteries may correspond to similar age-related alterations in the whole body

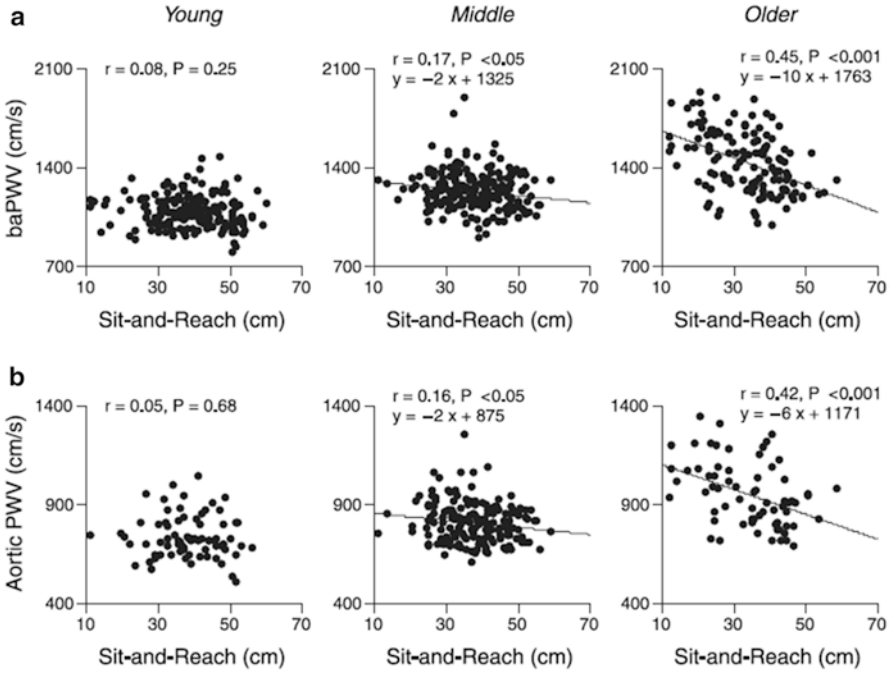

Fig. 10.11 Relationships between sit-and-reach as flexibility and baPWV (**a**) or cfPWV (**b**) in each age category. The baPWV and cfPWV correlated with sit-and-reach in middle-aged (*middle*) and older (*right*) subjects. In both baPWV and cfPWV, the slope of the relationship was steeper in older subjects than in middle-aged subjects ($P < 0.001$)

(Elvan-Taspinar et al. 2005). The investigation revealed negative relationships between flexibility and cfPWV or baPWV in middle-aged and older populations (Fig. 10.11). Stepwise multiple-regression analysis revealed that flexibility, age, and cardiorespiratory fitness were independent correlates of baPWV. Another study confirmed these findings by yoga exercise intervention, which indicated that 8 weeks of Bikram yoga improved the beta-stiffness index in young but not in older adults (Hunter et al. 2013). Therefore, light-intensity exercise may also prevent and improve arterial stiffening, leading to prevention and improvement of arterial stiffening in older and low-fitness populations.

10.10 Effects of Age and Cardiorespiratory Fitness on Arterial Wall Viscosity and Elasticity

Arterial mechanical properties are assessed by various methods (e.g. dynamic arterial compliance, beta-stiffness index, or PWV). This chapter focuses on viscosity and elasticity in central arteries. The central elastic arteries are viscoelastic tubes,

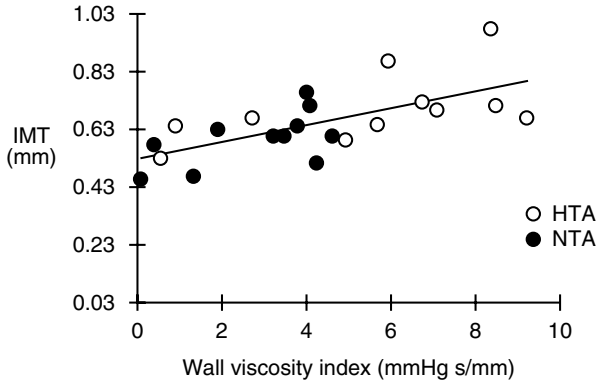

Fig. 10.12 Linear regression analysis between intima-media thickness (IMT) and arterial wall viscosity index in normotensive (NTA: *black circles*) and hypertensive (HTA: *white circles*) groups

which function to buffer the pulsatile flow energy generated by the left ventricle. Although purely elastic materials permit all of the stored energy to be released during the unloading phase, arteries are not purely elastic and exhibit marked viscous behavior. Arterial wall viscosity is a source of energy dissipation; viscosity is an energy-dissipating phenomenon during mechanical transduction (conversion of cardiac pulsatile energy into arterial elastic energy) (Bertram 1980; Bodley 1976; Nichols and O'Rourke 1998; Taylor 1966). Therefore, the arterial mechanical characteristics include both elastic and viscous properties. Dynamic arterial compliance or beta-stiffness index are assessed as arterial elastic properties; viscous properties have been considered to be less important in assessing vascular function. Arterial wall viscosity may be affected by neural and physical factors. It has been reported that wall viscosity is related to intima-media thickening in the carotid artery (Armentano et al. 1998) (Fig. 10.12). On the other hand, hypertensive patients showed greater wall viscosity in the carotid artery than normotensive patients, and greater wall viscosity in hypertensive patients was attenuated by treatment with an antihypertensive drug (Armentano et al. 2006). Interestingly, Armentano et al. (2006) reported that the isolated carotid artery showed lower wall viscosity and greater wall strain in vitro, suggesting that reduction of wall viscosity caused by denervation is associated with greater wall strain. Therefore, wall thickness, blood pressure, and sympathetic nerve activation may account for wall viscosity in central elastic arteries.

A recent study confirmed the effects of age and cardiorespiratory fitness on arterial wall viscosity. The study indicated that carotid arterial wall viscosity increased with advancing age, and the age-associated increase in wall viscosity was attenuated in men with high cardiorespiratory fitness (Kawano et al. 2013) (Fig. 10.13). These findings may have clinical implications for preventing and improving age-associated arterial stiffening by maintaining cardiorespiratory fitness. The central elastic artery flexibly stores the pulsatile energy imposed by

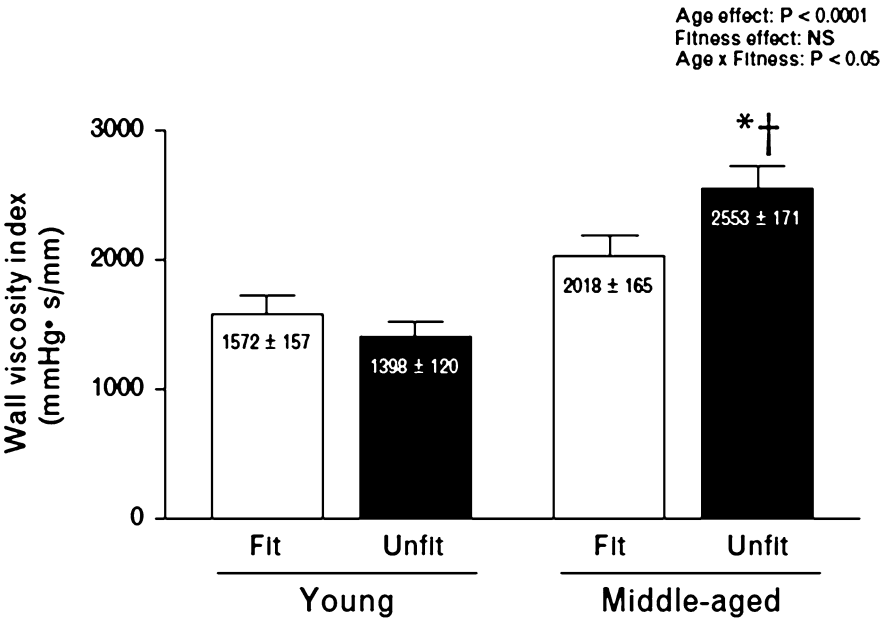

Fig. 10.13 Bar graph showing arterial wall viscosity index in fit and unfit young and middle-aged subjects. *$P<0.05$ vs. young at the same cardiorespiratory fitness level; †$P<0.05$ vs. men of the same age in the cardiorespiratory fit group. Data are means ± SEM

cardiac contractions, and the stored energy is effectively used for causing blood to flow into peripheral tissues. In this progression, wall viscosity reflects energy loss during conversion of mechanical energy from cardiac pulsation into elastic energy in the arterial wall. Thus, the results of the present study indicating greater wall viscosity in middle-aged men than in young men suggest that advancing age results in inefficient mechanical transduction, and consequently the efficiency of blood flow in elastic arteries may be impaired with advancing age. In addition, our results indicated that the age-related increase in wall viscosity was smaller in men with high cardiorespiratory fitness than in unfit men, and there were no significant differences in wall viscosity or elasticity between young and middle-aged men with high cardiorespiratory fitness. These findings suggest that the attenuation of age-associated reduction in cardiorespiratory fitness level prevents energy loss during mechanical transduction, leading to maintenance of effective blood flow in elastic arteries.

These results may be expanded to elucidate the mechanisms underlying changes in autonomic regulation with advancing age. Arterial wall viscosity is mainly related to vascular smooth muscle cells (Bertram 1980; Bodley 1976; Nichols 1998; Taylor 1966). Therefore, age-associated sympathoexcitation (Seals and Dinenno 2004) may induce an increase in wall viscosity through smooth muscle contraction. On the other hand, increased wall viscosity leads to a reduction in wall strain (Armentano et al. 2006). Decreased wall strain may contribute to attenuation of baroreceptor

sensitivity in response to blood pressure fluctuation. Therefore, age-related reductions in baroreflex sensitivity (Monahan et al. 2001) may be associated with age-related increases in wall viscosity. Accordingly, age-associated arterial stiffening and its prevention can be influenced by physical methods.

10.11 Exercise Training Modes and Arterial Wall Viscosity

As described above, endurance and resistance exercise training increase and decrease arterial compliance, respectively. Considering the effects of aging and cardiorespiratory fitness level on arterial wall viscosity, we hypothesized that endurance exercise training may augment and resistance exercise training may attenuate arterial wall viscosity. We determined arterial wall viscosity indexes among endurance-trained athletes, resistance-trained athletes, and age-matched sedentary control men. In contrast to our hypothesis, endurance-trained athletes exhibited a higher arterial wall viscosity index compared with sedentary control men (Fig. 10.14; unpublished data). This finding suggests that endurance-trained athletes dissipate pulsatile energy from the left ventricle. We speculated on the mechanisms responsible for the greater wall viscosity in endurance-trained athletes. Endurance-trained athletes have a greater stroke volume and bradycardia, leading to a large pulsatile energy of the left ventricle per beat. Briefly, the central artery in endurance-trained athletes dissipates energy as viscosity, because conversion of cardiac pulsatile energy into arterial elastic energy is sufficient. Therefore, adaptation of arterial wall viscosity may be affected by exercise intensity. Given various adaptations of arterial

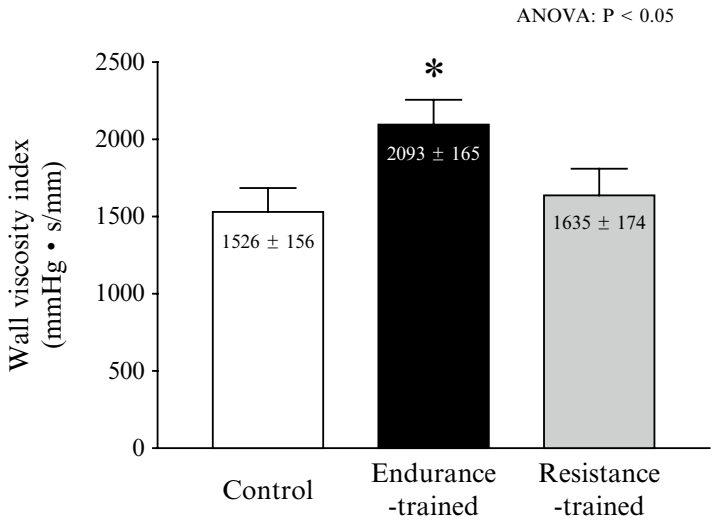

Fig. 10.14 Bar graph showing arterial wall viscosity index in control, endurance-trained, and resistance-trained young men. *$P<0.05$ vs. control. Data are means ± SEM

wall viscosity, further studies are needed to elucidate the effect of endurance or resistance exercise training on coupling the functions of cardiac pulsatility and arterial viscoelasticity.

10.12 Perspectives

Exercise prescription for health promotion is determined by intensity, amount, frequency, and time of training, and prevention of arteriosclerosis is no exception. To determine optimal exercise prescription for preventing arteriosclerosis, future intervention study is needed, particularly to elucidate the effects of endurance and resistance training on arterial wall viscosity. In 2013, "Physical Activity Reference for Health Promotion 2013" and "Active Guide 2013" were released by the Ministry of Health, Labour and Welfare of Japan, which recommends 10 min per day of physical activity (Plus 10). In the near future, the effects of Plus 10 will be verified for various outcomes, and dynamic arterial compliance, beta-stiffness index, PWV, and arterial wall viscosity will be evaluated. The underlying physiological mechanisms and clinical implications of vascular function adaptations to various exercise training regimens warrant further investigation in people of various ages.

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Chapter 11
Exercise, Appetite Control, and Body Weight Regulation

Mark Hopkins, Katy Horner, and Neil King

Abstract Exercise has many health benefits and should be an effective weight loss strategy because it increases energy expenditure. However, the success of exercise in producing and sustaining weight loss is influenced by compensatory changes in energy intake and non-exercise activity, among other factors (see King et al. Obesity 15(6):1373–1383, 2007 for a detailed review). The aim of this chapter is to discuss the evidence describing the relationship between exercise and body weight regulation, with a particular focus on appetite control. Evidence is discussed which demonstrates that weight loss responses to exercise are highly variable between individuals. The mechanisms underlying the relationship between exercise, appetite and energy intake, and hence body weight are also discussed. Some people experience an increase in fasting hunger in response to 12 weeks of supervised exercise. However, this is offset by an increase in meal-related satiety in overweight and obese individuals. It is worth noting that weight loss should not be considered as the only successful outcome of an exercise program. Indeed, exercise, even in the absence of weight loss, is associated with numerous health benefits. Nevertheless, an improved understanding of compensatory responses to exercise is vital so that exercise can be more effectively used in weight management; such an understanding may assist us to devise strategies to sustain greater long-term participation in physical activity.

Keywords Exercise • Appetite • Weight management • Compensatory responses

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_11

11.1 Introduction – Physical Activity and Weight Gain

Some estimates suggest that by 2030 over three billion people will be overweight and obese (Kelly et al. 2008). In many countries, governments and health agencies are strongly promoting physical activity (PA) as a means to prevent the accumulation of fatness that leads to weight gain and obesity. However, people often resist health promotion initiatives. In the UK, the Chief Medical Officer reported that 71 % of women and 61 % of men fail to meet the recommended levels of PA. However, despite the worldwide prevalence of obesity the primarily cause of the current obesity rates is still being debated (Cutler et al. 2003; Prentice and Jebb 1995; Philipson 2001). It has been argued that an increase in EI at the population level is the key driver of obesity (Swinburn et al. 2009a, b), as PA (and in particular, leisure time PA) has remained unchanged since the 1980s (Swinburn et al. 2009a; Westerterp and Speakman 2008). However, recent evidence suggests that occupational PA in America may have decreased by approximately 100 kcal·day^{-1} over the last 50 years (Church et al. 2011). This is of consequence as it has been suggested that the average 1 kg·year^{-1} increase in body weight seen in America over the last decade can be explained by an imbalance between daily EI and energy expenditure (EE) of just 50 kcal·day^{-1} (Hill et al. 2003). However, our ability to accurately determine this 'energy gap' is limited by inaccuracies inherent to the measurement of PA and EI, and it has been suggested that an imbalance of 300–1500 kcal·day^{-1} is likely to exist between normal weight and obese individuals (Bouchard 2008). Notwithstanding this, the promotion of PA would appear a viable approach to obesity management, as PA is a readily modifiable component of energy balance (Ravussin et al. 1986). Consequently, it is important that effects of PA on body weight regulation are fully understood. This is of particular importance given the complexities of body weight regulation, and the fact that this homeostatic regulation can ultimately be undermined by human behaviour (Biddle and Mutrie 2008).

This chapter will provide a current overview of the positive role that PA can play in obesity management. Particular focus will be given to the individual variability in exercise-induced weight loss and the compensatory adjustments in energy balance that mediate exercise-induced weight loss. This is vital if we wish to achieve a more complete understanding of the relationship between PA and body weight. While there are a range of compensatory responses that could occur to offset an exercise-induced increase in EE, such as changes in resting metabolic rate (RMR) and non-exercise activity thermogenesis (NEAT), the major focus of this chapter concerns appetite control and EI. For a more detailed review of the factors that likely contribute to variability in exercise-induced weight loss, see King et al. (2007). Mechanisms that may mediate changes in EI are briefly considered in this chapter and include both hedonic processes, e.g. pleasure, and homeostatic processes, e.g. signals arising from the gastrointestinal (GI) tract (for a more comprehensive review, see King et al. (2012)). NEAT is then briefly discussed. Finally, this chapter draws attention to the importance of considering the multiple health benefits of exercise in addition to weight management.

11.2 The Effect of Exercise on Body Weight Regulation and Energy Balance

Regular aerobic exercise is a commonly prescribed method of weight management in overweight and obese individuals (Donnelly et al. 2009). This approach stems from the fact that PA is a modifiable component of energy balance, accounting for approximately 30 % of total daily EE (Ravussin et al. 1986). Manipulating the amount of exercise performed can therefore create acute energy imbalance, and if maintained over a prolonged period, this imbalance can influence body composition (Donnelly et al. 2009). However, the classic depiction of energy balance, in which increased EE or decreased EI automatically leads to weight loss, is simplistic because it ignores the potential for adaptation and correction to restore energy balance (Schoeller 2009). This static view of energy balance assumes that if a specific component of energy balance is perturbed, the remaining components of energy balance will remain stable. However, the regulation of energy balance is a dynamic process, in which alterations to one component can elicit compensatory changes in other areas of the regulatory system (King et al. 2007; Boutcher and Dunn 2009). For example, an increase in EE (via exercise) could produce a compensatory change in food intake. Similarly, a decrease in food intake could alter daily EE (via changes in RMR or PA levels for example). Any such compensation following exercise- or dietary-induced energy deficits would act to minimise perturbations to energy balance, and, in turn, body weight (King et al. 2007). Consequently, the efficacy of exercise for weight management must be evaluated in the context of this dynamic regulatory system, in which perturbations to energy balance may elicit biological or behavioural compensation that attenuates the energy deficit (King et al. 2007; Boutcher and Dunn 2009). When the independent effect of exercise on body weight has been examined (i.e. without dietary restriction), chronic exercise (2–18 months) has been shown to produce only modest weight loss (1.5–3 kg) (Ballor and Keesey 1991; Fogelholm and Kukkonen-Harjula 2000; Jakicic and Otto 2006; Shaw et al. 2006; Catenacci and Wyatt 2007; Macfarlane and Thomas 2010). Importantly, the observed weight loss is typically below that theoretically expected based on objective measures of exercise-induced EE, with Borer (2008) noting that a daily exercise-induced EE of 400 kcal produces fat mass losses equivalent to only one third of the expected theoretical loss in fat mass (Borer 2008).

11.2.1 Individual Variability in Exercise-Induced Weight Loss

Until recently, there has been little attempt to understand the discrepancy between theoretically-predicted and actual weight loss; a lack of adherence to an exercise program has commonly been cited as the cause e.g. Donnelly and Smith (2005). However, even when compliance to an exercise intervention is high, actual weight loss has still been shown to be below that theoretically predicted (King et al. 2008;

Church et al. 2009). Consequently, despite being a commonly promoted means of weight management, our understanding of how exercise influences body weight regulation is lacking. This issue has been compounded by the fact that the mean (group) response to exercise is typically been used in studies examining the efficacy of exercise for weight loss. However, marked inter-individual variability has been noted in the biological responses to chronic exercise, e.g. maximal aerobic capacity (Bouchard 1995; Sisson et al. 2009), insulin sensitivity (Boulé et al. 2005), and resting fat oxidation (Barwell et al. 2009). Overlooking this variability makes the (incorrect) assumption that all individuals will respond similarly to standardized bouts of exercise, and any subsequent recommendations concerning the use of exercise in weight management will be appropriate for all individuals. This is not the case.

Marked heterogeneity in exercise-induced weight loss independent of the exercise-induced EE has been reported (King et al. 2008; Church et al. 2009; Barwell et al. 2009; Rosenkilde et al. 2012). For example, King et al. (2008) reported marked individual variability in the changes in body weight and fat mass following 12 weeks of supervised aerobic exercise in 35 overweight and obese individuals (See Fig. 11.1). Mean weight loss following the exercise intervention was 3.7 ± 3.6 kg, which was concordant with the predicted weight loss (based on the total exercise-induced EE). However, changes in body weight and fat mass ranged from −14.7 to +1.7 kg and −9.5 to +2.6 kg, respectively, despite the same volume of

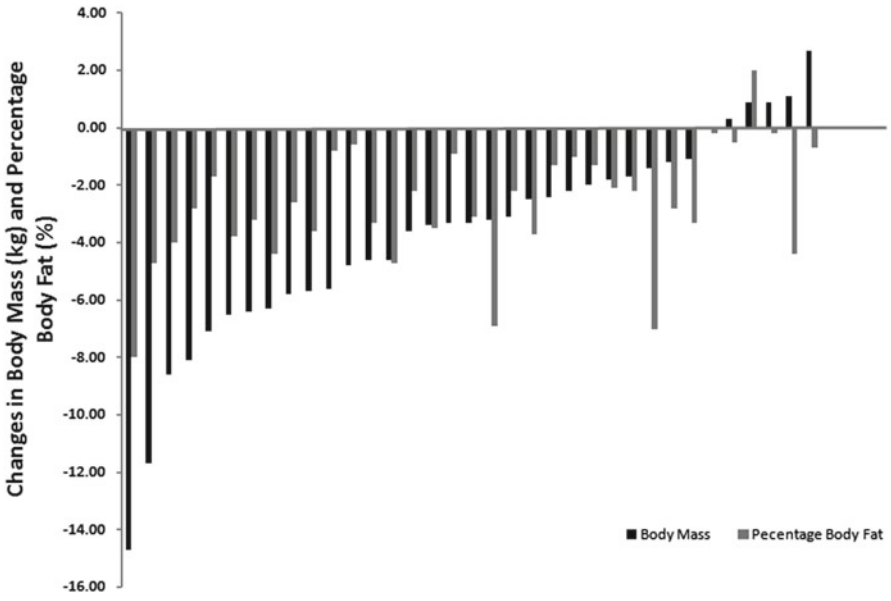

Fig. 11.1 Individual changes in body mass (kg) and percentage body fat following 12 weeks of supervised aerobic exercise in overweight and obese individuals (n = 35). Each pair of histograms represents one participant (Data previously published in King et al. (2008))

exercise being performed by all individuals (i.e., the total exercise-induced EE). During this study, participants were retrospectively classified as being either responders (n = 18) or non-responders (n = 17), based on the relationship between actual and predicted weight loss. Non-responders lost only 1.5 ± 2.5 kg (approximately half the predicted weight loss), while responders lost 6.3 ± 3.2 kg. Importantly, no differences existed in total exercise-induced EE between responders and non-responders ($p > 0.05$).

11.3 Compensatory Responses to Exercise-Induced Weight Loss

While the reported variability in exercise-induced weight loss indicates differences in susceptibility to exercise-induced weight loss, the underlying biological and behavioural mechanisms are poorly understood. Consequently, further characterisation of the factors that drive compensation in response to exercise is needed if more effective weight management programs are to be developed. Recent attempts have been made to identify the key biological and behavioural mechanisms that contribute to the heterogeneity in exercise-induced weight loss. Given the adaptive nature of energy balance, susceptibility to exercise-induced weight loss is likely to be mediated through a series of interdependent physiological and behavioural pathways. Unfortunately, our ability to discern the interrelationships between biological and behavioural aspects of energy balance during exercise-induced weight loss has been restricted, because previous studies have examined the contribution of individual components of energy balance in isolation. Therefore, if a greater understanding of how exercise influences appetite control and body weight regulation is to be achieved, it is important that both biological and behavioural components of energy balance are accurately and concurrently measured during exercise-induced energy deficit. Unfortunately, methodological limitations mean that this is difficult to achieve.

11.3.1 Compensatory Changes in Eating Behaviour

Compensatory increases in hunger and food intake have been suggested as reasons why exercise (alone) produces weight loss that is less than theoretically expected. However, the majority of research indicates that a single bout of aerobic exercise does not stimulate an automatic increase in hunger or food intake to restore energy balance (King and Blundell 1995; King et al. 1996, 1997; Blundell and King 1998). Indeed, a recent meta-analysis concluded that an acute bout of aerobic exercise is an effective means of eliciting short-term energy deficit, as individuals fail to compensate for increases in exercise-induced EE through increased food intake (Schubert

et al. 2012). However, it is important to note that these studies fail to acknowledge the issue of individual variability and examine the mean responses in hunger and food intake only. When post-exercise eating behaviour has been examined at the individual level, marked heterogeneity in EI compensation has been reported in lean (Finlayson et al. 2009) and obese females (Unick et al. 2010). Indeed, following acute exercise it appears that some people partially compensate for the increased exercise-induced EE via an increase in food intake, but others show no evidence of such compensation.

An acute bout of exercise does not adequately pose the same repeated and sustained challenge to energy balance as chronic exercise presents. Indeed, it has been suggested that the homeostatic regulatory system is insensitive to acute perturbations to energy balance (Levitsky 2005), but strongly defends against more sustained challenges (Westerterp 2010). It is possible that compensatory responses kick in at a threshold of energy deficit. Therefore, studying a single bout of acute exercise may be insufficient to achieve a complete understanding of the relationship between exercise and appetite. There is some evidence to suggest that food intake does not change in response to chronic exercise (7 weeks to 18 months) in overweight and obese individuals (King et al. 2008; Church et al. 2009; Barwell et al. 2009; Pritchard et al. 1997; Cox et al. 2003; Donnelly et al. 2003). However, these studies typically use unsupervised exercise interventions (with low total exercise-induced EE) and measure food intake using self-reporting. Therefore, such interventions may have been of insignificant magnitude to cause weight loss (and, therefore, compensation), and lacked the required sensitivity to detect small (but meaningful) changes in food intake.

When food intake has been accurately measured during exercise-induced weight loss (using laboratory-based test meals), there is evidence of partial compensation in food intake. For example, Stubbs et al. (2002) measured EI in six lean women over 7-day periods of no exercise, moderate (1.9 $MJ{\cdot}day^{-1}$) exercise, and high (3.4 $MJ{\cdot}day^{-1}$) exercise regimens. A significant increase in food intake was observed, with EI during the no, moderate, and high exercise periods equal to 8.9, 9.2, and 10.0 $MJ{\cdot}day^{-1}$, respectively. Approximately 30 % of the additional EE caused by the high exercise regimen was compensated for by increased EI (Stubbs et al. 2002). Similarly, Whybrow et al. (2008) demonstrated partial compensation in EI in six lean men and women performing 14 days of no, moderate (1.5–2.0 $MJ{\cdot}day^{-1}$), and high (3.0–4.0 $MJ{\cdot}day^{-1}$) levels of exercise. Again, partial compensation in EI was observed which equated to approximately 30 % of the exercise-induced EE (Whybrow et al. 2008). Collectively, these data appear to capture the initial stages of compensation in which EI begins to track the increases in total EE. While the degree of compensation was relatively modest (and did not fully compensate for the energy deficit), it is possible that if exercise were continued for longer (thus inducing a greater energy deficit), increases in EI may have more closely matched the increments in EE (Stubbs et al. 2004).

It is worth noting that King et al. (2008) also measured subjective appetite and food intake during their 12 week exercise study (King et al. 2008). As previously discussed, large heterogeneity was seen in the body composition responses to exercise, and participants were retrospective classified as either responders or non-

responders based on the relationship between actual and predicted weight loss. Interestingly, EI and daily hunger (measured using visual analogue scales) increased by 268 ± 455 kcal·day^{-1} and 6.9 ± 11.4 mm·day^{-1} in the non-responders (who lost 1.5 ± 2.5 kg). However, EI decreased by 130 ± 485 kcal·day^{-1} in the responders (who lost 6.3 ± 3.2 kg), while daily hunger remained constant. These data suggest that while some people can tolerate short-to-medium-term periods of exercise-induced energy deficit, the same exercise challenge triggers increased hunger and food intake in others. However, further research is needed to better understand the drivers of compensatory changes in hunger and food intake.

Exercise and Appetite Control: A Dual Process

To further understand the mechanisms behind compensatory changes in eating behaviour, King et al. (2009) examined the effects of 12 weeks of supervised aerobic exercise on hunger and satiety in 58 overweight and obese individuals (body mass index [BMI] = 31.8 ± 4.5 kg/m^2) (King et al. 2009). This approach revealed two processes that acted concurrently to mediate the effect of exercise on appetite control. Following the exercise intervention, a significant increase in fasting hunger was seen ($p < 0.001$). However, there was also a parallel increase in the satiating effect of a fixed-energy meal following the intervention ($p < 0.05$). Therefore, while the exercise intervention increased fasting hunger, this increased drive to eat was offset by a parallel increase in meal-related satiety.

Interestingly, this increase in meal-related satiety may have resulted from exercise-induced changes in postprandial satiety signalling. Peripheral signals, including long-term (tonic) signals such as leptin and insulin and short-term (episodic) signals released by the GI tract, play an important role in appetite control and could explain changes in appetite with exercise (see Martins et al. (2008) for a comprehensive review). Martins et al. (2010) measured fasting and postprandial levels of orexigenic (total and acylated ghrelin) and anorexigenic (peptide YY (PYY), glucagon-like peptide 1 (GLP-1)) peptides in 15 overweight and obese individuals during 12 weeks of supervised aerobic exercise (Martins et al. 2010). A significant increase in fasting hunger was again observed following the intervention ($p < 0.01$), but this increase was again offset by greater satiety in response to a fixed-energy meal. Interestingly, there was also a significant increase in the suppression of acylated ghrelin following the fixed-energy meal, and a tendency toward an increase in the postprandial release of GLP-1 following the exercise intervention ($p = 0.07$). These hormonal responses would have acted to augment satiety during the postprandial period. However, the mechanisms behind the exercise-induced increase in fasting hunger in the studies of King et al. (2009) and Martins et al. (2010) have yet to be established. An increase in fasting hunger has also been previously reported following dietary-induced weight loss (Keim et al. 1998; Doucet et al. 2000), and this increase in fasting hunger has been causally linked to a reduction in leptin (independent of fat mass) following weight loss (Keim et al. 1998). However, whether a decline in leptin also promotes increased hunger following exercise-induced weight loss has yet to be established.

Gastrointestinal Processes of Appetite Control

Changes in gastric emptying–the rate at which nutrients empty from the stomach into the small intestine–may also play an important role in exercise-induced changes in appetite and food intake (King et al. 2012; Horner et al. 2011). However, evidence concerning the short- and longer-term effects of exercise on gastric emptying has been poorly documented. One study reported faster gastric emptying in marathon runners compared to sedentary individuals, but the sample size was small (n = 10 per group), the study gave limited descriptors of body composition, and EI, appetite, and other eating behaviour characteristics were not reported (Carrio et al. 1989). Furthermore, cross-sectional studies do not enable a causal relationship between exercise, gastric emptying, and appetite control to be determined. Gut adaptations may only occur after chronic increases in EE or in response to other factors such as changes in habitual diet or body composition. It is intuitive that a period of transition or uncoupling between EE and EI will precede a re-coupling between EE and EI (King 1999). Therefore, changes in gastric emptying and other mechanisms linked to appetite control may vary over time as the exercise-induced EE continues. There is a need for further studies to systematically examine the interactions among gastric emptying, gut peptides, and appetite in response to short- and longer-term exercise and to determine the implications of any changes for EI and weight management.

The Effect of Exercise on Food Preference and Hedonic Reward

Daily food intake is a discontinuous process that consists of discrete feeding episodes, and this pattern of eating is coordinated through homeostatic (e.g. energy regulation) and non-homeostatic signals (e.g. food hedonics and environmental factors) (Schwartz et al. 2000). Homeostatic feeding is often described as a series of physiological processes that initiate and terminate feeding (i.e. hunger and satiation) and suppress inter-meal hunger (i.e. satiety) (Halford and Blundell 2000). Short-term (episodic) and long-term (tonic) inhibitory signals arising from adipose tissue and the GI tract are thought to drive this pattern of eating, and act to modulate an intrinsic excitatory drive to eat (Blundell and Gillett 2001). However, non-homeostatic factors such as food palatability and the hedonic value of food are thought to interact with these homeostatic signals and mediate the sensitivity of appetite control (Berthoud 2006). Indeed, recent research has highlighted the need to distinguish ‘affective liking’ from ‘motivational wanting’ when examining the hedonic determinants of eating behaviour, as these components of food reward may represent separable risk factors in overconsumption and weight gain (Berridge 1996; Finlayson and King 2007). In relation to the study of eating behaviour, liking is thought to reflect the perceived pleasurable sensory properties of food, while wanting is thought to reflect the attraction towards a specific food over available alternatives (Blundell and Gillett 2001). Both components of food reward act in parallel to influence eating behaviour (Finlayson et al. 2008), with obese individuals (Nijs et al. 2010) and those demonstrating binge eating displaying heightened liking and wanting for food (Davis et al. 2009).

In addition to EI, exercise could potentially influence other aspects of eating behaviour, such as food preference. However, Elder and Roberts (2007) note that it is difficult to establish whether exercise-induced changes in food preference influence compensatory eating behaviour (and, in turn, body weight regulation), as insufficient data currently exist (Elder and Roberts 2007). It has recently been shown that individual differences in the hedonic response to exercise may be an important determinant of exercise-induced overconsumption (Finlayson et al. 2009, 2011; Cornier et al. 2012). Following 50 min of cycling, Finlayson et al. (2009) identified a group of susceptible lean women (termed compensators; n = 11) who over-consumed relative to the energy cost of exercise. After exercise, these compensators exhibited enhanced implicit wanting for food (especially high fat, sweet foods), and rated their food as more palatable compared to those who displayed no evidence of post-exercise compensatory eating (n = 11) (Finlayson et al. 2009). Furthermore, Finlayson et al. (2011) reported that overweight and obese individuals who exhibited an immediate post-exercise increase in wanting for high fat, sweet foods demonstrated smaller losses in fat mass following 12 weeks of supervised aerobic exercise (Finlayson et al. 2011). These data suggest that exercise-induced changes in the hedonic response to food may influence susceptibility to exercise-induced overconsumption. However, further research is needed to establish how exercise influences the expression of food preference and reward.

11.3.2 Compensatory Changes in Non-exercise Activity Thermogenesis

Given the adaptive nature of energy balance, it is plausible that an increase in exercise-induced EE could influence other components of total daily EE. Indeed, it has been suggested that compensatory changes in NEAT, i.e. the EE due to all physical activities other than volitional exercise, could occur in response to exercise (Levine 2004). The effect of this would be to attenuate the energy deficit created through exercise, in turn, subsequent weight loss. However, at present evidence for such an effect is equivocal, as some (Colley et al. 2010; Manthou et al. 2010) but not all studies (McLaughlin et al. 2006; Hollowell et al. 2009; Turner et al. 2010; Rangan et al. 2011) have reported a reduction in NEAT in response to exercise (for a more detailed review, see (Garland et al. 2011). These inconsistencies may relate to methodological differences in exercise mode or intervention length, while the techniques used to measure total daily EE also vary markedly (Garland et al. 2011). There is also limited evidence that age and exercise intensity mediate compensatory changes in NEAT. A reduction in non-exercise activity has been reported in older (55–68 years) but not in younger (28–41 years) individuals (Meijer et al. 1991, 1999), while a delayed response (3 days) in NEAT has been reported after high-intensity exercise but not moderate intensity exercise (Alahmadi et al. 2011). However, further research using accurate measures of daily EE (i.e. doubly labelled water or indirect calorimetry) are needed to confirm (or refute) these findings.

11.4 Independent Health Benefits of Physical Activity

Body weight is typically used as the primary marker of success in exercise-based weight management. However, regular exercise can produce clinically meaningful improvements in health independent of changes in body weight. For example, regular aerobic exercise can improve insulin sensitivity, reduce the progression of type 2 diabetes, and ameliorate hepatic steatosis and blood lipid profiles independent of body weight (Knowler et al. 2002; Lindstrom et al. 2003; Johnson and George 2010). Consequently, exercise-based weight management should not use body weight as the sole marker of success (particualrly as changes in body weight can mask important changes in fat mass or fat-free mass). Indeed, cardiovascular fitness may actually be a better predictor of all-cause mortality than body weight, with high cardiovascular fitness thought to offer protection against cardiovascular disease (Blair et al. 1995; Wei et al. 1999). Indeed, individuals with a high BMI but high cardiovascular fitness are thought to be at lower risk than those with a normal BMI and poor cardiovascular fitness (Fogelholm 2009). However, it is important to note that BMI is still an independent risk factor for type 2 diabetes and cardiovascular disease (Lewis et al. 2009), and the evidence demonstrating a protective effect of high aerobic fitness is stronger than that for high levels of daily PA (Blair et al. 2001). Therefore, effective weight management should focus on improving both body composition and cardiovascular fitness (Blair and Church 2004). From a public health standpoint, these independent health benefits of regular aerobic exercise should be promoted, and the emphasis on body weight as the primary marker of success in exercise-based weight management reduced (King et al. 2010).

11.5 Conclusion

While it is still controversial how sustained increases in PA can be achieved at the population level (Stubbs et al. 2010), the provision of a clear rationale for the health benefits of exercise and a greater understanding of compensatory responses will be important if we wish to encourage and sustain long-term participation in PA. Even when exercise is supervised and EE is matched there is variability in weight loss responses to exercise among individuals. Among a variety of factors, changes in EI and/or non-exercise activity likely contribute to this inter-individual variability in weight loss. Characterisation of the range of psychological, behavioural, and physiological processes which potentially mediate exercise-induced changes in EI and non-exercise activity will aid in elucidating why some individuals lose less weight than predicted with exercise. It may then be possible to tailor weight management strategies more effectively to suit individuals.

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Chapter 12
Exercise and Food Intake: What's the Connection? What Are the Potential Sex Differences?

Amanda J. Morris and Todd A. Hagobian

Abstract Regular physical activity is widely regarded as playing a large role in obesity prevention and treatment efforts. However, current data suggest that men lose more weight with exercise training than women. Thus, in this chapter we review the impact of exercise on weight loss in men and women, and potential homeostatic (appetite hormones) and non-homeostatic (neuronal responses) explanations of sex differences. The evolving story may influence our view on the impact of exercise on weight loss, and whether a true sex difference exists.

Keywords Appetite hormones • Neuronal responses • Food intake • Exercise • Sex differences

12.1 Introduction

The obesity epidemic is the greatest public health crisis that the U.S. and other countries are facing. It is now estimated that 35 % of adults in the US and 1.4 billion adults worldwide are obese (Ogden et al. 2013). Regular physical activity, in the form of daily structured exercise, is widely regarded as playing a large role in obesity and weight management. In general, exercise directly impacts weight by increasing total daily energy expenditure and resting metabolic rate (Jamurtas et al. 2004). Emerging data suggest that exercise also affects energy intake, although sex differences may exist (Hagobian et al. 2013; Hagobian and Braun 2010). Thus, the purpose of this review is to discuss the impact on and potential mechanisms by which exercise may affect energy intake, and whether this differs by sex. The developing story may impact our view on the use of physical activity in obesity prevention and treatment, and elucidate whether a true sex difference exists.

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_12

12.2 Exercise and Weight Loss

Energy restriction is the most common method used to reduce weight (Wing 1999). Exercise alone, without restricting energy intake, results in modest weight loss but is critically important for the prevention of weight regain. For example, Jakicic (2009) found that exercise per se resulted in <3 % weight loss, while the National Weight Control Registry found that 60 min/day of exercise is the most important factor in preventing weight regain (Phelan et al. 2009). Based on these and other data, the American College of Sports Medicine position stand states "150–200 kcal/week of moderate intensity exercise does not result in clinically significant weight loss" (Donnelly et al. 2009). Thus, a larger amount of physical activity (>2,000 kcal/week) or physical activity combined with energy restriction may be necessary to produce greater weight loss (Jakicic 2003; Jeffery et al. 2003; Jakicic et al. 2003).

Surprisingly, there are limited data examining whether weight loss is different in men and women exposed to an exercise treatment. The Midwest Exercise Trial by Donnelly and colleagues is the only published randomized controlled, supervised exercise trial to compare weight loss between sexes (Donnelly et al. 2003a, b; Potteiger et al. 2003). Overweight and obese men and women were randomized to an exercise (45 min/day, 5 days/week) or a control group, and by design subjects were not given recommendations on dietary energy intake (i.e. no intervention to impact energy intake). After 16 months, men in the exercise group lost ~5 kg, whereas controls stayed at the same weight. In contrast, women in the exercise group had a small weight gain (approximately 0.6 kg), while the control group had a much larger weight gain (approximately 3.0 kg). Thus, these data suggest that (1) weight losses are different in men and women when both are exposed to a similar exercise treatment, (2) women more accurately match energy intake with exercise expenditure and ultimately maintain body weight, and (3) men do not completely compensate by increasing energy intake to maintain energy balance and therefore are able to maintain an energy deficit and lose weight.

12.3 Appetite Hormones

To explain sex differences in weight loss with exercise, previous research has mainly focused on appetite hormones and the impact they have on energy intake. Energy intake and, subsequently, body weight is regulated by a complex system in which the brain integrates both peripheral and central signals. Peripheral appetite hormones (e.g. acylated ghrelin, leptin, insulin, etc.) play a key role in this system, sending a signal to the brain to alter (or maintain) energy intake.

Appetite hormones are generally classified as either episodic (short-term) or tonic (long-term). Episodic signals, such as ghrelin, help control meal initiation, meal size, and meal termination (Cummings et al. 2001, 2004; Cummings 2006). Acylated (active) ghrelin is largely regarded as the only hormone to increase energy

intake in humans and a variety of animals. For example, Wren et al. (2001a) found that infusion with ghrelin, relative to saline infusion, increased both hunger and ad libitum energy intake in men. Similarly, Druce et al. (2005) observed that ghrelin infusion increased subsequent ad libitum energy intake in normal-weight and overweight men and women. This is corroborated by animal data suggesting that ghrelin infusion increases energy intake (Wren et al. 2001b). Others have found that an energy deficit, and ultimately weight loss, increases ghrelin concentrations (Leidy et al. 2004, 2007; Cummings et al. 2002). In addition to stimulating energy intake there is evidence for ghrelin's role as a meal initiator. Ghrelin concentrations follow a diurnal pattern; concentrations peak before meals and subsequently fall. Cummings et al. (2001) found that plasma ghrelin concentrations rose to twice baseline levels before meals and fell 1 h after meals. Interestingly, plasma ghrelin levels are lower in obese vs. normal-weight individuals (Tschop et al. 2001), which may be due to the presence of elevated leptin and insulin concentrations in obese individuals; ghrelin levels are typically inversely related to levels of insulin and leptin (Tschop et al. 2001). Additionally, ghrelin concentrations in obese, relative to normal-weight individuals, typically do not fall after a meal suggesting greater stimulus to eat (English et al. 2002).

Tonic signals, such as insulin and leptin, are long-term signals that regulate body weight. Several animal studies have shown that increases in insulin or leptin concentration decrease food intake and induce weight loss (Air et al. 2002; Halaas and Friedman 1997; Bruijnzeel et al. 2011). In humans, however, the impact of insulin and leptin on energy intake is less clear. Obese individuals typically have higher concentrations of these two hormones suggesting that they may be "resistant" to the effects of these hormones. On the other hand, emerging data suggest that lower concentrations of these hormones stimulate energy intake (Chan et al. 2003; Clegg et al. 2007; Woods et al. 2003). Thus, in humans, these hormones may be more sensitive and may stimulate energy intake in response to an energy deficit or lower weight, as opposed to decreasing energy intake as initially thought.

In addition to regulating storage of nutrients, insulin acts as an adiposity signal. Typically, insulin concentrations rise after eating, then fall shortly thereafter (Hansen and Johansen 1970). Polonsky et al. (1988) found that obese individuals had similar insulin pulse patterns to normal individuals; however, insulin secretion rate was increased in obese individuals. Leptin, which is secreted from adipose tissue, informs the brain of energy stores (Badman and Flier 2005) but does not appear to be impacted by meal ingestion (Caro et al. 1996). Moreover, leptin concentrations fall in response to fasting in both normal-weight and obese subjects with a more drastic response in the obese (Boden et al. 1996), most likely in an effort to preserve body weight.

Insulin and leptin levels are correlated with body fat, and obese individuals typically have higher levels of leptin and insulin (Benoit et al. 2004). Bagdade et al. (1967) found that obesity was positively correlated with elevated baseline insulin concentrations, and that subjects with higher baseline insulin experienced an increased response of insulin to glucose. Similarly, Sinha et al. (1996) found that leptin concentrations were significantly higher in obese subjects versus lean sub-

jects. Taken together, these results indicate that insulin and leptin are strong appetite and adiposity signals that suppress energy intake, but obese individuals are resistant to their effects.

12.3.1 Short-Term Exercise and Appetite Hormones

In general, short-term exercise (1–8 bouts) alters appetite hormones in a direction expected to suppress energy intake, at least in men. For example, Broom et al. (2007) examined the effects of exercise on acylated ghrelin concentration in trained runners. Subjects ran for 60 min at 75 % of maximal oxygen consumption ($VO_{2\,Max}$) and then rested for 8 h. Acylated ghrelin was significantly lower during exercise (38 %) and post exercise (35 %) relative to the no-exercise condition. Similarly, others found that short-term exercise alters ghrelin concentrations in a direction expected to suppress energy intake (King et al. 2010b), and that higher-intensity exercise may cause a more dramatic decrease in ghrelin concentrations (King et al. 2010b). Interestingly, resistance exercise has a similar impact and suppresses ghrelin concentrations (Broom et al. 2009). Taken together, these data suggest that short-term exercise, regardless of exercise mode, decreases acylated ghrelin and that higher-intensity exercise may have a more profound impact.

In general, insulin concentrations are lower after exercise and remain lower for up to 48 h (Essig et al. 2000; Kindermann et al. 1982). For example, Kindermann et al. (1982) found a significant decrease in insulin concentrations after a 50-min treadmill run, and others found lower insulin levels to continue for up to 48 h (Essig et al. 2000). Despite the impact exercise has on lowering insulin, to our knowledge no published human studies have distinguished whether lower insulin stimulates energy intake post-exercise or whether it is just an artifact of intermediary metabolism.

On the other hand, post-exercise alterations in leptin concentrations are delayed and appear to be tied to changes in energy balance. For example, previous research has shown that leptin does not change until 24–48 h post-exercise when an energy deficit is maintained (Essig et al. 2000; van Aggel-Leijssen et al. 1999; Olive and Miller 2001). Olive and Miller (2001) found that leptin concentrations were not immediately altered after a maximal exercise test, but were significantly lower 48 h after the endurance test. This is corroborated by Essig et al.'s (2000) study showing that leptin concentrations start to decrease beginning at 24 h post-exercise, continuing through 48 h post-exercise.

Despite the findings mentioned above, there is a dearth of data evaluating the impact of exercise on appetite hormones while energy balance is maintained. To do this, energy intake must be raised to match (or exceed) the new higher energy expenditure.

To comprehensively assess the role of exercise in energy balance, we previously evaluated the effects of short-term exercise on appetite hormones while maintaining energy balance (Hagobian et al. 2008). Appetite hormones were assessed in nine

healthy, habitually-active subjects at baseline, after three days of overfeeding (+750 kcal/day), and after one day of overfeeding (+1,500 kcal) plus exercise (expenditure −750 kcal). The critical component of the study design was that energy balance was similar in the overfeeding and overfeeding-plus-exercise days (+750 kcal/day). Fasting leptin and insulin concentrations were significantly higher after 3 days of overfeeding and remained elevated after the overfeeding-plus-exercise day. However, ghrelin concentrations were significantly lower after the overfeeding-plus-exercise day.

Hilton and Loucks (2000) studied the effects of 4 daily bouts of exercise on 24-h leptin concentrations with and without energy replacement in women. Exercise without energy replacement resulted in suppressed 24 h amplitude and mean concentrations of leptin. Additionally, leptin concentrations were not affected when energy was replaced. In a similar study, Black et al. (2005) examined the effects of short-term exercise training in energy balance and energy deficit on appetite hormones. Fasting insulin and leptin levels were lower after exercise without energy replacement; however, exercise in energy balance had no impact on these hormones. Collectively, these data suggest that (1) exercise in energy balance does not impact fasting leptin and insulin concentrations, (2) exercise per se has an effect on ghrelin concentrations, and (3) most changes in these hormones may be dependent on energy availability rather than exercise.

12.3.2 Medium- to Long-Term Exercise Training

In medium- to long-term (12 weeks to 12 months) exercise training studies, changes in appetite hormones appear to be tied to weight loss. For example, Foster-Schubert et al. (2005) examined the effects of a 12-month moderate intensity (60–75 % heart rate max, 45 min/day, 5 days/week) aerobic exercise intervention on circulating hormone levels in overweight women. Ghrelin concentrations significantly increased (~18 %) in subjects who lost more than 3 kg, whereas there was no change in subjects who lost less than 1.5 kg. Leidy et al. (2004) found similar results after a 3-month aerobic (5 days/week, 70–80 % heart rate max) exercise program in normal-weight women; exercise-induced weight loss increased ghrelin concentrations and ghrelin was negatively correlated with changes in body weight. Moreover, others have found that exercise-induced weight loss lowers insulin concentrations (Martins et al. 2010; Okazaki et al. 1999; Potteiger et al. 2003), lowers leptin concentrations (Okazaki et al. 1999; Thong et al. 2000), and increases ghrelin concentrations (Martins et al. 2010). Taken together, these data suggest that (1) medium- to long-term aerobic exercise programs resulting in weight loss alter appetite hormones (lower insulin and leptin, higher ghrelin) in a direction expected to stimulate energy intake, (2) exercise training per se has no impact on these hormones, and (3) alterations in energy balance appear to be the critical factor in altering appetite hormones.

12.3.3 Sex Differences

Surprisingly, few studies have directly addressed whether exercise alters appetite hormones differently in men vs. women, and whether this difference might potentially explain sex differences in weight loss with exercise. Hickey et al. (1997) assessed sex differences in insulin and leptin concentrations in response to 12 weeks of exercise training (45 min/day, 4 days/week) in energy balance (weight was maintained in both sexes). Insulin and leptin concentrations were significantly lowered (~20 % each) after exercise training in women. In men, however, there was no difference in the concentrations of these hormones. This study provided initial evidence that the appetite hormones in men and women respond differently to exercise.

To directly tackle both the "exercise versus energy status" and the "sex differences in appetite hormones" questions, we assessed the effects of short-term exercise training on appetite hormones in sedentary, overweight/obese men and women (Hagobian et al. 2009). Using a randomized, counterbalanced, cross-over study design, appetite hormones were assessed in the fasted state and during a meal tolerance test in three different conditions: no-exercise baseline, after four daily bouts of exercise with dietary energy added to maintain energy balance, and after four daily bouts of exercise without dietary energy added (energy deficit). To control for the confounding influence of sex hormones, all women were tested in the early follicular phase of the menstrual cycle. We noted a clear sex difference in the way exercise impacts appetite hormones. In women, acylated ghrelin was significantly higher and insulin was significantly lower after exercise in energy deficit, both of which would be expected to stimulate energy intake. When dietary energy was added back to maintain energy balance, the same pattern of appetite hormones persisted. In contrast, men experienced no change in any appetite hormone while exercising in energy balance, and slightly lower insulin after exercise in energy deficit. Thus, the main findings were: (1) in women, exercise in energy balance alters appetite hormones in a direction expected to increase energy intake, (2) this response is potentiated by an energy deficit, and (3) in men, there are subtle if any changes in appetite hormones with exercise in either energy balance or energy deficit. Taken together, these data suggest that women more accurately match energy intake to expenditure and this may be driven by differences in appetite hormones.

12.4 Neuronal Control of Food Intake

There is a clear sex difference in the response of appetite hormones to exercise, but little is known about how exercise impacts neural (brain) activity and whether this differs by sex. The regulation of energy intake is a multifaceted, complex interaction that involves both homeostatic and non-homeostatic signals. While hormones have a large influence on energy intake, other factors such as environment,

emotional/cognitive state, visual cues, and sensory response have an effect as well. One way to gain insight into how the brain incorporates these signals is by using functional magnetic resonance imaging (fMRI) (Tataranni and DelParigi 2003). fMRI accurately and non-invasively assesses changes in blood-oxygen-level-dependent (BOLD) signals (ratio of oxygenated to deoxygenated blood) to map neural activity (Tataranni and DelParigi 2003).

Killgore et al. (2003) found significant activation in brain regions associated with food reward, inhibitory control, and vision-attention in response to high-calorie food cues. Furthermore, the BOLD signal change was significantly greater after visual presentation of high-calorie foods versus low-calorie foods. Others have found a difference between sexes in response to visual food cues. Killgore and Yurgelun-Todd (2010) examined sex differences in cerebral responses to food cues. Sixteen males and females (8 M, 8 F) underwent fMRI while looking at images of high and low calorie foods. Women had significantly greater whole-brain responses than men to images of high- versus low-calorie food. Additionally, Uher et al. (2006) found that women had greater responses to food-related stimuli (visual and gustatory) than men. These data suggest that women generally have a stronger response to food-related stimuli than men in a direction expected to stimulate energy intake.

12.4.1 Exercise, Neuronal Response, and Sex Differences

To our knowledge, only two published studies have assessed the effects of exercise on neuronal responses to visual food cues. We recently (Evero et al. 2012) examined the effects of a single bout of exercise on neuronal responses in food reward brain regions. Thirty healthy males and females (17 M, 13 W) completed either 60 min of rest or 60 min of high intensity (~80 % heart rate max) exercise on a cycle ergometer in a crossover design. Immediately after each condition, changes in BOLD signals in response to high- and low-calorie foods were assessed using fMRI. Exercise significantly reduced neuronal response to food cues in food reward (insula, putamen, rolandic operculum) and visual attention (inferior and middle occipital gyrus) brain regions. In exploratory analyses (unpublished observation), we assessed exercise-induced changes in neuronal responses in men and women analyzed separately. We found that men had reduced neuronal responses in visual-attention brain regions (e.g., right inferior occipital gyrus, etc.). Women displayed reduced neuronal responses in both visual-attention (e.g., left middle occipital gyrus, etc.) and motor control brain regions (e.g., left supplemental motor area, etc.). Interestingly, in men the extent of deactivation in visual attention regions was greater, suggesting that they are less responsive to food cues.

In a similar, but longer duration, study Cornier et al. (2012) examined the effects of 24 weeks of exercise training on the neuronal response to food cues in overweight/obese men and women. Exercise training significantly reduced neuronal responses in food-reward and other brain regions (bilateral parietal cortices, left

insula, and visual cortex). Taken together, these two exercise studies indicate that exercise reduces neuronal responses to visual food cues in food reward and visual brain regions, consistent with suppressed post-exercise energy intake. However, further research needs to be conducted to determine whether a true sex difference is evident in neuronal responses to exercise.

12.5 Exercise, Relative Energy Intake, and Sex Differences

In general, exercise alters relative energy intake (energy intake minus exercise expenditure) but not absolute energy intake. In a series of studies, Stensel and colleagues showed that high-intensity exercise suppresses relative energy intake (King et al. 2010a, b, 2011). For example, King et al. (2011) noted that relative energy intake (not absolute energy intake) was significantly reduced after 60 min of swimming, compared to a no-exercise condition. This is corroborated by others showing that exercise suppresses relative energy intake (Unick et al. 2010; Ueda et al. 2009; Stubbs et al. 2002a, b; Imbeault et al. 1997).

In women, exercise may also lower relative energy intake (Unick et al. 2010), but weight status seems to play a pivotal role because obese, compared to normal-weight, women appear to consume more food after exercise (George and Morganstein 2003). Surprisingly, none of these studies were designed to directly assess sex differences. To our knowledge, only three studies have addressed this pertinent issue.

Stubbs et al. (2002a, b) examined the effect of different levels of energy expenditure on energy intake in men and women. Different levels of exercise were used: none, moderate (two 40 min sessions/day), and high (three 40 min sessions/day) for 7–9 days. In men, energy intake did not differ across conditions. However, women partially compensated in response to the high-exercise condition; they increased energy intake by 30 % compared to baseline. This is consistent with another study showing that men and women do not fully compensate with increased energy intake for five daily bouts of exercise (Staten 1991).

We recently determined whether men and women, when exposed to the same relative exercise treatment, have different ad libitum energy intake and whether this may be explained by differences in appetite hormones (Hagobian et al. 2013). Men and women either rested or exercised on a cycle ergometer at 70 % of peak oxygen consumption (VO_2 peak) until 30 % of total daily energy expenditure was expended, in a randomized, crossover, counterbalanced fashion. To potentially control for confounding variables, we matched men and women on body mass index and cardiorespiratory fitness levels, and all women were studied in the early follicular phase of the menstrual cycle. In contrast to our primary hypothesis, we found a clear effect of exercise on relative energy intake regardless of sex. Specifically, relative energy intake was significantly lower after exercise, compared to rest, in both men (672 ± 827 after exercise, $1{,}133 \pm 619$ kcal after rest) and women (-121 ± 243 after exercise, 530 ± 233 kcal after rest). Additionally, there was no compensatory increase in total energy intake after exercise (i.e., similar total energy intake in exer-

cise and rest conditions) in either sex. We also noted that the majority of men and women (19 of 21 subjects) were able to maintain an energy deficit after the exercise condition (i.e. energy intake was not increased to match or exceed exercise expenditure in a majority of subjects). However, there was a large variability in energy intake, as ~30 % of subjects lowered energy intake after exercise compared to the rest condition, whereas the other subjects had higher energy intake after exercise compared to the rest condition, which is consistent with previous reports (Finlayson et al. 2009; Unick et al. 2010). Thus, these data suggest that exercise suppresses relative energy intake regardless of sex, but the energy intake response is highly variable.

12.6 Conclusion

It is generally assumed that exercise interventions result in modest weight loss, but the response appears to differ by sex (men lose more weight than women). This suggests that women increase energy intake to match the new, higher energy expenditure in response to exercise training. In support, others and we have found that appetite hormones and neuronal responses are altered in a direction expected to increase energy intake in women but not in men. However, data directly assessing *ad libitum* energy intake after exercise do not support sex differences (i.e. men and women respond similarly by suppressing relative energy intake). Dissemination of these data to the lay public is vital to show that exercise may suppress energy intake, and to therefore potentially influence physical activity recommendations. In ensuing years, the Midwest Exercise Trial II (Donnelly et al. 2012) will provide insight into whether a threshold for exercise-induced weight loss exists in both men and women. Thus, the evolving story as to whether there is a true sex difference in exercise-induced weight loss will continue to progress as more research is amassed.

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Chapter 13
Role of Physical Exercise on Postprandial Blood Glucose Responses to Low-Carbohydrate/High-Fat Diet Intake

Shigeharu Numao

Abstract Postprandial blood glucose responses may be an effective predictor of mortality and cardiovascular diseases. Abnormal postprandial blood glucose response is associated with the development of arteriosclerosis. Therefore, postprandial blood glucose response has become an increasingly important indicator of whether individuals are leading a healthy life. Daily diet and physical exercise play important roles in optimizing postprandial blood glucose response. Consuming a low-carbohydrate/high-fat (LC/HF) diet (<40 % of its calorie as carbohydrate) for short and long periods contributes to an increase in postprandial blood glucose concentrations. In contrast, physical exercise (a single bout of physical exercise and exercise training) increases glucose uptake and insulin sensitivity, subsequently leading to improvements in postprandial blood glucose response. However, a single bout of physical exercise has less effect on abnormal postprandial blood glucose responses induced by short-term intake of a LC/HF diet. Presumably, the effects of a single bout of physical exercise may be impaired by a short-term LC/HF diet. Performing physical exercise before but not after ingesting a LC/HF diet may improve the LC/HF diet-induced attenuation of postprandial blood glucose response. Moreover, physical exercise training should improve the postprandial blood glucose response induced by a LC/HF diet. However, there is little direct evidence regarding the effects of physical training on abnormal postprandial blood glucose response induced by a LC/HF diet, and, thus, future intervention studies are required.

Keywords Impaired glucose tolerance • Postprandial hyperglycemia • Single bout of physical exercise • Low-carbohydrate/high-fat diet • Insulin • Glucagon-like peptide 1

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_13

13.1 Introduction

Abnormal postprandial blood glucose response is considered better for predicting mortality and metabolic disorders, including cardiovascular diseases (CVDs), than fasting blood glucose concentrations, and has received considerable attention in recent years. Typical symptoms of an abnormal postprandial blood glucose response include impaired glucose tolerance (IGT) and/or postprandial hyperglycemia. IGT is defined as a 2-h blood glucose concentration of 140–199 mg/dl during a 75-g oral glucose tolerance test (OGTT) (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997; Genuth et al. 2003). Postprandial hyperglycemia has been less certainly defined, although it is an abnormal condition wherein high blood glucose concentrations are maintained for several hours after a meal.

IGT and postprandial hyperglycemia primarily result from an imbalance between glucose uptake and glucose release (production) in the postprandial state, which reflects a decrease in glucose uptake into the liver and peripheral tissues (skeletal muscles and adipose tissues), attenuation of suppressed glucose release in the liver, or both. These abnormal blood glucose conditions are associated with a poor life style, including overeating and/or high-fat diet intake and minimal physical exercise.

This chapter reviews associations between postprandial blood glucose responses and metabolic disorders, and the effects of diet and physical exercise on postprandial blood glucose response.

13.2 Postprandial Blood Glucose Responses and the Risk of Cardiovascular Diseases and Arteriosclerosis

Epidemiological and clinical studies have indicated the importance of postprandial blood glucose concentrations to all-cause mortality, CVDs, and arteriosclerosis. The Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study group assessed associations between 2-h blood glucose concentrations after the 75-g OGTT and mortality and the risk of CVDs based on 13 prospective European cohort studies (DECODE Study Group and The European Diabetes Epidemiology Group 1999; 2001). They reported that high 2-h blood glucose concentrations after OGTT were associated with increased risk of all-cause mortality and CVDs, which was independent of fasting glucose concentrations and other well-known CVDs risk factors. Moreover, nearly similar results were observed in an Asian population (Nakagami and DECODA Study Group 2004).

Mechanisms by which postprandial blood glucose concentrations contribute to mortality and CVDs are unclear, although it has been assumed that high postprandial blood glucose concentrations induce oxidative stress (Monnier et al. 2006), inflammation (Esposito et al. 2002), endothelial cell dysfunction (Kawano et al.

1999; Williams et al. 1998), and platelet hyperaggregability (Sakamoto et al. 2000). These consequently lead to the development of CVDs and arteriosclerosis. Moreover, improvements in postprandial blood glucose response should prevent increased mortality and CVDs risks. In fact, suppressing increased postprandial blood glucose concentrations by administering medication (α-glucosidase) resulted in decreased incidence of diabetes (Chiasson et al. 2002; Kawamori et al. 2009) and CVDs (Chiasson et al. 2003) as well as decreased development of arteriosclerosis (Hanefeld et al. 2004). Therefore, an important part of living a long and healthy life is preventing and improving abnormal postprandial blood glucose response.

13.3 Postprandial Blood Glucose Responses and Low-Carbohydrate/High-Fat Diets

Postprandial blood glucose response is directly affected by diet contents and the amounts of food consumed, although this response is not always constant during the postprandial period. An increase in postprandial blood glucose concentrations is primarily caused by carbohydrates, and varies widely based on the nature (i.e., glycemic index) and amount of carbohydrates in the diet. Although dietary fat does not directly increase postprandial blood glucose concentrations, consuming a low-carbohydrate high-fat (LC/HF) diet over a certain period of time can facilitate the decrease in postprandial blood glucose disposal and lead to an abnormal postprandial blood glucose response. Although there is no universally accepted definition of a LC/HF diet, one definition is that a LC/HF diet contains <40 % of its kcal as carbohydrates (Wheeler et al. 2012). Effects of LC/HF diet intake on postprandial blood glucose response are somewhat different depending on the intake period (a few days to several years).

13.3.1 Short-Term Intake of a Low-Carbohydrate High-Fat Diet

Short-term intake of a LC/HF diet has harmful effects on subsequent postprandial blood glucose response. A LC/HF diet [protein, fat, and carbohydrate (PFC) ratio = 17–22 %:70–73 %:5–13 %] for 36–56 h induced abnormally high postprandial blood glucose concentrations in response to an oral glucose load when compared with a control diet (PFC ratio = 9–20 %:16–29 %:51–75 %) in healthy young males (Sparti and Décombaz 1992) and exercise-trained young males (Pehleman et al. 2005). Moreover, we observed that consuming a LC/HF diet [PFC ratio = 11 %:69 %:20 %] for 72 h increased postprandial blood glucose concentrations (Fig. 13.1) and decreased insulin first-phase secretion (Fig. 13.2) during the 75-g OGTT (Numao et al. 2012) and oral meal tolerance test results (Numao et al. unpublished data) to a greater degree compared with a standardized control diet

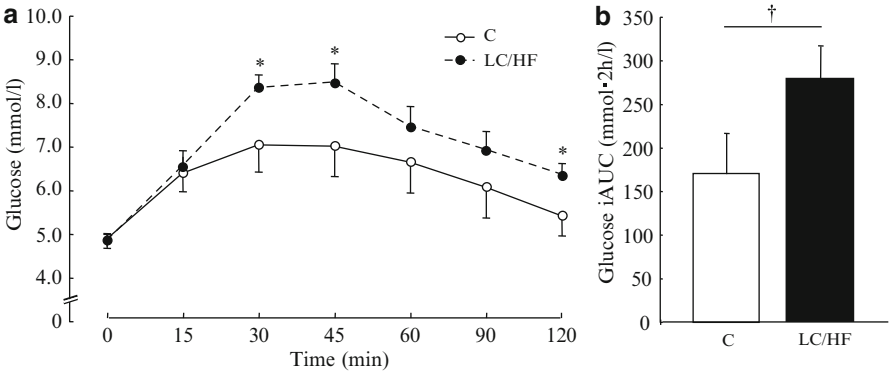

Fig. 13.1 Blood glucose concentrations (**a**) and incremental areas under the curve (iAUC) (**b**) during a 75-g oral glucose tolerance test after a 3-day standardized control diet (C) or a 3-day low-carbohydrate/high-fat diet (LC/HF). *significantly different from C at each time ($P<0.05$). †significant difference between C and LC/HF ($P<0.05$) (Adapted from Numao et al. 2012)

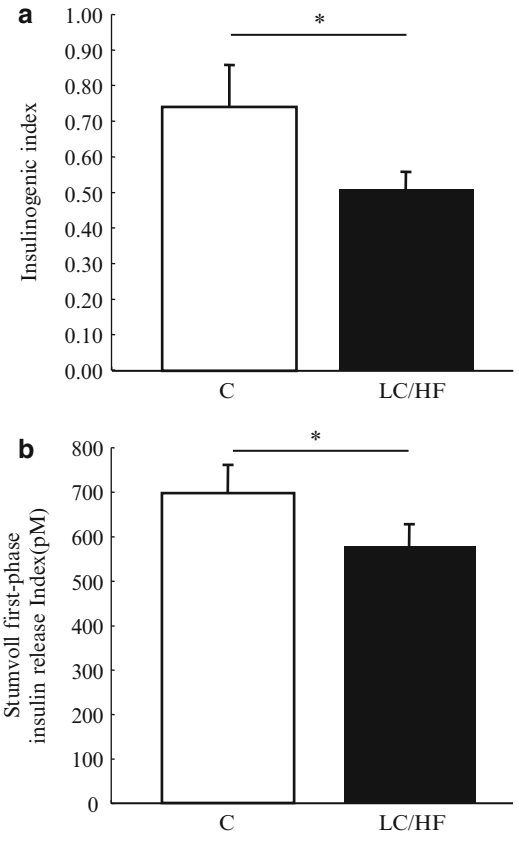

Fig. 13.2 Insulin first-phase release index [insulinogenic index (**a**) and Stumvoll first-phase insulin release index (**b**)] during a 75-g oral glucose tolerance test after a 3-day standardized control diet (C) or a 3-day low-carbohydrate/high-fat diet (LC/HF). *significant difference between C and LC/HF ($P<0.05$) (Adapted from Numao et al. 2012)

[PFC ratio = 11 %:22 %:67 %] in healthy young males. Moreover, a 14-day LC/HF diet intake [PFC ratio = 20 %:50 %:30 %] adversely affected postprandial blood glucose responses concomitant with decreased insulin secretion during OGTT compared with a control diet [PFC ratio = 15 %:15 %:70 %] in Pima Indians and Caucasians (Swinburn et al. 1991).

Factors associated with an excessive increase in postprandial blood glucose concentrations induced by ingesting a LC/HF diet primarily involve decreased glucose uptake in various tissues by (1) decreased insulin first-phase release (Numao et al. 2012; Swinburn et al. 1991), (2) increased free fatty acid (FFA) concentrations in blood (Sparti and Décombaz 1992), (3) decreased glucose oxidative capacity (Pehleman et al. 2005), and (4) accumulation of intramyocellular lipids (Bachmann et al. 2001). Moreover, ingesting a LC/HF diet increases endogenous glucose production and release in the liver (Bisschop et al. 2001; Brøns et al. 2009). However, the duration of these negative effects of short-term LC/HF diet intake on postprandial blood glucose concentrations is not known.

Interestingly, despite an increase in postprandial blood glucose concentrations, short-term LC/HF diet intake increases blood concentration of the incretins, glucagon-like peptide 1 (GLP 1) and glucose-dependent insulinotropic polypeptide (GIP), both during fasting (Brøns et al. 2009; Numao et al. 2012) and in the postprandial state (Numao et al. 2012) (Fig. 13.3). Although incretins have stimulatory effects on insulin secretion, insulin concentrations remain suppressed during OGTT after short-term LC/HF diet intake (Numao et al. 2012). These incretin responses to short-term LC/HF diet intake imply an adaptive response to promote insulin secretion to replenish glycogen stores depleted in the liver and muscles. Mechanisms for these incretin responses remain uncertain. With regard to postprandial GLP-1

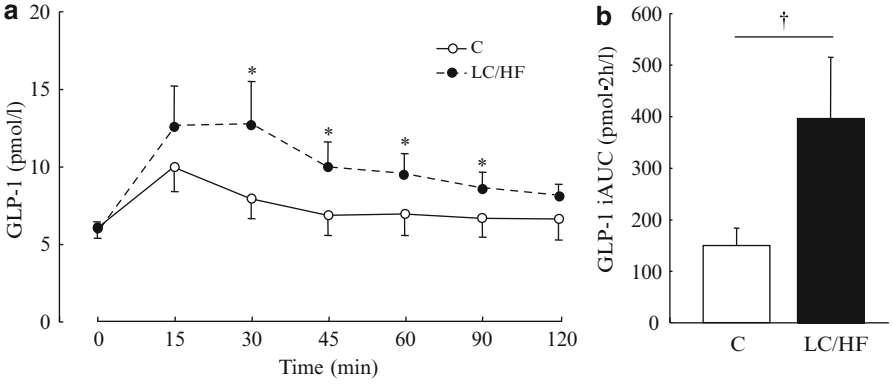

Fig. 13.3 Blood glucagon-like peptide 1 (GLP-1) concentrations (**a**) and incremental areas under the curve (iAUC) (**b**) during a 75-g oral glucose tolerance test after a 3-day standardized control diet (C) or a 3-day low-carbohydrate/high-fat diet (LC/HF). *significantly different from C at each time ($P < 0.05$). †significant difference between C and LC/HF ($P < 0.05$) (Adapted from Numao et al. 2012)

response, increased synthesis of bile acids in response to increased secretion of bile acids into feces after an LC/HF diet (Bianchini et al. 1989; Cummings et al. 1978) may stimulate GLP-1 secretion.

13.3.2 Long-Term Intake of a Low-Carbohydrate/ High-Fat Diet

In contrast, effects of long-term intake of a LC/HF diet on blood glycemic control have been debated and remain controversial. It was recently reported that long-term intake of a LC/HF diet exerted positive effects on blood glycemic control (Shai et al. 2008; Wheeler et al. 2012). In contrast, long-term intake of a LC/HF diet has also been shown to have no effects on blood glycemic control (Bradley et al. 2009; Larsen et al. 2011). Moreover, effects and safety of a long-term LC/HF diet (more than 2 years) on blood glycemic control and CVD risk factors remain to be elucidated. In Japan, the increased incidence of type 2 diabetes appears to parallel the increase in daily fat (animal fat) consumption (Ministry of Health, Labour and Welfare of Japan 2011). Therefore, there is skepticism regarding any beneficial effects of long-term LC/HF diet intake on postprandial blood glucose responses. There have been many investigations into the effects of long-term LC/HF diet intake on fasting glucose concentrations (Hu et al. 2012). However, there is little direct evidence to indicate whether long-term LC/HF diet intake is associated with an abnormal postprandial blood glucose response in humans (Foster et al. 2003; McAuley et al. 2006). Moreover, in animal studies, long-term LC/HF diet intake leads to an excessive increase in postprandial blood glucose concentrations and insulin resistance despite the decrease in fasting glucose and insulin concentrations (Bielohuby et al. 2013; Garbow et al. 2011). Therefore, long-term intake of a LC/HF diet may attenuate postprandial blood glucose response.

13.4 Postprandial Blood Glucose Response and Physical Exercise

An abnormal postprandial blood glucose response is primarily attributed to decreased glucose uptake in peripheral tissues. Therefore, the improving glucose uptake may be a key factor in ameliorating the abnormal postprandial blood glucose response. Physical exercise has significant effects on glucose homeostasis and improves glucose uptake. A single bout of physical exercise can improve glucose uptake during both exercise (Rose and Richter 2005) and the post-exercise period (Hayashi et al. 2005; Houmard et al. 2004). Effects during the post-exercise period could result from the persistent skeletal muscle contraction-stimulated glucose uptake independent of insulin and increased sensitivity to insulin in skeletal muscles (Garetto et al. 1984; Richter et al. 1984).

The improvement in glucose uptake can last for approximately 48–72 h after exercise (King et al. 1995; Mikines et al. 1998). In fact, a single bout of physical exercise improves postprandial blood glucose concentrations and insulin concentrations during subsequent glucose loading, depending on the intensity and duration of exercise (Ben-Ezra et al. 1995; Bonen et al. 1998; King et al. 1995; Rynders et al. 2014). Moreover, a single bout of physical exercise during the postprandial period significantly decreases the postprandial blood glucose and insulin concentrations when compared with no exercise, although these effects do not persist during the postprandial period after consuming a subsequent meal (Colberg et al. 2009; Larsen et al. 1997, 1999). Average daily blood glucose concentrations and daily time spent in hyperglycemia, as measured using a continuous glucose monitor, are lower on a physical exercise day than on a control day (no-physical-exercise day) despite no effects on fasting glucose concentrations (Macleod et al. 2013). These observations highlight the importance of physical exercise in controlling postprandial blood glucose response.

13.5 Postprandial Blood Glucose Responses Induced by Short-Term Low-Carbohydrate/High-Fat Diet Intake and a Single Bout of Physical Exercise

As mentioned above, short-term intake of a LC/HF diet induces an excessive increase in the subsequent postprandial blood glucose concentration (Numao et al. 2012; Pehleman et al. 2005; Sparti and Décombaz 1992; Swinburn et al. 1991). In contrast, a single bout of physical exercise can improve glucose and insulin concentrations during the post-exercise period and prevent excessive increases in postprandial blood glucose concentrations during a subsequent glucose load (Ben-Ezra et al. 1995; Bonen et al. 1998; King et al. 1995; Rynders et al. 2014) and during daily free-living (Macleod et al. 2013). On the basis of these observations, it can be hypothesized that "a single bout of physical exercise is effective for preventing abnormal postprandial blood glucose response induced by short-term intake of a LC/HF diet".

However, positive effects of a single bout of physical exercise on postprandial blood glucose response induced by short-term intake of a LC/HF diet are likely to be small. When a single bout of physical exercise (200 kcal expended at 50 % peak oxygen uptake) is performed on the last day of a 3-day LC/HF diet intake period, the exercise does not improve the abnormal postprandial blood glucose response (Fig. 13.4) and insulin first-phase release during the 75-g OGTT after LC/HF diet intake in young healthy males (Numao et al. 2013). Although high-intensity, long-duration exercise should improve postprandial blood glucose response (Ben-Ezra et al. 1995; Rynders et al. 2014), even a single bout of high-intensity exercise [80 % maximal heart rate (HRmax), 30-min bicycle ergometer + resistance training using a rubber band + 90% HRmax, and repeated 2-min bicycle ergometer followed by

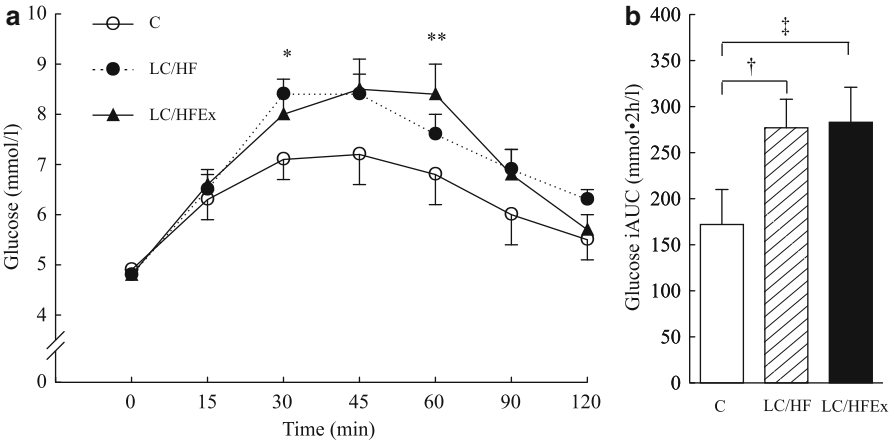

Fig. 13.4 Blood glucose concentration (**a**) and incremental areas under the curve (iAUC) (**b**) during a 75-g oral glucose tolerance test after a 3-day standardized control diet (C), a 3-day low-carbohydrate/high-fat diet (LC/HF), or a 3-day LC/HFD + a single bout of physical exercise (LC/HFEx). *significant difference between C and LC/HF trials at each time point ($P < 0.05$). **significant difference between C and LC/HFEx trials at each time point ($P < 0.05$). †significant difference between C and HF ($P < 0.05$). ‡significant difference between C and HFEx ($P < 0.05$) (Reprinted from *Metabolism*, 62, Numao et al. 2012. Effects of a single bout of aerobic exercise on short-term low-carbohydrate/high-fat intake-induced postprandial glucose metabolism during an oral glucose tolerance test, 1410, Copyright 2013, with permission from Elsevier)

2-min rest until exhaustion] does not prevent an abnormal postprandial blood glucose response induced by a 36-h LC/HF diet intake in young healthy males (Sparti and Décombaz 1992). These findings suggest that the improvement effects of a single bout of physical exercise on glucose tolerance and insulin sensitivity are impaired by LC/HF diet intake.

In support of this, in an animal study, the rates of insulin-dependent and insulin-independent glucose transport in skeletal muscles were blunted in high-fat-diet fed rats when compared with control-diet fed rats after acute moderate-intensity endurance exercise (Tanaka et al. 2007). The factor underlying the impaired effect of a single bout of physical exercise may be the high exposure to blood-borne FFAs throughout the entire body. Short-term intake of a LC/HF diet promotes lipolysis and the release of FFAs into the blood as a metabolic resource to compensate for the lack of glucose throughout the intake period (Bisschop et al. 2002; Numao et al. 2012). This high exposure to FFAs in the entire body over several hours results in impaired insulin sensitivity and responsiveness in peripheral tissues (Ferrannini et al. 1983). Moreover, this high exposure to FFAs impairs β-cell function in the pancreas (Leung et al. 2004).

A single bout of physical exercise would not be sufficient to compensate for the impairment caused by short-term intake of a LC/HF diet. However, the positive effects of a single bout of physical exercise on postprandial blood glucose response appear to be elicited when a high-fat diet is consumed *after* a single bout of physical

exercise (Fox et al. 2004). In other words, a single bout of physical exercise before the intake of a high-fat diet may prevent the high-fat diet intake-induced attenuation of postprandial blood glucose response. This is supported by an experimental study that used lipid infusion after a single bout of physical exercise (Schenk et al. 2005; Schenk and Horowitz 2007). A single bout of exercise before lipid infusion protected against insulin resistance induced by a lipid infusion by improving skeletal muscle metabolism (Schenk and Horowitz 2007). Therefore, it may be important to perform exercise before consuming a high-fat diet to insure the beneficial effects of a single bout of exercise on postprandial blood glucose response. The timing of performing the exercise vs. consuming the diet would be key.

13.6 Postprandial Blood Glucose Responses Induced by Low-Carbohydrate/High-Fat Diet Intake and Physical Exercise Training

The effects of physical exercise training on abnormal postprandial blood glucose response induced by LC/HF diet intake are unclear. Considering that (1) trained individuals experience smaller increases in plasma insulin concentrations in response to a glucose load compared with sedentary individuals and have unchanged or improved glucose tolerance (Björntorp et al. 1972; Johansen and Munck 1979; LeBlanc et al. 1979; Lohmann et al. 1978; Seals et al. 1984) along with decreased insulin response, (2) trained individuals reveal higher rates of insulin-stimulated glucose disposal compared with sedentary individuals (Hollenbeck et al. 1985; King et al. 1987; Mikines et al. 1989; Rosenthal et al. 1983), and (3) physical exercise training improves insulin sensitivity (Hughes et al. 1993; Oshida et al. 1989), physical exercise training should improve the postprandial blood glucose response induced by LC/HF diet intake. However, there is little direct evidence regarding the effects of physical exercise training on abnormal postprandial blood glucose response induced by LC/HF diet intake, and, thus, future intervention studies are required.

13.7 Conclusion

Postprandial blood glucose response is effective in predicting risks of cardiovascular diseases and arteriosclerosis. Abnormal postprandial blood glucose response is associated with daily diet and physical exercise. Low-carbohydrate/high-fat diet intake for both long and short periods of time contributes to increasing postprandial blood glucose concentrations. In contrast, a single bout of physical exercise and exercise training improves glucose uptake and insulin sensitivity and consequently leads to optimal postprandial blood glucose response. However, a single bout of

physical exercise has lesser effects on abnormal postprandial blood glucose response induced by short-term intake of a low-carbohydrate and high-fat diet. Apparently, the effects of a single bout of physical exercise may be reversed by the short-term intake of a low-carbohydrate/high-fat diet. A single bout of physical exercise before ingesting a low-carbohydrate/high fat meal may improve the low-carbohydrate/high fat diet-induced attenuation of the postprandial blood glucose response. Future intervention studies are required to investigate the effects of physical exercise training on abnormal postprandial blood glucose response induced by a low-carbohydrate high-fat diet.

Acknowledgments This research was supported by a Grant-in-aid for the Young Scientists (B) (22700703) and for the Global COE program "Sport Sciences for the promotion of Active Life" (2010–2011) award by the Ministry of Education, Culture, Sports Science and Technology of Japan.

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Chapter 14
Posttranslational Modification of Proteins

Zsolt Radak

Abstract Proteins are subject to continuous reversible and irreversible modifications. These posttranslational modifications directly influence the stability and/or the function of proteins. Aging results in an increased half-life of proteins, which is associated with enhanced oxidative modifications of amino acid residues. Lysine residues are carbonylated, acetylated, and ubiquitinated, and cross talk between these modifications is crucial for the fate of proteins.

Keywords Acetylation • Sirtuins • Carbonylation • Reactive oxygen species • Ubiquitination

Aging is a progressive, highly complex process, associated with the decline of many cellular and somatic functions. It is heavily influenced by the environment and is not completely understood. The free radical theory of aging, one of the prominent aging hypotheses, postulates that aging/senescence is a manifestation of low-level, chronic oxidative stress, generated by reactive oxygen species (ROS). ROS are normal products of aerobic organisms. Oxidative stress occurs when ROS overwhelm cellular antioxidant defenses. Oxidative stress is produced intracellularly by peroxisomes, cytochrome P450 enzymes, and mitochondria or nicotinamide adenine dinucleotide phosphate (NADPH) oxidases during inflammatory responses associated with organismal defense and from environmental exposures. Among these possible sources, mitochondrial ROS appear to be the most relevant, especially in aging processes. Therefore, many hypotheses have arisen to explain the aging process and among them the mitochondrial theory of aging has received the most attention (Harman 1956, 1972; Miquel et al. 1980; Cortopassi and Wong 1999; Van Remmen and Richardson 2001). This theory suggests that accumulation of DNA damage and mutations in the mitochondrial genome leads to mitochondrial dysfunction and locked-in chronic ROS generation (Harman 1956, 1972; Beckman and Ames 1996, 1998). In aged tissues, the electron transport chain (ETC) increases ROS generation due to oxidatively damaged proteins, lipids, and encoding DNA. Increased ROS generation adversely affects mitochondrial and cellular function, leading to a

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_14

vicious cycle of continuous mitochondrial dysfunction and chronic oxidative stress (Sohal and Sohal 1991; Shigenaga et al. 1994; Sohal et al. 1995; Perez-Campo et al. 1998; Sastre et al. 2000; Golden and Melov 2001; Osiewacz 2002). Therefore, the data from the above-mentioned studies indeed suggest that increased generation of ROS and related oxidative damage could be one of the causative factors of aging. On the other hand, data from other studies might conflict with the well-accepted ROS-dependent theory of aging, since it has been shown that increased mitochondrial metabolism could lead to a positive response by enhanced formation of ROS, resulting in extended life span (Vanfleteren 1993; Houthoofd et al. 2002; Johnson et al. 2002; Kharade et al. 2005; Sinclair 2005; Zarse et al. 2007). These interpretations are supported by the fact that exercise increases ROS formation (Radak et al. 2008a, b), and physical activity is positively correlated with longevity (Lindsted et al. 1991; Manini et al. 2006). Moreover, some evidence indicates that antioxidant supplementation may even decrease the life span in humans (Bjelakovic et al. 2007). These observations suggest that the ROS concentration in the cell can be described by the hormesis curve (Radak et al. 2005).

Organisms favor "optimal" conditions, including the level of ROS, or even so-called oxidative damage (Radak et al. 2005, 2008b); therefore, levels of ROS that are too high or too low could accelerate the aging process. The increase in oxidative damage is much more pronounced in proteins than in DNA or lipids. The age-associated changes in protein structure and the post-translational modification of proteins readily affect the function and stability of proteins.

Carbonylation is the most-often measured marker of oxidative protein damage; such damage can indeed result in loss of enzyme activity (Nakamura and Stadtman 1984) or mark the proteins for degradation by changing their hydrophobicity (Khan et al. 2005). On the other hand, massive accumulation of carbonyl groups can cause cross-links between proteins; as a result these proteins cannot respond to chaperons and cannot be degraded. Indeed, it is well documented that aging increases the half-life of proteins (Goto et al. 2001, 2007). Longer half-life results in a longer time to accumulate damage; because cross-linked proteins cannot be degraded, they have longer life-spans. Accumulation of damaged proteins, which occurs with aging, is closely linked to impaired cellular and organ function. Therefore, therapies which could prevent the age-associated increase in the accumulation of damaged proteins could delay some important symptoms of aging.

However, it must be mentioned that the age-associated increase in the accumulation of damaged proteins is not true for every protein. The carbonylation of histone residues is very interesting. Contrary to most cellular proteins, the carbonylation of histone residues decreases as a result of aging (Sharma et al. 2006). Due to the electric charge of carbonylation, a significant degree of carbonylation would result in open chromatin. This could jeopardize the integrity of the DNA; hence, as a protective mechanism, histone carbonylation decreases, leading to closed chromatin. This phenomenon shows very clearly that carbonylation of protein residues is not just a damage marker, but an important regulator of protein function. Carbonylation is a ROS-mediated posttranslational modification which is often used as a marker of oxidative damage to proteins; it appears to be a regulatory mechanism of gene

expression through the modification of histones. Moreover, the relationship between protein degradation and carbonylation also emphasizes the fact that carbonylation directly regulates the half-life of proteins, which affects the biochemical function of a number of enzymes. Therefore, in certain conditions the ROS-associated posttranslational modifications are necessary for cell survival.

Sirtuins are redox-sensitive lysine deacetylases. The redox sensitivity of sirtuins depends on NAD/NADH levels as well as on the regulation of transcription factors that modulate anti- and pro-oxidant levels (Radak et al. 2013a). Deacetylation of protein lysine residues not only modulates enzyme activity, but also regulates protein stability (Radak et al. 2013b). Proteasome-associated degradation is regulated by the ubiquitination of lysine residues. However, acetylation of these residues could prevent the attachment of ubiquitin to lysine, and hence curb the marking for degradation. With aging there is a significant loss of SIRT1 activity, which results in increased acetylation of proteins (Koltai et al. 2010; Marton et al. 2010). It has been suggested that this increased acetylation results in decreased ubiquitination and suppressed degradation of proteins leading to increased half-life and accumulation of oxidative damage. This suggests cross talk between acetylation and carbonylation and the regulation of protein turnover.

On the other hand, it must be mentioned that this straightforward mechanism is an oversimplification of the situation, since the position and the site of posttranslational modifications are extremely important. This phenomenon is well known in histone proteins, but almost completely undiscovered for other cellular proteins. We suggest that the location of posttranslational modification is extremely important and readily affects the function and fate of proteins.

One of the most studied posttranslational modifications of proteins is phosphorylation, which directly activates a number of proteins and constitutes a key regulatory modification. However, it is also known that hyper-phosphorylation impairs the function of proteins.

Acetylation and deacetylation have received attention recently, especially after the discovery of sirtuin proteins. Interestingly enough, acetylation can serve as both an activator and an inhibitor of proteins, and the effect can be dependent on the site of acetylation or deacetylation. Ubiquitination can adopt both mono- and poly-ubiquitinated forms, and the site of this posttranslational modification also alters the effect. Sumo (small ubiquitin-related modifier) family proteins are members of a growing family of ubiquitin-related proteins. Two modes of function for SUMOylation have been suggested: a role in the regulation of protein/protein interactions (often leading to altered subcellular localizations), and a role as an antagonist of ubiquitin.

Methylation of histone proteins was discovered long ago (Murray 1964) and, as it turned out, it regulates such core cellular processes as transcription and translation, influencing protein–protein and potentially protein–nucleic acid interactions (Moore and Gozani 2014).

Other posttranslational modifications are also present, but are not as well studied. It is clear that these posttranslational modifications are sensitive to aging and also to exercise interventions. It has been suggested that the attenuating effect of exercise

on the aging process is largely mediated through reversible modification of proteins; hence, to delineate the detailed mechanisms behind exercise-mediated posttranslational mechanisms, it is important to understand exercise-mediated adaptation. Moreover, it appears that the dose-response curve of posttranslational modification can be described by the hormesis curve. There is an optimal degree of posttranslational modifications; levels of posttranslational modifications that are either too low or too high could lead to impaired cell and organ function, which often takes place in aging organisms.

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Chapter 15
Relationship of Cardiorespiratory Fitness and Obesity Genes to Metabolic Syndrome in Adult Japanese Men

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Abstract There has been a considerable increase in the number of studies reporting associations between DNA sequence variation in specific genes and metabolic syndrome (MetS). A low level of cardiorespiratory fitness is also a strong determining factor in the development of MetS. This cross-sectional study was performed to investigate the influence of the interaction between obesity genes and cardiorespiratory fitness on the risk of MetS. Healthy Japanese men ($n=287$) participated in this study. All subjects were divided into four groups, fitness level (high and low fitness groups), and age (younger, age <40 years and middle-aged/older, age ≥ 40 years).

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_15

The peroxisome proliferator-activated receptor gamma 2 (PPARγ2), the uncoupling protein-2 (UCP2), and the fatty acid binding protein 2 (FABP2) genotypes were analyzed by using real-time polymerase chain reaction (PCR) with Taq-Man probes. Two-way analysis of covariance (ANCOVA) with adjustment for age as a covariate indicated that fitness, the CC genotype of C1431T in the PPARγ2, and the ValVal genotype of Ala55Val in the UCP2 genes interacted to produce a significant effect on MetS risk in Japanese adult men. We concluded that the CC genotype of C1431T in the PPARγ2 and the ValVal genotype of Ala55Val in the UCP2 genes together with low cardiorespiratory fitness may increase the risk of MetS in younger men (age < 40 years), even with adjustment for age.

Keywords Metabolic syndrome • Genotype • Physical fitness • PPARγ2 • UCP2 • FABP2

15.1 Introduction

There has been a considerable increase in the number of studies reporting associations between DNA sequence variation in specific genes and obesity phenotypes (Rankinen et al. 2006). One such gene, that for peroxisome proliferator-activated receptor gamma 2 (PPARγ2), is reported to be associated with metabolic syndrome (MetS) or adipocytokine dysregulation (Okuno et al. 1998; Yamauchi et al. 2001a, b). The CT + TT genotypes of C1431T in the PPARγ2 gene in Scotland (Cecil et al. 2006) and in Greek children (Lagou et al. 2008) are associated with increases in body mass index (BMI) and waist circumference compared with the CC genotype, and were associated with a reduced risk for MetS in 647 Caucasian-Australian patients (Masud and Ye 2003). However, some investigators have shown that the C1431T variant by itself is not associated with BMI or risk factors for MetS (Haseeb et al. 2009; Morini et al. 2008).

In addition, the fatty acid binding protein 2 (FABP2) shows high affinity for saturated and unsaturated long-chain fatty acids and plays a key role in the absorption and intracellular transport of dietary fatty acids in the small intestine (Alpers et al. 2000). Several studies have suggested that individuals who are homozygous for the 54Thr codon in FABP2 had an increased dyslipidemia risk owing to elevated total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, and triglyceride (TG) levels, or reduced high-density lipoprotein (HDL) cholesterol levels (Galluzzi et al. 2001; Georgopoulos et al. 2000; Helwig et al. 2007; Zhao et al. 2010). Other studies, however, showed the FABP2 Ala54Thr polymorphism did not affect serum lipid profiles (Gastaldi et al. 2007; Ishii et al. 2001; Sipilainen et al. 1997; Tahvanainen et al. 2000).

Uncoupling protein 2 (UCP2), a physiological down-regulator of reactive oxygen species (ROS), might play an important role in cardiovascular diseases (Gioli-Pereira et al. 2013). Described effects of UCP2 include an anti-atherogenic effect in the vascular wall (Blanc et al. 2003), improved tolerance to cardiac ischemia (Cheurfa et al. 2008; McLeod et al. 2005), and protection of cardiomyocytes from oxidative stress-induced cell death (Teshima et al. 2003). The association of UCP2

gene polymorphisms with insulin resistance and type 2 diabetes mellitus has also been reported in several studies (Bulotta et al. 2005; D'Adamo et al. 2004; Shen et al. 2006; Wang et al. 2004). UCP2 gene polymorphisms were linked to an increased BMI in Pima Indians and other populations (Bao et al. 1998; Barbe et al. 1998; Millet et al. 1997), although this has not been confirmed by other studies (Digby et al. 2000; Pinkney et al. 2000). Thus, conflicting effects of these obesity-related gene polymorphisms on the risk of MetS have been reported.

Previous studies regarding the relationship between cardiorespiratory fitness and MetS suggested that a low level of physical fitness is a strong determining factor in the prevalence of MetS (Carroll et al. 2000; Finley et al. 2006; Lakka et al. 2003; LaMonte et al. 2005; Lee et al. 2005; Orakzai et al. 2006; Whaley et al. 1999), because cardiorespiratory fitness is strongly correlated with physical activity (Paffenbarger et al. 1993). Lakka et al. (2003) suggested that a sedentary lifestyle and an especially low cardiorespiratory fitness measured by maximal oxygen uptake ($\dot{V}O_2max$) are not only associated with MetS but could also be considered features of MetS. In addition, Lee et al. (2005) reported that high levels of cardiorespiratory fitness are associated with a substantial reduction in health risk for a given level of visceral and subcutaneous fat. Therefore, it is important to consider individual cardiorespiratory fitness to clarify the relationship between the obesity genes and MetS. The present study was performed to investigate the influence of interaction between obesity genes and cardiorespiratory fitness on MetS risk.

15.2 Methods

15.2.1 Subjects

The 287 Japanese adult subjects between 19 and 85 years of age included in this cross-sectional study were the same subjects included in our previous study (Miyatani et al. 2008). All subjects were free of any overt signs or symptoms of chronic disease. They were sedentary or moderately-active people who participated in a swimming, stretching, and "healthy gymnastics" program; however, they did not participate in other vigorous sports activities. All subjects were divided according to age (young: <40 years and middle-aged/older: ≥40 years), because metabolic profiles differ according to age. The purpose, procedures, and risks of the study were explained to each participant prior to enrollment, and all subjects gave their written informed consent before participating in the study, which was approved by the Human Ethical Committee of Waseda University. The study was performed in accordance with the guidelines of the Declaration of Helsinki. Body weight and height were recorded, and BMI was calculated as weight in kilograms divided by the square of height in meters. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) were measured at rest by using a vascular testing device (Colin Medical Technology, Tokyo, Japan).

15.2.2 Measurements of Blood Samples

All blood samples were drawn from the subjects in the seated position. Fasting (>12 h) blood samples were collected by venipuncture in tubes with or without ethylenediamine tetraacetic acid (for plasma or serum). The blood samples were centrifuged at 1,500 rpm for 15 min and stored at −20 °C. Serum concentrations of triglycerides were determined by using commercial kits (Mitsubishi Chemical Medience, Tokyo, Japan). Serum HDL-cholesterol was measured by an enzymatic method (Mitsubishi Chemical Medience). Fasting plasma glucose (FPG) was measured by the glucose dehydrogenase method (Kuan et al. 1977). Whole-blood glycohemoglobin A1c (HbA1c) was measured by an enzymatic method (Glycohemoglobin A1c kit; Mitsubishi Chemical Medience). Because waist circumference data were not available, the following MetS risk factors (highest value = 4) were used: (1) BMI ≥ 25 kg/m^2; (2) SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg; (3) TG ≥ 150 mg/dL and/or HDL-cholesterol ≤ 40 mg/dL; and (4) FPG ≥ 110 mg/dL. Moreover, MetS risk (Z-score) was derived by standardizing and then summing the following continuously-distributed variables: BMI, MBP, HbA1c, and serum triglyceride/HDL cholesterol, to obtain the Z-score. It is known that a high serum triglyceride/HDL cholesterol ratio is a marker of insulin resistance (McLaughlin et al. 2003). Like waist circumference, BMI values can predict the presence of multiple metabolic risk factors in middle-aged Japanese subjects (Satoh et al. 2010).

15.2.3 Measurement of $\dot{V}O_2$max

The $\dot{V}O_2$max was measured by an incremental cycle exercise test using a cycle ergometer (Monark, Varberg, Sweden) (Miyachi et al. 2001). The incremental cycle exercise began at a work rate of 90 W (60 rpm), and power output was increased by 30 W/min until the subjects could not maintain the fixed pedaling frequency. The subjects were encouraged during the ergometer test to exercise at maximum intensity. $\dot{V}O_2$ was monitored during the last 30 s of each increase in work rate. Subjects breathed through a low-resistance two-way valve, and the expired air was collected in Douglas bags. Expired O_2 and CO_2 gas concentrations were measured by mass spectrometry (WSMR-1400; Arco System, Chiba, Japan), and gas volume was determined with a dry gas meter (NDS-2A-T; Shinagawa Dev., Tokyo, Japan). The highest value of $\dot{V}O_2$ during the exercise test was designated as $\dot{V}O_2$max. These values were consistent with reference values for the maximal oxygen uptake for health promotion by gender and age, as described by the Japanese Ministry of Health, Labor, and Welfare to prevent lifestyle-related diseases (Gando et al. 2010; Ishikawa-Takata and Tabata 2007).

15.2.4 Single Nucleotide Polymorphism (SNP) Genotyping

Genomic DNA was extracted from buffy coats and buccal cells by using a QIAamp DNA Blood Maxi Kit (Qiagen, Tokyo, Japan). SNP genotypes were determined by real-time polymerase chain reaction (PCR) with TaqMan probes using an ABI Prism 7700 Sequence Detector (Perkin-Elmer Applied Biosystems, Foster, CA) as described previously, with minor modifications (Fujie et al. 2013; Iemitsu et al. 2006). The gene-specific primers and TaqMan probes for each SNP were synthesized using Primer Express v.1.5 software (Perkin-Elmer Applied Biosystems) according to the published DNA sequences for each SNP as follows: the C1431T of PPARγ2, the Ala54Thr of FABP2, and the Ala55Val of UCP2 genes.

An ABI-7700 was used to read 96-well PCR plates using the end-point analysis mode of the SDS v.1.7a software package (Perkin-Elmer Applied Biosystems). Genotypes were determined automatically by the signal processing algorithms in the software.

15.2.5 Statistical Analysis

The allelic frequencies were calculated using a gene-counting method, and Hardy–Weinberg equilibrium was confirmed by performing the χ^2 test. The variables BMI, MBP, HbA1c, and serum triglyceride/HDL cholesterol were standardized to Z-score variables with mean = 0 and standard deviation (SD) = 1 ([individual value–sex- and age-specific mean value]/SD). We tested the influence of genotype and fitness on the risk of MetS by using two-way analysis of covariance (ANCOVA) with adjustment for age as a covariate (genotype and fitness), and when a significant difference was observed in the interaction, comparisons between groups were tested by using the unpaired Student's *t* test. Regression analyses were conducted to explore the relationship between $\dot{V}O_2$max and MetS risk, excluding variance produced by age, by use of partial correlations (partial correlation coefficient). Values were expressed as means ± S.E. (standard error of the mean). In all analyses, $P < 0.05$ was taken to indicate statistical significance.

15.3 Results

There were no significant differences in the frequencies of the C1431T of PPARγ2, the Ala54Thr of FABP2, and the Ala55Val of UCP2 polymorphisms between age groups (Tables 15.1 and 15.2). The genotype frequencies did not deviate from the expected Hardy–Weinberg equilibrium. There was no significant difference with age among all polymorphisms in either young or middle-aged/older men. In young men, TG and TG/HDL scores in the ValVal UCP2 genotype were significantly

Table 15.1 Genotype of obesity-related genes and metabolic syndrome risk factors in young subjects (age < 40)

	C1431T of PPARG		Ala54Thr of FABP2		Ala55Val of UCP2	
	CC	CT, TT	AlaAla	AlaThr, ThrThr	AlaAla, AlaVal	ValVal
n (%)	105 (79.5 %)	23 (17.4 %)	56 (42.4 %)	60 (45.4 %)	33 (24.2 %)	
		4 (3.0 %)		16 (12.1 %)	78 (59.1 %)	21 (15.9 %)
Allele frequency		11.7 %		34.8 %	54.5 %	
Age (years)	27.8 ± 0.7	25.3 ± 1.4	27.3 ± 1.0	27.3 ± 0.8	27.2 ± 0.7	27.9 ± 1.7
BMI ($kg \cdot m^{-2}$)	23.7 ± 0.4	22.5 ± 0.4	23.2 ± 0.4	23.7 ± 0.4	23.2 ± 0.3	24.9 ± 1.3
% Body fat (%)	16.4 ± 0.5	15.4 ± 0.7	15.9 ± 0.7	16.4 ± 0.6	15.8 ± 0.5	18.1 ± 1.3
SBP (mmHg)	116.3 ± 1.3	115.4 ± 1.6	114.0 ± 1.3	117.7 ± 1.5	115.4 ± 0.9	120.1 ± 4.6
DBP (mmHg)	66.2 ± 1.0	62.8 ± 1.5	64.3 ± 1.1	66.4 ± 1.2	65.1 ± 0.8	67.9 ± 3.2
MBP (mmHg)	84.9 ± 1.0	83.0 ± 1.4	83.2 ± 0.9	85.5 ± 1.2	84.1 ± 0.7	86.6 ± 3.5
TG ($mg \cdot dL^{-1}$)	83.5 ± 6.3	72.4 ± 7.3	82.5 ± 9.6	80.3 ± 5.8	74.8 ± 3.8	115.4 ± 25.1*
HDLC ($mg \cdot dL^{-1}$)	56.8 ± 1.2	60.7 ± 2.4	58.2 ± 1.7	57.2 ± 1.4	58.1 ± 1.2	54.9 ± 2.6
TG/HDLC	1.57 ± 0.12	1.31 ± 0.19	1.50 ± 0.17	1.52 ± 0.13	1.38 ± 0.08	2.24 ± 0.46*
FPG ($mg \cdot dL^{-1}$)	90.0 ± 0.8	90.8 ± 1.1	90.5 ± 1.1	89.9 ± 0.9	89.6 ± 0.7	93.1 ± 1.8
HbA1c (%)	4.78 ± 0.03	4.72 ± 0.05	4.78 ± 0.03	4.77 ± 0.04	4.76 ± 0.03	4.84 ± 0.06
MetS No.	0.88 ± 0.09	0.63 ± 0.14	0.79 ± 0.12	0.86 ± 0.11	0.77 ± 0.08	1.14 ± 0.23
MetS score	0.11 ± 0.29	−0.77 ± 0.39	−0.37 ± 0.25	0.15 ± 0.39	−0.27 ± 0.22	1.00 ± 1.02
$\dot{V}O_2max$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	42.5 ± 1.2	48.3 ± 2.6*	43.8 ± 1.6	43.6 ± 1.5	44.1 ± 1.2	41.2 ± 3.3

Data are means ± S.E. unless otherwise indicated

*$P < 0.05$ for a significant difference from the CC variants of C1431T or the Ala carriers of Ala55Val using an unpaired student's *t*-test

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MBP* mean blood pressure, *TG* triglycerides, *HDLC* high-density lipoprotein cholesterol, *FPG* fasting plasma glucose, *MetS No.* number of metabolic syndrome risk factors, $\dot{V}O_2max$ maximal oxygen uptake

Table 15.2 Genotype of obesity-related genes and metabolic syndrome risk factors in middle-aged/older (age ≥ 40) subjects

	C1431T of PPARG		Ala54Thr of FABP2		Ala55Val of UCP2	
	CC	CT, TT	AlaAla	AlaThr, ThrThr	AlaAla, AlaVal	ValVal
n (%)	109 (70.3 %)	39 (25.2 %)	62 (40.0 %)	63 (40.6 %)	38 (24.5 %)	
		7 (4.5 %)		30 (19.4 %)	81 (52.3 %)	36 (23.2 %)
Allele frequency		17.1 %		39.7 %	50.6 %	
Age (years)	57.0 ± 1.1	59.5 ± 1.8	58.3 ± 1.7	57.3 ± 1.1	57.6 ± 1.1	58.0 ± 2.1
BMI ($kg \cdot m^{-2}$)	24.2 ± 0.3	24.0 ± 0.4	24.7 ± 0.4	23.8 ± 0.3 *	24.2 ± 0.3	24.0 ± 0.5
% body fat (%)	21.3 ± 0.5	20.7 ± 0.6	22.1 ± 0.6	20.4 ± 0.5 *	28.9 ± 0.4	21.9 ± 0.7
SBP (mmHg)	128.1 ± 1.7	129.5 ± 2.3	130.8 ± 2.4	127.0 ± 1.5	128.9 ± 1.6	127.3 ± 2.6
DBP (mmHg)	79.0 ± 1.1	78.8 ± 1.4	79.3 ± 1.5	78.7 ± 1.0	79.3 ± 1.0	77.7 ± 1.6
MBP (mmHg)	98.9 ± 1.5	99.0 ± 1.9	100.2 ± 2.0	98.1 ± 1.4	99.3 ± 1.4	97.8 ± 2.2
TG ($mg \cdot dL^{-1}$)	119.8 ± 6.8	114.5 ± 9.5	127.5 ± 10.0	112.0 ± 6.3	118.5 ± 6.6	117.3 ± 9.3
HDLC ($mg \cdot dL^{-1}$)	58.3 ± 1.2	58.3 ± 1.9	56.3 ± 1.7	59.7 ± 1.3	57.8 ± 1.1	59.9 ± 2.4
TG/HDLC	2.29 ± 0.16	2.13 ± 0.20	2.51 ± 0.23	2.06 ± 0.14	2.27 ± 0.15	2.15 ± 0.22
FPG ($mg \cdot dL^{-1}$)	98.1 ± 1.3	99.6 ± 3.0	98.0 ± 1.8	99.0 ± 1.7	99.1 ± 1.5	96.9 ± 2.2
HbA1c (%)	5.14 ± 0.06	5.20 ± 0.11	5.13 ± 0.06	5.17 ± 0.08	5.16 ± 0.07	5.13 ± 0.08
MetS No.	1.61 ± 0.10	1.57 ± 0.14	1.77 ± 0.12	1.47 ± 0.10	1.61 ± 0.09	1.56 ± 0.17
MetS score	−0.11 ± 0.25	−0.05 ± 0.32	0.42 ± 0.27	−0.43 ± 0.27*	−0.04 ± 0.22	−0.24 ± 0.41
$\dot{V}O_2max$ ($mL \cdot kg^{-1}\ min^{-1}$)	33.2 ± 0.7	32.4 ± 1.1	32.9 ± 1.0	33.0 ± 0.8	33.2 ± 0.7	33.2 ± 1.3

Data are means ± S.E. unless otherwise indicated

*$P < 0.05$ for a significant difference from the AlaAla variants of Ala54Thr using an unpaired student's *t*-test

Abbreviations as defined for Table 15.1

higher than those found in the Ala carriers ($P<0.05$, Table 15.1). In middle-aged/older men, BMI, %BF (body fat), and MetS score in the AlaAla genotype of FABP2 were significantly higher than those found in the Thr carriers ($P<0.05$, Table 15.2).

Significant simple and partial age-adjusted correlations were observed between $\dot{V}O_2$max (ml/kg/min) and MetS risk (Z-score) in both young men (simple correlation r=–0.496, $P<0.05$, partial correlation r=–0.300, $P<0.05$) and middle-aged/older men (simple correlation r=–0.381, $P<0.05$, partial correlation r=–0.383, $P<0.05$); therefore, these findings were independently associated with age.

The interaction between fitness and the C1431T genotype of the PPARγ2 gene significantly affected MetS risk in younger men ($P<0.05$, Table 15.3). The MetS risk in low-fitness younger men with the CC genotype in the C1431T polymorphism of the PPARγ2 gene was significantly higher than that in the low-fitness younger men with the T carriers ($P<0.05$, Table 15.3). There was no significant interaction between fitness and genotype in determining MetS risk in middle-aged/older men.

On the other hand, with regard to the Ala54Thr genotype of the FABP2 gene, there were no significant differences in fitness or genotype effects, nor were there any interactions between measurement variables (Table 15.4).

The interaction between fitness and the Ala55Val genotype of the UCP2 gene significantly affected the risk of MetS, SBP, DBP, MBP, TG, and TG/HDL in younger men ($P<0.05$, Table 15.5). Moreover, the MetS risk in low-fitness younger men with the ValVal genotype in the Ala55Val polymorphism of the UCP2 gene was significantly higher than that in the other groups ($P<0.05$, Table 15.5). There was no significant interaction between fitness and genotype in determining MetS risk in middle-aged/older men.

15.4 Discussion

The associations reported previously between DNA sequence variation in specific genes and obesity phenotypes have increased considerably, with 426 findings of positive associations with 127 candidate genes (Rankinen et al. 2006). One of these genes, PPARγ2, which encodes a transcription factor belonging to the nuclear receptor family, is related to lipid metabolism, carbohydrate metabolism, and fatty acid transport (Willson et al. 1996), and is a candidate gene for susceptibility to obesity and type 2 diabetes (Altshuler et al. 2000; Deeb et al. 1998; Kao et al. 2003; Mori et al. 1998). It is directly involved in adipogenesis (Tontonoz et al. 1995) and muscle responses to glucose (Hevener et al. 2003). A common structural defect has been detected in the PPARγ2 gene, resulting in a Pro-to-Ala substitution (Yen et al. 1997), located at codon 12 (Pro12Ala); a synonymous C-to-T substitution in exon 6 has been identified at nucleotide1431 (C1431T) of this gene (Meirhaeghe et al. 1998). However, the reported associations between increased body mass and BMI with the Pro12Ala genotype are inconsistent; some studies indicate that the Ala allele is associated with a higher BMI (Beamer et al. 1998; Kao et al. 2003; Meirhaeghe et al. 2000; Valve et al. 1999), while others indicate an association with

Table 15.3 The relationships among cardiorespiratory fitness, genotypes of the peroxisome proliferator-activated receptor γ2 gene (C1431T), and metabolic syndrome risk in young (age < 40 years) and middle-aged/older (age ≥ 40 years) subjects

	Low fitness		High fitness				
	CC	T carriers	CC	T carriers	*P* genotype	*P* fitness	*P* interaction
Young (age < 40 years)							
n	114	56	87	38			
Age (years)	34.8 ± 0.7	33.4 ± 2.1	26.9 ± 1.1	25.5 ± 1.9			
BMI ($kg \cdot m^{-2}$)	25.9 ± 0.8	22.9 ± 0.6	23.3 ± 0.4	23.4 ± 0.4	0.448	0.548	0.090
SBP (mmHg)	120.7 ± 2.9	117.2 ± 1.9	116.0 ± 1.7	118.4 ± 2.2	0.581	0.880	0.678
DBP (mmHg)	72.9 ± 1.9	71.1 ± 2.6	64.0 ± 1.3	62.3 ± 2.0	0.728	0.642	0.919
MBP (mmHg)	90.0 ± 2.0	86.0 ± 1.8	83.4 ± 1.3	84.8 ± 1.9	0.923	0.853	0.401
TG ($mg \cdot dL^{-1}$)	123.1 ± 17.6	80.0 ± 12.1	63.0 ± 4.0	80.2 ± 12.6	0.825	0.227	0.180
HDLC ($mg \cdot dL^{-1}$)	49.7 ± 1.4	56.2 ± 5.5	60.4 ± 1.7	63.6 ± 3.6	0.274	0.065	0.297
TG/HDLC	2.47 ± 0.31	1.54 ± 0.34	1.10 ± 0.09	1.41 ± 0.33	0.597	0.453	0.102
FPG ($mg \cdot dL^{-1}$)	90.4 ± 1.1	88.6 ± 3.5	90.6 ± 1.6	92.9 ± 1.3	0.520	0.514	0.294
HbA1c (%)	4.79 ± 0.04	4.64 ± 0.13	4.76 ± 0.04	4.76 ± 0.08	0.075	0.691	0.108
MetS No.	1.53 ± 0.16	0.80 ± 0.37 a	0.66 ± 0.13	0.56 ± 0.20 a	0.483	0.129	**0.037**
MetS risk (Z-score)	1.81 ± 0.61	−0.40 ± 0.64 a	−0.55 ± 0.26	−0.11 ± 0.61	0.262	0.883	**0.038**
$\dot{V}O_2max$ ($mL \cdot kg^{-1}\ min^{-1}$)	33.6 ± 0.6	36.5 ± 0.4	49.4 ± 1.3	52.5 ± 2.8	0.152	**0.000**	0.377
Middle/older (age ≥ 40 years)							
n	54	22	31	12			
Age (years)	52.8 ± 1.9	53.4 ± 2.2	53.4 ± 1.8	56.1 ± 2.9			
BMI ($kg \cdot m^{-2}$)	25.1 ± 0.4	24.7 ± 0.6	23.2 ± 0.5	24.1 ± 0.7	0.246	0.168	0.159
SBP (mmHg)	125.0 ± 2.2	129.0 ± 3.5	127.0 ± 2.5	125.3 ± 4.1	0.704	0.393	0.321
DBP (mmHg)	78.8 ± 1.6	78.6 ± 2.3	78.6 ± 1.9	80.1 ± 3.0	0.540	0.198	0.796
MBP (mmHg)	96.2 ± 2.0	97.9 ± 3.1	97.8 ± 2.4	95.6 ± 3.6	0.769	0.206	0.444
TG ($mg \cdot dL^{-1}$)	125.7 ± 8.9	124.7 ± 15.4	109.2 ± 8.5	109.6 ± 15.7	0.848	0.686	0.985

(continued)

Table 15.3 (continued)

	Low fitness		High fitness				
	CC	T carriers	CC	T carriers	*P* genotype	*P* fitness	*P* interaction
HDLC (mg·dL^{-1})	54.1 ± 1.6	55.8 ± 3.3	61.8 ± 2.0	59.8 ± 2.5	0.417	0.710	0.355
TG/HDLC	2.54 ± 0.23	2.43 ± 0.34	1.94 ± 0.21	1.91 ± 0.30	0.947	0.450	0.918
FPG (mg·dL^{-1})	97.9 ± 1.8	96.4 ± 3.3	93.8 ± 2.8	98.7 ± 4.5	0.564	0.344	0.573
HbA1c (%)	5.19 ± 0.12	5.10 ± 0.14	4.96 ± 0.09	5.02 ± 0.10	0.691	0.243	0.741
MetS No.	1.76 ± 0.16	1.80 ± 0.26	1.34 ± 0.14	1.33 ± 0.23	0.242	0.614	0.983
MetS risk (Z-score)	0.26 ± 0.36	0.18 ± 0.54	−1.11 ± 0.39	−0.65 ± 0.42	0.917	0.540	0.562
$\dot{V}O_2$max (mL·kg^{-1} min^{-1})	29.2 ± 0.6	29.3 ± 0.9	40.0 ± 0.8	38.1 ± 1.4	0.974	0.119	0.327

Data are means ± S.E. unless otherwise indicated

$P < 0.05$ for a significant difference from CC individuals with the C1431T variant in the "low fitness" group using the unpaired Student's *t*-test. *P* values are for significant effects using 2-way ANCOVA with adjustment for the covariate of age (genotype × fitness). Boldface indicates significance ($P < 0.05$)

Abbreviations as defined for Table 15.1

Table 15.4 The relationships among cardiorespiratory fitness, genotypes of the fatty acid binding protein 2 (Ala54Thr), and metabolic syndrome risk in young (age < 40 years) and middle-aged/older (age ≥ 40 years) subjects

	Low fitness		High fitness				
	AlaAla	Thr carriers	AlaAla	Thr carriers	*P* genotype	*P* fitness	*P* interaction
Young (age < 40 years)							
n	114	56	87	38			
Age (years)	34.5 ± 1.2	34.7 ± 0.7	27.3 ± 1.5	26.0 ± 1.2			
BMI ($kg \cdot m^{-2}$)	25.8 ± 1.1	25.3 ± 1.1	23.3 ± 0.5	23.3 ± 0.4	0.633	0.546	0.544
SBP (mmHg)	114.9 ± 2.0	123.5 ± 3.8	116.8 ± 2.2	116.5 ± 1.7	0.819	0.928	0.305
DBP (mmHg)	69.4 ± 2.0	74.7 ± 2.3	64.1 ± 1.7	63.1 ± 1.5	0.837	0.681	0.241
MBP (mmHg)	86.1 ± 1.4	91.6 ± 2.6	83.7 ± 1.7	83.9 ± 1.4	0.820	0.829	0.332
TG ($mg \cdot dL^{-1}$)	124.9 ± 30.7	112.1 ± 16.0	71.3 ± 8.4	64.3 ± 4.5	0.913	0.231	0.806
HDLC ($mg \cdot dL^{-1}$)	51.7 ± 2.1	49.8 ± 1.9	61.3 ± 2.7	61.2 ± 1.9	0.395	0.065	0.713
TG/HDLC	2.34 ± 0.49	2.34 ± 0.33	1.28 ± 0.21	1.10 ± 0.10	0.987	0.481	0.831
FPG ($mg \cdot dL^{-1}$)	89.1 ± 1.7	90.9 ± 1.4	92.5 ± 2.2	90.0 ± 1.4	0.618	0.527	0.478
HbA1c (%)	4.75 ± 0.03	4.78 ± 0.06	4.81 ± 0.06	4.72 ± 0.05	0.519	0.844	0.234
MetS No.	1.47 ± 0.24	1.41 ± 0.20	0.75 ± 0.18	0.68 ± 0.13	0.375	0.140	0.564
MetS risk (Z-score)	0.83 ± 0.31	1.98 ± 0.90	−0.19 ± 0.42	−0.63 ± 0.30	0.907	0.814	0.289
$\dot{V}O_2max$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	34.7 ± 0.8	33.5 ± 0.7	49.4 ± 1.7	50.8 ± 1.6	0.213	**0.000**	0.172
Middle/older (age ≥ 40 years)							
n	54	22	31	12			
Age (years)	53.1 ± 1.8	52.9 ± 1.3	51.7 ± 2.6	55.4 ± 1.9			
BMI ($kg \cdot m^{-2}$)	25.4 ± 0.6	24.7 ± 0.4	24.1 ± 0.6	23.2 ± 0.5	0.448	0.300	0.895
SBP (mmHg)	127.1 ± 3.2	125.4 ± 2.3	126.5 ± 3.9	126.5 ± 2.5	0.590	0.352	0.871
DBP (mmHg)	79.2 ± 2.1	78.3 ± 1.6	78.3 ± 2.8	79.4 ± 2.0	0.326	0.243	0.721
MBP (mmHg)	97.6 ± 2.9	96.1 ± 2.0	96.3 ± 3.5	97.7 ± 2.5	0.477	0.189	0.725
TG ($mg \cdot dL^{-1}$)	126.0 ± 11.8	124.9 ± 10.2	116.7 ± 13.8	105.4 ± 8.9	0.851	0.671	0.594

(continued)

Table 15.4 (continued)

	Low fitness		High fitness				
	AlaAla	Thr carriers	AlaAla	Thr carriers	*P* genotype	*P* fitness	*P* interaction
HDLC (mg dL^{-1})	52.4 ± 2.7	56.2 ± 1.7	57.9 ± 2.6	63.0 ± 2.0	0.635	0.478	0.959
TG/HDLC	2.67 ± 0.30	2.39 ± 0.24	2.20 ± 0.34	1.80 ± 0.20	0.544	0.420	0.809
FPG (mg·dL^{-1})	95.1 ± 2.1	99.2 ± 2.3	95.6 ± 3.4	97.1 ± 3.2	0.995	0.288	0.411
HbA1c (%)	5.05 ± 0.07	5.25 ± 0.15	5.01 ± 0.07	4.96 ± 0.10	0.732	0.217	0.256
MetS No.	1.86 ± 0.20	1.70 ± 0.18	1.40 ± 0.24	1.31 ± 0.13	0.887	0.736	0.878
MetS risk (Z-score)	0.47 ± 0.39	0.06 ± 0.43	−0.46 ± 0.46	−1.26 ± 0.40	0.993	0.706	0.689
$\dot{V}O_2$max (mL·kg^{-1}·min^{-1})	29.5 ± 0.9	29.1 ± 0.6	40.3 ± 1.3	39.1 ± 0.8	0.514	0.123	0.892

Data are means ± S.E. unless otherwise indicated

P values are for significant effects using 2-way ANCOVA with adjustment for the covariate of age (genotype × fitness). Boldface indicates significance ($P < 0.05$)

Abbreviations as defined for Table 15.1

Table 15.5 The relationships among cardiorespiratory fitness, genotypes of the uncoupling protein-2 (Ala55Val), and metabolic syndrome risk in young (age < 40 years) and middle-aged/older (age ≥ 40 years) subjects

	Low fitness		High fitness				
	Ala carriers	ValVal	Ala carriers	ValVal	*P* genotype	*P* fitness	*P* interaction
Young (age < 40 years)							
n	56	114	38	87			
Age (years)	34.8 ± 0.7	34.1 ± 1.2	26.4 ± 1.0	27.4 ± 3.0			
BMI ($kg \cdot m^{-2}$)	24.4 ± 0.6	29.5 ± 2.5	23.3 ± 0.3	23.5 ± 1.1	0.128	0.582	0.163
SBP (mmHg)	116.1 ± 1.5	137.0 ± 9.7	116.8 ± 1.5 a	115.4 ± 2.3	0.142	0.872	**0.047**
DBP (mmHg)	70.3 ± 1.4 a	82.4 ± 5.1	63.6 ± 1.2 a	62.9 ± 2.8 a	0.394	0.505	**0.020**
MBP (mmHg)	86.6 ± 1.2 a	101.5 ± 5.7	84.0 ± 1.2 a	82.4 ± 2.9 a	0.087	0.954	**0.031**
TG ($mg \cdot dL^{-1}$)	92.0 ± 10.2 a	209.1 ± 51.3	69.4 ± 5.0 a	53.3 ± 4.7 a	0.638	0.172	**0.002**
HDLC ($mg \cdot dL^{-1}$)	51.5 ± 1.6	47.3 ± 3.3	61.4 ± 1.8	60.1 ± 3.2	0.404	0.053	0.383
TG/HDLC	1.82 ± 0.19 a	4.23 ± 0.80	1.22 ± 0.12 a	0.89 ± 0.08 a	0.996	0.439	**0.000**
FPG ($mg \cdot dL^{-1}$)	89.4 ± 1.3	92.9 ± 1.7	89.9 ± 1.2	99.3 ± 3.5	0.582	0.375	0.291
HbA1c (%)	4.71 ± 0.04	4.96 ± 0.12	4.75 ± 0.04	4.81 ± 0.09	0.880	0.763	0.389
MetS No.	1.24 ± 0.16	2.13 ± 0.23	0.69 ± 0.12	0.86 ± 0.34	0.648	0.134	0.341
MetS risk (Z-score)	0.54 ± 0.34 a	5.05 ± 1.81	−0.41 ± 0.27 a	−0.62 ± 0.75 a	0.374	0.823	**0.011**
$\dot{V}O_2max$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	34.6 ± 0.5 a	31.7 ± 1.4	49.9 ± 1.2 a	52.1 ± 4.0 a	0.164	**0.000**	**0.011**
Middle/older (age ≥ 40 years)							
n	22	54	12	31			
Age (years)	52.1 ± 1.2	55.2 ± 2.1	54.9 ± 1.7	50.3 ± 3.9			
BMI ($kg \cdot m^{-2}$)	25.3 ± 0.4	24.1 ± 0.7	23.6 ± 0.4	22.8 ± 1.2	0.344	0.231	0.963
SBP (mmHg)	126.5 ± 2.3	125.1 ± 3.2	127.6 ± 2.4	120.7 ± 4.0	0.532	0.200	0.594
DBP (mmHg)	79.3 ± 1.6	77.2 ± 2.2	79.5 ± 1.8	76.6 ± 3.9	0.957	0.128	0.843
MBP (mmHg)	97.0 ± 2.1	96.0 ± 2.6	98.2 ± 2.2	91.9 ± 5.0	0.799	0.106	0.661
TG ($mg \cdot dL^{-1}$)	120.8 ± 9.2	137.4 ± 14.0	110.6 ± 8.2	102.1 ± 19.0	0.090	0.435	0.671
HDLC ($mg \cdot dL^{-1}$)	54.4 ± 1.7	55.1 ± 3.0	60.7 ± 1.8	64.1 ± 3.8	0.069	0.386	0.535

(continued)

Table 15.5 (continued)

	Low fitness		High fitness				
	Ala carriers	ValVal	Ala carriers	ValVal	*P* genotype	*P* fitness	*P* interaction
TG/HDLC	2.44 ± 0.23	2.69 ± 0.33	1.99 ± 0.20	1.68 ± 0.37	**0.032**	0.228	0.655
FPG ($mg \cdot dL^{-1}$)	96.6 ± 1.7	99.7 ± 3.7	97.3 ± 2.7	92.9 ± 3.8	0.166	0.163	0.696
HbA1c (%)	5.17 ± 0.12	5.15 ± 0.12	4.98 ± 0.08	4.91 ± 0.11	0.153	0.176	0.787
MetS No.	1.76 ± 0.15	1.79 ± 0.27	1.38 ± 0.13	1.14 ± 0.34	**0.031**	0.916	0.939
MetS risk (Z-score)	0.30 ± 0.34	0.07 ± 0.61	−0.85 ± 0.32	−1.70 ± 0.90	0.067	0.709	0.833
$\dot{V}O_2max$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	29.2 ± 0.6	29.3 ± 1.0	39.1 ± 0.7	41.3 ± 1.7	0.064	0.166	0.439

Data are means ± S.E. unless otherwise indicated

$P < 0.05$ for a significant difference from ValVal individuals of the Ala55Val variant in the "low fitness" group using the unpaired Student's *t*-test. *P* values are for significant effects using 2-way ANCOVA with adjustment for the covariate of age (genotype × fitness). Boldface indicates significance ($P < 0.05$)

Abbreviations as defined for Table 15.1

a lower BMI (Deeb et al. 1998; Doney et al. 2002; Ek et al. 1999; Pihlajamaki et al. 2000; Vigouroux et al. 1998), and others find no association (Hamann et al. 1999; Mori et al. 1998; Ringel et al. 1999; Tai et al. 2004). Kao et al. (2003) reported that among overweight individuals (BMI 25–29.9 kg/m^2), the ProAla genotype of PPARγ2 is associated with a higher BMI ($P=0.02$), waist-to-hip ratio ($P=0.01$), and waist circumference ($P=0.04$) in non-obese African-Americans. Our previous data and this study indicated that neither C1431T nor Pro12Ala variants were associated with a lower BMI regardless of the age of healthy Japanese adults in the study groups (Sanada et al. 2011).

Prochazka et al. (1993) investigated a significant linkage between maximal insulin action and the intestinal FABP2 gene on chromosome 4. It is well recognized that fatty acid metabolism is linked to insulin resistance. Chiu et al. (2001) examined the influence of this polymorphism on insulin resistance in 55 healthy, normotensive Caucasian subjects with normal glucose tolerance and found that the A54T polymorphism at the FABP2 locus is a risk factor for insulin resistance in a Caucasian population. Albala et al. (2004) also suggested that the Ala54Thr polymorphism of the FABP2 gene is associated with obesity and insulin resistance, and the effect of this polymorphism might be mediated by elevated production of tumor necrosis factor (TNF) alpha. In this study, BMI, %BF, and MetS scores in middle-aged/older men with the AlaAla genotype of FABP2 were significantly higher than values found in the Thr carriers (Table 15.2), but this difference was not found in young men (Table 15.1). These results support the hypothesis that the Ala54Thr polymorphism of the FABP2 gene is associated with obesity or insulin resistance in Japanese middle-aged/older men. However, with regard to the Ala54Thr genotype of the FABP2 gene, there were no significant differences in fitness or genotype effects nor were there any interactions between measurement variables (Table 15.4). These results suggest that the influence of the interaction between the Ala54Thr genotype of FABP2 gene and cardiorespiratory fitness might not be associated with inflammatory cytokines such as TNF alpha.

UCP2 plays an important role in cardiovascular diseases and recent studies have suggested that the A55V polymorphism can cause UCP2 dysfunction. The A55V polymorphism has been associated with energy metabolism misbalance (Klannemark et al. 1998), higher risk of type 2 diabetes, lower HDL, high atherogenic index (Cha et al. 2007), and lower levels of leptin (Rance et al. 2007). Other studies have associated the VV genotype with a lower degree of uncoupling, more efficient energy utilization, lower fat oxidation, and increased ROS production, suggesting that A55V causes UCP2 dysfunction (Astrup et al. 1999). Recently, Gioli-Pereira et al. (2013) investigated the association of the A55V polymorphism with cardiovascular events in a group of 611 patients enrolled in the Medical, Angioplasty or Surgery Study II (MASS II). They concluded that the A55V polymorphism is associated with UCP2 functional alterations that increase the risk of cardiovascular events in patients with previous coronary artery disease and dysglycemia. In the present study, the TG and TG/HDL scores in the ValVal UCP2 genotype in young men were significantly higher than those in the Ala carriers (Table 15.1), but not higher than those seen in middle-aged/older men (Table 15.2). These results support the hypoth-

esis that the A55V UCP2 gene polymorphism is associated with dyslipidemia or risk of arteriosclerosis in young Japanese men.

At present, it is unclear which of the two contributions to MetS is more important: the obesity-related genotypes or cardiorespiratory fitness. In the present study, the subjects were classified into high- and low-fitness groups according to the criteria issued by the Ministry of Health, Labor, and Welfare of Japan (Ishikawa-Takata and Tabata 2007). We examined the relationship between the fitness level and some obesity-related genotypes when the subjects were divided based on their age. The results of this study indicated that younger men with low levels of fitness and the CC genotype of C1431T (Table 15.3) and the ValVal genotype of Ala55Val (Table 15.5) possessed more risk factors for MetS than those subjects with high fitness levels and the other genotypes, even after adjustment for age. These results, therefore, suggest that in younger men (age < 40 years) with these obesity-related genotypes and low cardiorespiratory fitness, these factors increase the risk of MetS.

In conclusion, we found that low cardiorespiratory fitness was associated with MetS risk independent of age and that the CC genotype of C1431T in the PPARγ2 gene and the ValVal genotype of Ala55Val in the UCP2 gene combined with low cardiorespiratory fitness increased the risk of MetS in younger men (age < 40 years), even if these factors were adjusted for age.

Grants This study was partly supported by funding from the Establishment of Consolidated Research Institute for Advanced Science and Medical Care program (K. Sanada); the Encouraging Development Strategic Research Centers Program; Special Coordination Funds for Promoting Science and Technology (K. Sanada); a grant-in-aid (no. 21300258) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (K. Sanada); the Uehara Memorial Foundation of Japan (M. Iemitsu); and a grant-in-aid for scientific research from the Ministry of Health, Labor, and Welfare of Japan (M. Miyachi).

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Chapter 16
Mechanisms Underlying the Suppression of Inflammatory Responses in Peritoneal Macrophages of Middle-Aged Mice

Ken Shirato and Kazuhiko Imaizumi

Abstract We investigated the molecular mechanisms underlying the deterioration of macrophage inflammatory responses in middle-aged mice, focusing on the age-related reduction in protein synthesis rate. Peritoneal macrophages were isolated from male BALB/c mice aged 2 months (young) and 12 months (middle-aged), and stimulated with lipopolysaccharide (LPS). At the protein level, LPS-stimulated pro-inflammatory cytokine release and intracellular accumulation of bactericidal mediators from macrophages were clearly lower in middle-aged mice than in young mice. However, LPS caused a marked increase in the mRNA expression of these genes in the macrophages of both young and middle-aged mice. Moreover, LPS induced comparable phosphorylation levels of signaling proteins downstream of toll-like receptor (TLR) in young and middle-aged mice. In contrast, levels of the inactive (phosphorylated) form of eukaryotic initiation factor 2α (eIF-2α) were higher in macrophages from middle-aged mice than in macrophages from young mice. Suppression of the LPS-stimulated inflammatory responses observed in middle-aged mice could be mimicked by treating the murine macrophage RAW264.7 cells with salubrinal, an inhibitor of the phosphatase that dephosphorylates eIF-2α. In conclusion, post-transcriptional suppression of macrophage inflammatory responses during middle age requires phosphorylation of eIF-2α.

Keywords Aging • Inflammatory response • Eukaryotic initiation factor • Peritoneal macrophages • Middle-aged mice

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_16

16.1 Introduction

Increased susceptibility to infectious diseases is a hallmark of old age. The age-related susceptibility to infectious diseases is caused, at least in part, by reduced activity of various immune cell types (Gomez et al. 2008; Kovacs et al. 2009; Panda et al. 2009; Weiskopf et al. 2009; Dunston and Griffiths 2010; Shaw et al. 2010), including macrophages. The cellular functions of macrophages against pathogenic microorganisms, which include inflammatory responses and phagocytosis, have been reported to decrease with advancing age in rodent and human experimental models (Gomez et al. 2008; Kovacs et al. 2009; Panda et al. 2009; Weiskopf et al. 2009; Dunston and Griffiths 2010; Shaw et al. 2010). Macrophages use TLRs on the surface of the cell and intracellular organelles to recognize various pathogen components, such as LPS (gram-negative bacteria), lipoteichoic acid (gram-positive bacteria), flagellin (bacterial flagella), and double-stranded RNA (virus). Subsequent activation of downstream intracellular signaling leads to the production of pro-inflammatory and bactericidal mediators, including tumor necrosis factor-α (TNF-α), inducible nitric oxide synthase (iNOS), etc. (Kawai and Akira 2011). The inflammatory responses of macrophages facilitate the accumulation and activation of immune cells in infectious foci and pathogen killing.

The capacity of macrophages to produce pro-inflammatory cytokines in response to LPS stimulation gradually reduces with age (Kohut et al. 2004; Vega et al. 2004) (Fig. 16.1). LPS-stimulated iNOS production by macrophages is also impaired with advancing age (Cecílio et al. 2011) (Fig. 16.1). In previous studies, scientists, with the aim of clarifying the molecular mechanisms responsible for age-related deterioration of macrophage inflammatory responses, have predominantly focused on intracellular signal transduction downstream of TLR in advanced-age (18–24-month-old) mice, which are comparable to 70–80-year-old humans (Fig. 16.1). The cell surfaces of peritoneal and splenic macrophages from advanced-aged mice show reduced levels of the TLR4 co-receptor CD14 (Vega et al. 2004; Chelvarajan et al. 2005) (Fig. 16.1). Advanced-age mice also show lower levels of intracellular signaling proteins, such as mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK), than young mice (Boehmer et al. 2004, 2005) (Fig. 16.1). In addition, DNA microarray analysis showed significant suppression of gene expression of the TLR signaling molecules responsible for nuclear factor-κB (NF-κB) activation in advanced-age mice (Chelvarajan et al. 2006) (Fig. 16.1). However, the mechanisms responsible for attenuation of these macrophage inflammatory responses have not been fully elucidated in middle-aged (9–12-month-old) mice, which are comparable to 50–60-year-old humans. Elucidation of the reason for the decline at this point could provide a clue for the prevention of unresponsive macrophages in advanced age.

A decreased rate of bulk protein synthesis in cells is one of the most common age-related biochemical changes (Rattan et al. 1992; Rattan 1996). Translation of mRNA into protein is initiated by physical interactions among the methionyl-tRNA specialized for initiation (Met-tRNAi), several eukaryotic initiation factor (eIF)

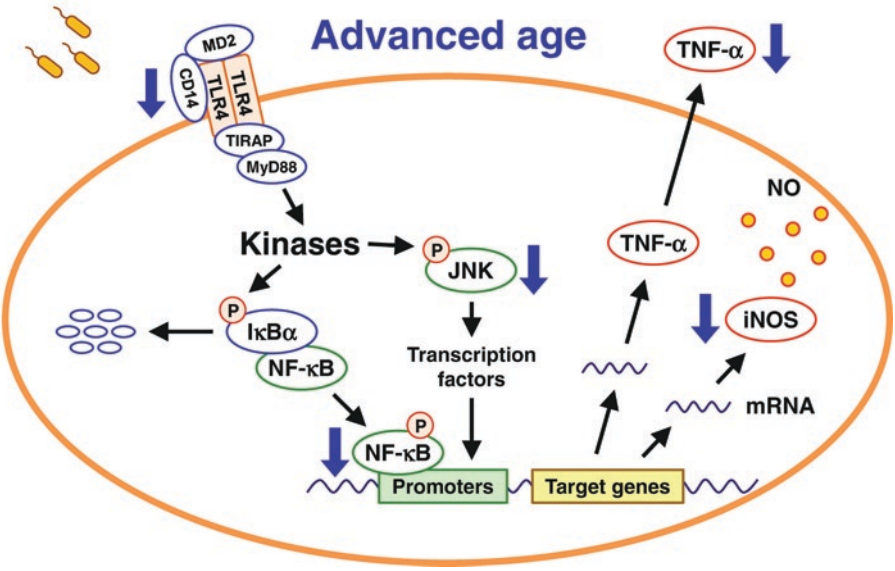

Fig. 16.1 TLR signaling defects in macrophages from advanced-age mice. Macrophages from advanced-age mice show reduced levels of the TLR4 co-receptor CD14 on their cell surface (Vega et al. 2004; Chelvarajan et al. 2005) and reduced levels of intracellular signaling proteins such as MAPK and JNK (Boehmer et al. 2004, 2005). In addition, DNA microarray analysis showed suppressed expressions of the TLR signaling molecules responsible for NF-κB activation in advanced-age mice (Chelvarajan et al. 2006)

subunits, and the 40S ribosome (Morel et al. 2009) (Fig. 16.2). Among the eIF subunits, phosphorylation of eIF-2α at Ser51 competitively inhibits the guanosine diphosphate (GDP)/guanosine triphosphate (GTP) exchange activity of eIF-2B; this suppresses binding of the Met-tRNAi complex with messenger ribonucleic acid (mRNA) and subsequent protein synthesis (Dever et al. 1993; Krishnamoorthy et al. 2001) (Fig. 16.2). Compared with young mice, advanced-age mice express higher levels of phosphorylated eIF-2α and its kinase, double-stranded RNA-dependent protein kinase (PKR), in the liver and kidney (Ladiges et al. 2000). The levels of phosphorylated eIF-2α in the cerebral cortex of middle-aged mice are higher than in cerebral cortex of young mice (Segev et al. 2013). In contrast, it has been reported that phosphorylation of various eIF subunits, including eIF-2α, is reduced in different rat tissues during aging (Hussain and Ramaiah 2007). However, no information is available on how advancing age affects eIF-2α phosphorylation in macrophages and what roles eIF-2α plays in macrophage inflammatory responses.

In this study, to better understand the molecular mechanisms underlying age-related deterioration of macrophage inflammatory responses, we examined LPS-stimulated mRNA and protein expression of TNF-α and iNOS; phosphorylation of JNK, NF-κB, and inhibitor of κBα (IκBα); and the levels of phosphorylated and

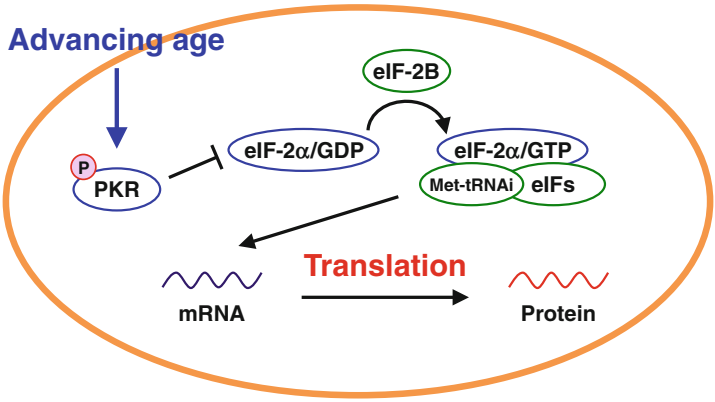

Fig. 16.2 Role of eIF-2α in the age-related reduction of protein synthesis rate. Translation is initiated by physical interactions among Met-tRNAi, several eIF subunits, and the 40S ribosome (Morel et al. 2009). Phosphorylation of eIF-2α at Ser51 competitively inhibits the GDP/GTP exchange activity of eIF-2B; this suppresses binding of the Met-tRNAi complex with mRNA and subsequent protein synthesis (Dever et al. 1993; Krishnamoorthy et al. 2001). Increased phosphorylation of eIF-2α is observed in different murine tissues during aging (Ladiges et al. 2000; Segev et al. 2013)

unphosphorylated eIF-2α and PKR in resident peritoneal macrophages isolated from male BALB/c mice aged 2 months (young) and 12 months (middle-aged). Moreover, to elucidate the functional role of the inactive form of eIF-2α, we examined the effects of salubrinal, a selective inhibitor of an eIF-2α phosphatase (Tsaytler et al. 2011; Hamamura et al. 2013; Tsaytler and Bertolotti 2013), on the LPS-stimulated inflammatory responses in murine macrophage RAW264.7 cells.

16.2 Post-transcriptional Suppression of LPS-Stimulated Inflammatory Responses in Peritoneal Macrophages from Middle-Aged Mice

In previous studies, reduced secretion of pro-inflammatory cytokines from LPS-stimulated macrophages was observed in both middle-aged and advanced-age mice (Kohut et al. 2004; Vega et al. 2004; Sun et al. 2012). Therefore, in this study, we first examined LPS-stimulated release of TNF-α from resident peritoneal macrophages isolated from young and middle-aged mice. After macrophages from young and middle-aged mice were stimulated with 100 ng/mL LPS for 6 h, the concentration of TNF-α in the culture supernatants of LPS-stimulated middle-aged mouse cells was significantly lower than that in the culture supernatants of LPS-stimulated young mouse cells (Shirato and Imaizumi 2014). In addition to the reduction in LPS-stimulated TNF-α secretion, western blot analysis showed that intracellular accumulation of iNOS in response to LPS stimulation was also clearly lower in

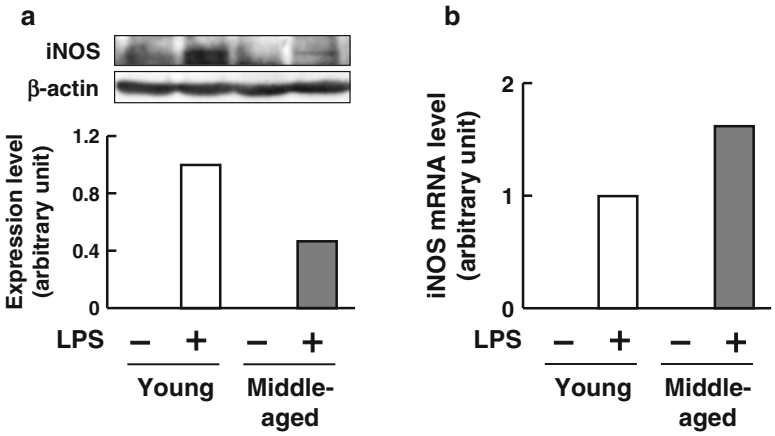

Fig. 16.3 LPS-stimulated production of iNOS by peritoneal macrophages from young and middle-aged mice. Resident peritoneal macrophages from four mice were pooled to obtain a sufficient number of cells for the experiments (Shirato and Imaizumi 2014). The cells were cultured with or without 100 ng/mL LPS from *Escherichia coli* 055:B5 (Sigma-Aldrich, St. Louis, MO, USA) for 6 h. (**a**) The expression levels of iNOS in whole cell lysates were analyzed by western blotting. (**a**) Total RNA extracted from macrophages was converted to cDNA to determine the levels of TNF-α mRNA by polymerase chain reaction

middle-aged mice than in young mice (Fig. 16.3a). This result agreed with previous findings (Cecílio et al. 2011). However, LPS stimulation induced a significantly higher increase in TNF-α mRNA levels in macrophages from middle-aged mice than in macrophages from young mice (Shirato and Imaizumi 2014). A similar tendency was also observed for the mRNA expression of iNOS (Fig. 16.3b). These results suggest that the onset of middle age is associated with post-transcriptional suppression of LPS-stimulated TNF-α production by peritoneal macrophages (Shirato and Imaizumi 2014). The adequacy of this speculation was tested by examining the difference between the magnitude of the LPS-stimulated increase in JNK and NF-κB signaling in macrophages from young and middle-aged mice.

To verify transduction of the LPS-induced, TLR4-initiated signal in macrophages from middle-aged mice, we compared LPS-stimulated phosphorylation of p54 and p46 JNK, p65 NF-κB, and IκBα in macrophages from young and middle-aged mice. Macrophages from both young and middle-aged mice showed similar levels of p54 JNK phosphorylation in response to LPS, and the total expression levels in macrophages collected from mice of both age groups were similar (Shirato and Imaizumi 2014). Exposure to LPS caused comparable increases in the levels of phosphorylated p46 JNK in macrophages from young and middle-aged mice (Shirato and Imaizumi 2014). Although the level of phosphorylated p65 in cells from middle-aged mice was lower than that in cells from young mice in the absence of LPS stimulation, the levels of phosphorylated p65 increased to similar levels in the two age groups after LPS stimulation (Shirato and Imaizumi 2014). In addition, LPS stimulated comparable levels of IκBα phosphorylation

and degradation in macrophages from young and middle-aged mice (Shirato and Imaizumi 2014). These results indicate that following LPS stimulation, peritoneal macrophages from middle-aged mice exhibit normal JNK activation and NF-κB signaling.

The molecular mechanisms underlying attenuation of macrophage inflammatory responses against bacterial components have been mainly explored in advanced-age mice (Boehmer et al. 2004, 2005; Kohut et al. 2004; Vega et al. 2004; Chelvarajan et al. 2005, 2006). These previous studies focused on age-related reductions in the expression levels of TLRs, their co-receptors, such as CD14, and downstream signal proteins, such as MAPK and JNK (Boehmer et al. 2004, 2005; Kohut et al. 2004; Vega et al. 2004; Chelvarajan et al. 2005, 2006). Renshaw et al. (2002) reported that the mRNA expression levels of all TLRs in splenic and thioglycollate-elicited peritoneal macrophages from 18 to 24-month-old C57BL/6 mice were significantly lower than in those from their 2–3-month-old counterparts. In addition, the levels of CD14 on the surface of peritoneal and splenic macrophages were lower in advanced-age BALB/c and C57BL/6 mice than in their young counterparts (Vega et al. 2004; Chelvarajan et al. 2005). Despite earlier reports of the age-dependency of reduced CD14 expression and LPS-stimulated TNF-α secretion (Kohut et al. 2004; Vega et al. 2004), the details of the intracellular molecular events in macrophages from middle-aged mice have not yet been fully elucidated. The levels of LPS-stimulated p54 and p46 JNK phosphorylation and NF-κB activation were lower in advanced-age BALB/c mice than in their young counterparts (Boehmer et al. 2004, 2005).

Along with the previously reported observations, our findings suggest that aging is associated with a gradual reduction in LPS-stimulated production of pro-inflammatory mediators by macrophages, although the mechanistic bases of the age-related changes in advanced-age and middle-aged mice differ.

16.3 A possible Role for eIF-2α in Attenuated Inflammatory Responses of Macrophages in Middle-Aged Mice

A reduced overall rate of protein synthesis is one of the most common age-related biochemical changes (Rattan et al. 1992; Rattan 1996). The rate of protein synthesis is partially regulated by the activities of eIF family members. For instance, phosphorylation of eIF-2α at Ser51 reduces the rate of mRNA translation (Dever et al. 1993; Krishnamoorthy et al. 2001). Therefore, we compared the phosphorylation levels of eIF-2α in macrophages from young and middle-aged mice. In both the presence and absence of LPS, phosphorylation of eIF-2α at Ser51 in cells from middle-aged mice was higher than that in cells from young mice (Shirato and Imaizumi 2014). To evaluate the functional role of the inactive form of eIF-2α in LPS-stimulated inflammatory responses, we examined the effects of salubrinal, a selective inhibitor of eIF-2α phosphatase (Tsaytler et al. 2011; Hamamura et al. 2013; Tsaytler and Bertolotti 2013), on LPS-stimulated TNF-α production and

intracellular signal transduction in RAW264.7 cells. After RAW264.7 cells were treated with 10 μM salubrinal for 6 h, eIF-2α phosphorylation increased approximately 2-fold in either the absence or presence of LPS (Shirato and Imaizumi 2014). The treatment of RAW264.7 cells with salubrinal significantly suppressed the LPS-stimulated release of TNF-α without affecting the abundance of TNF-α mRNA (Shirato and Imaizumi 2014). Moreover, LPS-stimulated phosphorylation of p54 JNK was similarly increased in response to LPS stimulation regardless of the presence of salubrinal (Shirato and Imaizumi 2014). These results suggest a possible role for increased eIF-2α phosphorylation in the age-related attenuation of macrophage inflammatory responses.

Moreover, macrophages from middle-aged mice contained more PKR than those from young mice in the absence of LPS (Shirato and Imaizumi 2014), and the levels of PKR phosphorylation in macrophages from both groups of mice were consistent with the levels of PKR (Shirato and Imaizumi 2014). Therefore, the overall level of phosphorylated PKR was higher in macrophages from middle-aged mice than in macrophages from young mice. These findings are qualitatively consistent with a previous report of age-related up-regulation of PKR expression and eIF-2α phosphorylation in a variety of tissues, which suggested that these changes might be adaptive responses to age-related cellular stresses, including oxidative stress (Ladiges et al. 2000). Indeed, activation of the *PKR* promoter by H_2O_2 treatment was demonstrated in Jurkat T-lymphocytes (Pyo et al. 2008). Future studies might clarify the effects of oxidative stress on the PKR/eIF-2α pathway, and determine whether antioxidants can improve age-related activation of this pathway and the associated attenuation of macrophage inflammatory responses. In addition, in the absence of LPS, macrophages from middle-aged mice also contained more protein kinase RNA-like endoplasmic reticulum kinase (PERK; the other eIF-2α kinase) than those from young mice (Shirato and Imaizumi 2014). Furthermore, total PERK protein showed a similar tendency to increase compared to PKR, suggesting that the increased eIF-2α phosphorylation during aging may be mediated by functional modulation of the endoplasmic reticulum.

In contrast, there were no significant differences in the mRNA expression of activating transcription factor 4 (ATF4), one of the transcriptional target genes of eIF-2α, in macrophages from young and middle-aged mice (Shirato and Imaizumi 2014). According to the pharmacological experiment, the expression level of ATF4 mRNA increased approximately 1.1-fold in RAW264.7 cells and eIF-2α phosphorylation increased 2.0-fold following treatment with 10 μM salubrinal for 6 h (Shirato and Imaizumi 2014). These results indicate that the magnitude of the increase in eIF-2α phosphorylation observed in middle-aged mice is moderate and does not reach the minimum threshold of transcriptional activation. Moreover, the suppressive effect of salubrinal on LPS-stimulated TNF-α secretion is lesser than that observed in macrophages from middle-aged mice. Therefore, future studies should involve an assessment of whether the expression of other eIF subunits and/or other regulatory systems responsible for mRNA translation, such as the mammalian target of rapamycin (mTOR) pathway, are also impaired during aging.

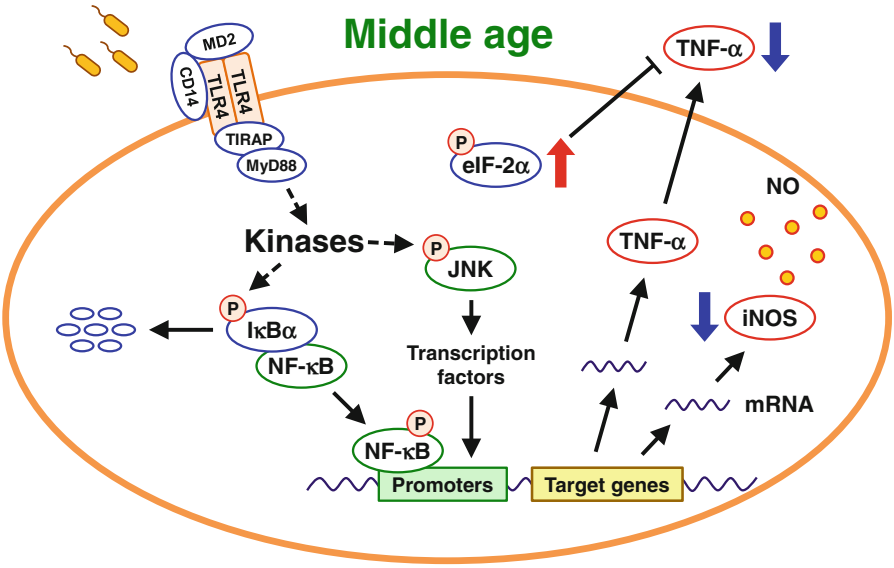

Fig. 16.4 Overview of the major findings of this research. In peritoneal macrophages from middle-aged mice, LPS-stimulated production of inflammatory mediators such as TNF-α and iNOS was suppressed at the protein level but not at the mRNA level. Moreover, the cells showed normal activation of JNK and NF-κB signaling in response to LPS stimulation. In contrast, phosphorylation of eIF-2α was enhanced in these cells. According to our pharmacological experiment using salubrinal, increased phosphorylation of eIF-2α might contribute to the age-related attenuation of macrophage inflammatory responses

16.4 Conclusion

Macrophage inflammatory responses against LPS are suppressed at the post-transcriptional level in middle-aged mice. Age-related attenuation of macrophage inflammatory responses may involve increased phosphorylation of eIF-2α. An overview of the findings of this research is shown in Fig. 16.4.

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Chapter 17
Effects of β_2-Agonist Administration on Bacterial Phagocytosis by Splenic Macrophages in Mice

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Abstract We examined the effects of 6-week daily administration of an anabolic dose of a β_2-agonist clenbuterol (1.0 mg/kg body weight/day) on the phagocytic capacity of splenic macrophages of 5-week-old male C57BL/6 J mice against *Escherichia coli*. After 24 h of cessation of clenbuterol or vehicle administration, splenic adherent cells were isolated and analyzed by flow-cytometry. The cells were separated into three subpopulations based on their size. The isolated cells included small cells, which expressed markedly higher levels of macrophage receptor with collagenous structure. Furthermore, these cells exhibited higher phagocytic capacity

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_17

against *E. coli* when compared to other subpopulations. The phagocytic capacity of the small cells was clearly suppressed after clenbuterol administration. These results suggest that chronic utilization of clenbuterol as a doping drug impairs bacterial clearance mediated by highly phagocytic splenic macrophages.

Keywords β_2-agonist • Clenbuterol • Phagocytosis • Macrophage receptor with collagenous structure • Splenic macrophages

17.1 Introduction

Clenbuterol [4-amino-α(t-butyl-amino)methyl-3,5-dichlorobenzyl alcohol], a β_2-agonist, is commonly used as a nonsteroidal anabolic agent for doping by athletes (Akama and Abe 2013). Indeed, the World Anti-Doping Agency reported that clenbuterol was the seventh most commonly used anabolic agent in 2009, accounting for 2 % of all doping cases (Sato et al. 2011). β-adrenergic receptors (β-ARs) are expressed on a variety of cells, including immune cells as well as skeletal muscle cells. Macrophages, a subtype of immune cells, are regulated by a negative feedback mechanism of the sympathetic nervous system involving the β-ARs (Boomershine et al. 1999; Sigola and Zinyama 2000). Of the β-ARs, the expression levels of β_2-AR in murine resident peritoneal macrophages were down-regulated after 4 weeks of treadmill training, which correlated to augmented inflammatory responses to lipopolysaccharide (Itoh et al. 2004; Kizaki et al. 2008, 2009). In addition, several in vitro studies have demonstrated that overactivation of the sympathetic nervous system reduces the phagocytic capacity of macrophages against bacteria (Gosain et al. 2007; Petty and Berg 1988; Roy and Rai 2004, 2008; Serio et al. 1996). In a previous study, our group reported that administration of an anabolic dose of clenbuterol induces redistribution of white blood cells in rats (Shirato et al. 2007). In addition, such systemic responses were observed after prolonged periods of physical inactivity; activation of the sympathetic nervous system may underlie such responses (Shirato et al. 2006). However, the mechanisms by which the host defense mechanisms are affected by chronic intake of clenbuterol as a doping drug are yet to be elucidated.

Macrophages are ubiquitously distributed in the body and differentiated into organ-specific cells with specialized cellular functions. One of the organs is the spleen, which contains a branched splenic artery (Kraal and Mebius 2006). The terminal arterioles from the central arteriole run through the white pulp of the lymphoid compartment, while most of the arterial blood ends in the marginal zone, located at an anatomical border between the white pulp and the more scavenging compartment of the red pulp (Kraal 1992; Kraal and Mebius 2006; Schmidt et al. 1993) (Fig. 17.1). Thus, blood-borne antigens that enter the spleen initially infiltrate into the marginal zone (Kraal and Mebius 2006). This site contains highly phagocytic marginal zone macrophages (Fig. 17.1), which constitutively express macrophage receptor with collagenous structure (MARCO), a class a macrophage scavenger receptor (Elomaa et al. 1995; Kraal and Mebius 2006; Kraal et al. 2000; McGaha et al. 2011). MARCO possesses affinity for both gram-negative and gram-positive bacteria (Elomaa et al. 1995),

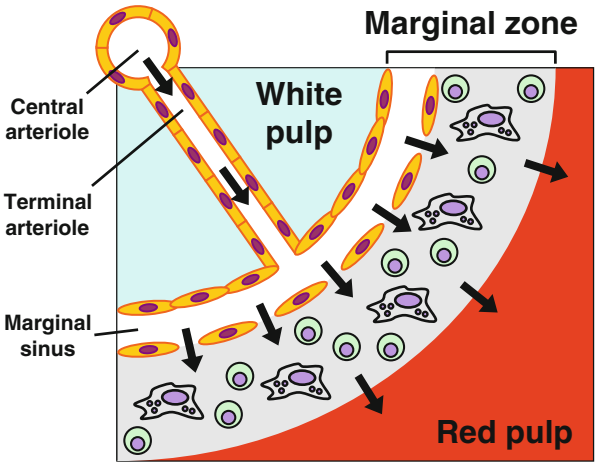

Fig. 17.1 Overview of splenic structure (Cyster 2000). The terminal arteriole originating from the central arteriole runs through the *white pulp*, while most of the arterial blood vessels end in the marginal zone located at an anatomical border between the *white pulp* and the *red pulp* (Kraal 1992; Kraal and Mebius 2006; Schmidt et al. 1993). Thus, blood-borne antigens that enter the spleen initially infiltrate into the marginal zone (Kraal and Mebius 2006). This site contains highly phagocytic marginal zone macrophages that express macrophage receptor with collagenous structure (MARCO)

and its constitutive expression contributes to efficient clearance of *Streptococcus pneumoniae* in the spleen (Aichele et al. 2003; Koppel et al. 2005; Lanoue et al. 2004; van der Laan et al. 1999). Therefore, we sought to provide detailed evidence of the side effects of chronic clenbuterol intake on the host defense system. Using flow-cytometry, we examined the effects of daily administration of an anabolic dose of clenbuterol (1.0 mg/kg body weight/day) for 6 weeks on bacterial phagocytosis by splenic macrophages in 5-week-old male C57BL/6 J mice.

17.2 Fractionation of Splenic Adherent Cells Based on Cell Size, Intracellular Complexity, MARCO Expression, and Bacterial Phagocytosis

The expression of MARCO is limited to macrophages located at the splenic marginal zone, the peritoneal cavity, and the medullary cord of lymph nodes under pathogen-free conditions (Elomaa et al. 1995; Ito et al. 1999). The marginal zone macrophages are a minor subset of splenic macrophages, which can interact with blood-borne antigens via MARCO (van der Laan et al. 1999). We first harvested splenic adherent cells to enrich splenic macrophages (Fig. 17.2), and subsequently fractionated the cells based on cell size and intracellular complexity using flow-cytometry (Fig. 17.3). Our data reveal the separation of splenic adherent cells into three subpopulations with varying cell sizes (Fig. 17.3). The proportion of the large cells, the medium-sized cells, and the small cells were approximately 60 %, 34 %,

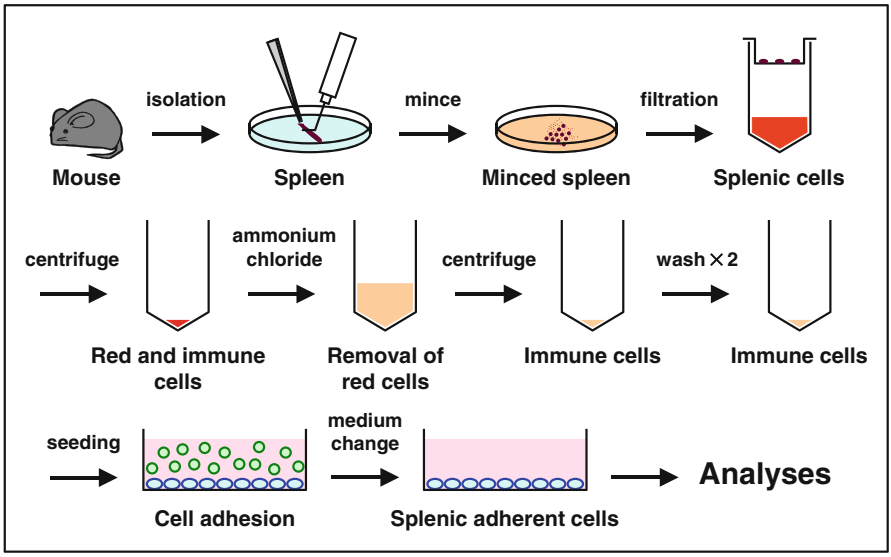

Fig. 17.2 Preparation of the splenic adherent cells (Shirato et al. 2013). After 24 h of cessation of clenbuterol or vehicle administration, the mice were anesthetized with isoflurane, and their spleens were immediately isolated. The spleens were minced with the help of a 22-gauge needle in phosphate-buffered saline (PBS; pH: 7.4) and filtered through a cell strainer (pore diameter: 70 μm). After centrifugation at 1,000 rpm for 3 min, red blood cells were lysed by incubating for 5 min with a hemolytic buffer containing 0.83 % NH_4Cl and 0.17 mol/L Tris–HCl (pH: 7.65) in the ratio 9:1 (v/v). After centrifugation, the cells were washed twice with PBS and resuspended with RPMI-1640 medium supplemented with 10 % heat inactivated fetal bovine serum, 100 units/mL penicillin, and 100 mg/mL streptomycin. Then, the cells were seeded into plastic culture dishes. After culturing the cells for 2 h in a CO_2 incubator containing 5 % CO_2, non-adherent cells were discarded, and the adherent cells, including the splenic macrophages, were washed three times with PBS and collected by scraping with a silicone rubber sheet. Thereafter, the splenic adherent cells were subjected to flow-cytometric analyses

and 6 %, respectively, of the total splenic adherent cells (Shirato et al. 2013). The fluorescence intensity of the large cells and the medium-sized cells stained with fluorescein isothiocyanate (FITC)-conjugated anti-MARCO antibody was almost identical to those cells stained with FITC-conjugated isotype control antibody (Fig. 17.4). The small cell fraction revealed high levels of cell surface MARCO (Fig. 17.4).

MARCO is a class A macrophage scavenger receptor that has affinity for gram-negative bacteria such as *E. coli* and gram-positive bacteria such as *Staphylococcus aureus* (Elomaa et al. 1995). In fact, it was revealed that MARCO expressed on the marginal zone macrophages contributes to the clearance of *S. pneumoniae* in the spleen (Aichele et al. 2003; Koppel et al. 2005; Lanoue et al. 2004; van der Laan et al. 1999). In addition, marginal zone macrophages display greater phagocytic capability than other subsets of splenic macrophages, including marginal metallophilic macrophages (Kraal 1992; Kraal and Janse 1986). With the help of flow-cytometry, we analyzed bacterial phagocytosis by the splenic adherent cells using

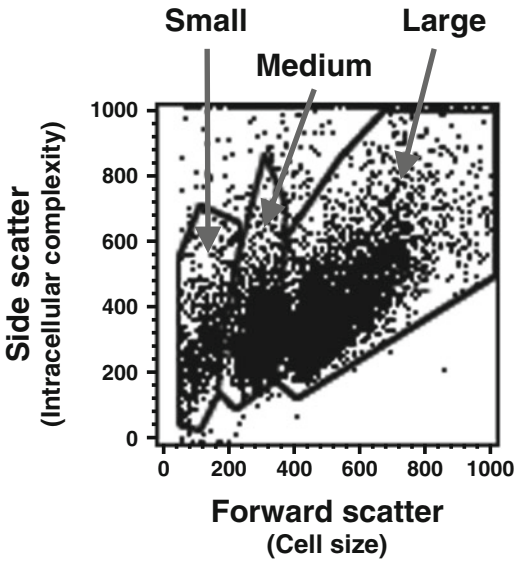

Fig. 17.3 Fractionation of the splenic adherent cells based on cell size and intracellular complexity (Shirato et al. 2013). Two-dimensional plots of splenic adherent cell forward light scatter (FSC) and side light scatter (SSC) are presented. The cells were separated into three subpopulations based on their size

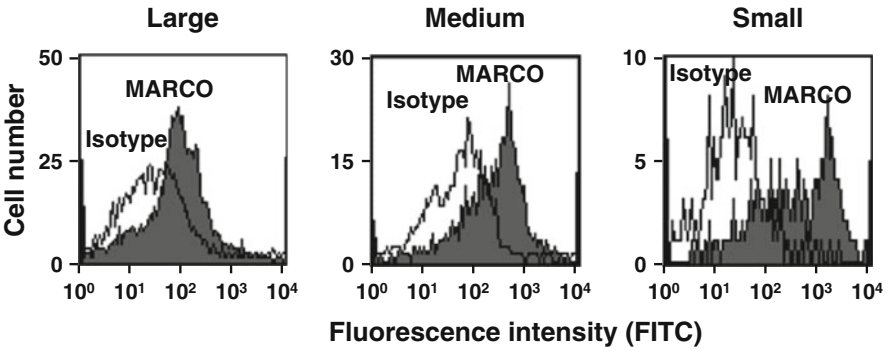

Fig. 17.4 Flow-cytometric analysis of the cell surface of the large cells, the medium-sized cells, and the small cells for macrophage receptor with collagenous structure (MARCO) expression (Shirato et al. 2013). The histograms of fluorescein isothiocyanate (FITC) fluorescence intensity of the large cells, the medium-sized cells, and the small cells stained with anti-MARCO antibody and the isotype control antibody are presented. One of the cellular fractions of the small cells showed high levels of cell surface MARCO. Open histogram: FITC-conjugated isotype control antibody-stained cells; closed histogram: FITC-conjugated anti-MARCO antibody-stained cells

E. coli transformed with green fluorescent protein (GFP) expression plasmid vector (Fig. 17.5). The GFP-positive cells were detected in the large cells, the medium-sized cells, and the small cells; however, the fluorescence intensity for the small splenic adherent cells was markedly higher than that seen in large cells and medium-sized cells (Fig. 17.5). This finding indicates that the small cells possess higher phagocytic activity. It is, therefore, possible that the small cells contain marginal zone macrophages.

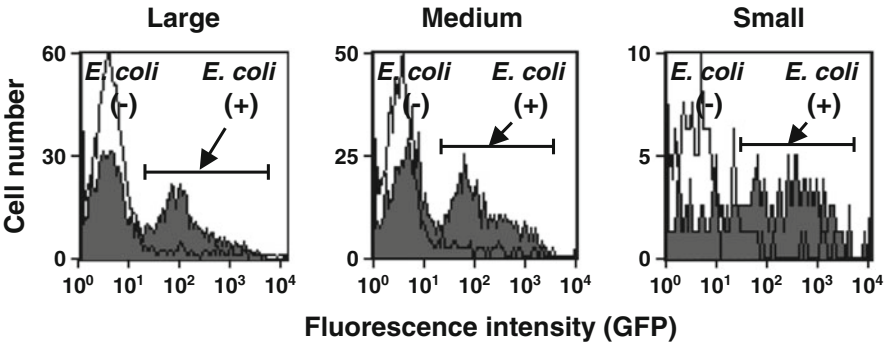

Fig. 17.5 Flow cytometric analysis of *Escherichia coli* phagocytosis by large, medium-sized, and small splenic adherent cells (Shirato et al. 2013). The histograms of green fluorescent protein (GFP) fluorescence intensity of *E. coli*-phagocytized cells and *E. coli*-free cells for each cell-size group are presented. The small cells showed higher proportion of phagocytic cells. Open histogram: the cells phagocytized with *E. coli* transformed with GFP expression plasmid vector; closed histogram: cells without *E. coli*

17.3 Effects of Chronic Clenbuterol Administration on Bacterial Phagocytosis and MARCO Expression of the Splenic Adherent Cell Subpopulations

Phagocytosis of aggregated γ-globulin by rat peritoneal macrophages vaccinated with Bacille de Calmette et Guérin (BCG) was reduced by treatment with metaproterenol, which is a moderately selective β_2-agonist (Abrass et al. 1985). In addition, phagocytic ability against *E. coli* was reduced when macrophages isolated from a murine cutaneous injury site were treated with physiologic and pharmacologic concentrations of noradrenalin; however, the phagocytic activity of splenic macrophages remained unaltered (Gosain et al. 2007). In contrast, several studies have demonstrated that the phagocytic activity of splenic macrophages is suppressed by sympathetic overactivation (Gosain et al. 2007; Roy and Rai 2004, 2008). However, the mechanisms by which adrenergic receptors modulate the phagocytic capacity of certain subsets of splenic macrophages are yet to be elucidated. Our flow-cytometric data show the phagocytic capacity of the small splenic adherent cells against *E. coli* to be significantly reduced by daily administration of an anabolic dose of clenbuterol for 6 weeks (Fig. 17.6); small splenic cells possess higher phagocytic activity and higher levels of MARCO. However, the phagocytic activity of other subpopulations remained unchanged (Fig. 17.6). These results suggest that the responses to chronic β_2-adrenergic stimulation are different among splenic macrophage subsets. It is also possible that the susceptibility to desensitization is different among these cells.

On the contrary, the expression levels of MARCO on the cell surface of splenic adherent cells were not affected by clenbuterol (Fig. 17.7). In addition, the mRNA expression levels of macrophage scavenger receptor 1, which is generally expressed

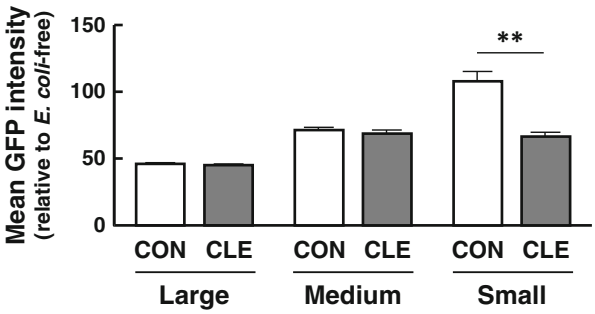

Fig. 17.6 Effects of clenbuterol administration on *Escherichia coli* phagocytosis by large, medium-sized, and small splenic adherent cells (Shirato et al. 2013). The mean green fluorescent protein (GFP) fluorescence intensity is the relative ratio of the anti-MARCO antibody-stained cells to the isotype control antibody-stained cells. The phagocytic capacity of the small splenic adherent cells against *E. coli* was significantly reduced after daily administration of an anabolic dose of clenbuterol for 6 weeks. Open bar: vehicle control (CON) group; closed bar: clenbuterol-administered (CLE) group. The values are shown as mean±standard error of the mean (n=9). $^{**}P<0.01$ (vs. CON; one-way analysis of variance)

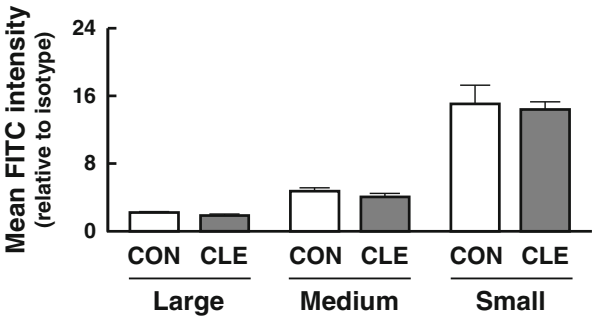

Fig. 17.7 Effects of clenbuterol administration on the cell surface MARCO expression of large, medium-sized, and small splenic adherent cells (Shirato et al. 2013). The mean green fluorescent protein (GFP) fluorescence intensity is the relative ratio of the *E. coli*-phagocytized cells to the *E. coli*-free cells. Cell surface MARCO expression of the splenic adherent cells was not affected by daily administration of an anabolic dose of clenbuterol for 6 weeks. Open bar: vehicle control (CON) group; closed bar: clenbuterol-administered (CLE) group. The values are shown as mean±standard error of the mean (n=9)

on macrophage lineage, remained unchanged (unpublished data). These results suggest that the reduction in phagocytic capacity of the small-cell subpopulation after chronic administration of clenbuterol is due to factors other than altered receptor-mediated phagocytosis. For instance, it was revealed that noradrenalin-induced suppression of macrophage phagocytosis is mediated by the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) signaling cascade involving α-adrenergic and β-adrenergic receptors (Gosain et al. 2007). In morphine-induced reduction of Fcγ receptor-mediated bacterial phagocytosis, inhibition of Ras-related

C3 botulinum toxin substrate 1 (Rac1)-guanosine triphosphatase (GTPase) activity triggered by elevation of the intracellular cAMP levels led to attenuation of actin polymerization and reduction in membrane ruffling (Ninković and Roy 2012). Another study found that a decrease in cell spreading and F-actin content through the activation of cAMP-PKA signaling plays a role in *Bacillus anthracis* edema; toxin-induced reduction in macrophage phagocytosis was found to underlie edema seen in infection due to *B. anthracis* (Yeager et al. 2009). Thus, it is possible that clenbuterol affects cellular membrane trafficking via the β_2-AR signaling cascade.

17.4 Acute *In Vitro* Effects of Clenbuterol Treatment on the Bacterial Phagocytic Activity of the Splenic Adherent Cell Subpopulations

Our in vitro experiment demonstrated that the direct treatment of the splenic adherent cells with β_2-agonists, such as clenbuterol and isoproterenol, results in decreased cell ratio of *E. coli*-phagocytized cells in the large-cell subpopulation (Fig. 17.8). In addition, the suppressive effect was observed in the medium-sized cells treated with clenbuterol; however, isoproterenol did not affect the number of *E. coli-phagocytized* cells (Fig. 17.8). Reduction in the phagocytic capacity of the small cells observed in the in vivo experiment was not seen in the in vitro study (data not shown). These results indicate that the reduction in the bacterial phagocytic capacity by daily administration of clenbuterol for 6 weeks is due to indirect effects of the β_2-adrenoceptor; nevertheless, it cannot be ruled out that the chronic in vivo and acute in vitro experimental conditions are fundamentally different.

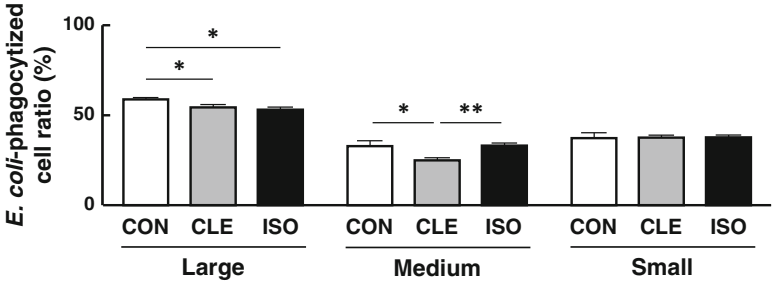

Fig. 17.8 ***In vitro*** **effects of clenbuterol and isoproterenol treatments on the cell ratios of *Escherichia coli*-phagocytized large, medium-sized, and small splenic adherent cells** (Shirato et al. 2013). The splenic adherent cells were treated with vehicle (control: CON), 100 μM clenbuterol (CLE), or 100 μM isoproterenol (ISO) for 3 h. The ratio of cells that show phagocytosis against *E. coli* for each subpopulation is presented as a percentage value. The values are shown as mean±standard error of the mean (n=7). *P<0.05 and **P< .01 (one-way analysis of variance)

17.5 Conclusion

Chronic administration of an anabolic dose of clenbuterol could impair bacterial phagocytic activity of highly phagocytic splenic macrophages expressing high levels of MARCO, and this may lead to a reduction in the clearance of blood-borne pathogens in the spleen. The experimental duration was >4 weeks; however, studies conducted for varying time durations, including acute studies, are necessary for the elucidation of β_2-agonist-mediated effects on the phagocytic activity of splenic macrophages.

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Chapter 18
Functional Roles of β_2-Adrenergic Receptors in Skeletal Muscle Hypertrophy and Atrophy

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Abstract We discuss the functional roles of β_2-adrenergic receptors in skeletal muscle hypertrophy and atrophy, as well as the adaptive responses of β_2-adrenergic receptor expression to anabolic and catabolic conditions. Stimulation of the β_2-adrenergic receptor using anabolic drugs increases muscle mass by promoting muscle protein synthesis and/or attenuating protein degradation. These effects are prevented by the downregulation of the receptor. Endurance training improves oxidative performance, partly by increasing β_2-adrenergic receptor density in exercise-recruited slow-twitch muscles. However, excessive stimulation of β_2-adrenergic receptors negates their beneficial effects. Although preventive effects of β_2-adrenergic receptor stimulation on atrophy induced by muscle disuse and catabolic

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_18

hormones or drugs were observed, these catabolic conditions decreased β_2-adrenergic receptor expression in slow-twitch muscles. These findings present evidence against the use of β_2-adrenergic agonists in therapy for muscle wasting and weakness. Thus, β_2-adrenergic receptors in the skeletal muscles play an important physiological role in the regulation of protein and energy balance.

Keywords β_2-adrenergic receptors • Skeletal muscles • β_2-agonists • Clenbuterol • Skeletal muscle atrophy • Hypertrophy • Sports doping

18.1 Introduction

Skeletal muscle is the most abundant tissue in the human body, constituting approximately 40 % of the total body weight. The mass and composition of skeletal muscle are critical for its function and can be regulated in response to several types of changes in physiological conditions. For example, resistance and weight training, and the use of β_2-agonists and anabolic steroids, increase muscle mass, fiber hypertrophy, and muscle strength (Ishii et al. 2012). In contrast, prolonged periods of skeletal muscle inactivity due to unloading, bed rest, denervation, immobilization, or microgravity can result in significant muscle atrophy (Teshima-Kondo and Nikawa 2013). It is well known that skeletal muscle protein is regulated by the balance between the rates of protein synthesis and degradation. Physical activity (exercise training) and anabolic hormones and drugs (sports doping) increase muscle protein content. However, sarcopenia and muscle disuse (due to unloading, microgravity, or inactivity) decrease muscle protein content. The rate of protein synthesis is at least in part mediated by β_2-adrenergic receptors (β_2-ARs) in skeletal muscles in both anabolic and catabolic conditions.

ARs belong to the guanine nucleotide-binding G protein-coupled receptor (GPCR) family. Skeletal muscle contains a significant proportion of β-ARs. The β_2 subtype is the most abundant, whereas 7–10 % of ARs are of the β_1 subtype in skeletal muscles (Kim et al. 1991). Furthermore, the distribution of β_2-AR is denser in slow-twitch muscles than in fast-twitch muscles (Ryall et al. 2006). However, the magnitude of anabolic responses to β_2-adrenergic agonists is greater in fast-twitch muscles than in slow-twitch muscles (Sato et al. 2008, 2010).

The family of β-ARs was originally thought to signal predominantly via coupling with a stimulatory guanine nucleotide-binding protein, $G\alpha_s$; however, recent studies revealed that both β_2- and β_3-ARs in skeletal muscle are also capable of coupling to an inhibitory guanine nucleotide-binding protein, $G\alpha_i$ (Gosmanov et al. 2002). β_2-AR activates the $G\alpha_s$/adenyl cyclase (AC)/cyclic adenosine monophosphate (cAMP)/cAMP-dependent protein kinase A (PKA) signaling pathway. The signaling pathway is, at least in part, responsible for the anabolic response of skeletal muscle to β_2-AR stimulation. Further, in addition to the well-documented inhibition of AC activity (Abramson et al. 1988), β_2-AR coupling to $G\alpha_i$ activates $G\alpha_s$-independent pathways (Communal et al. 2000).

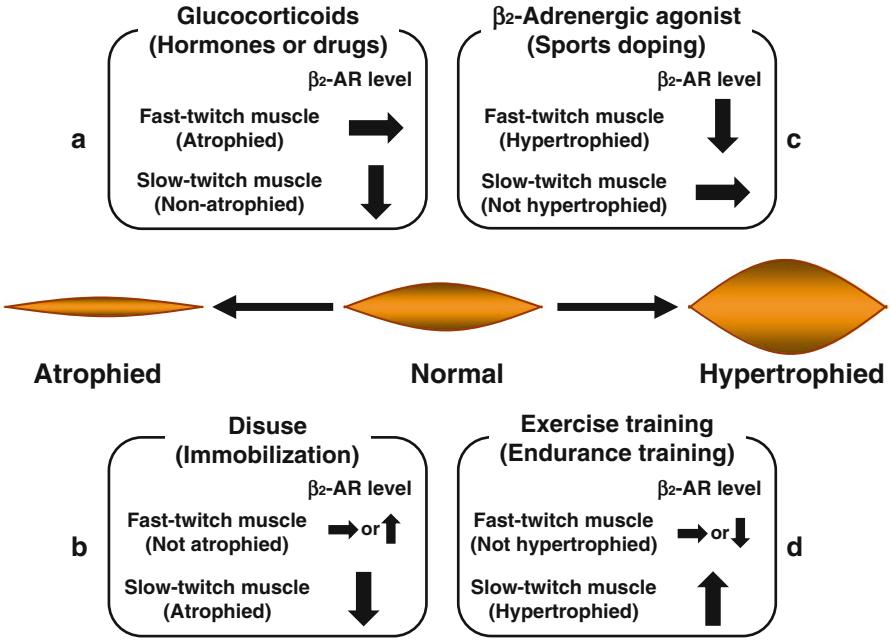

Fig. 18.1 Changes in β_2-AR expression in hypertrophied and atrophied skeletal muscles (Sato et al. 2011a). (**a**) Catabolic hormones or drugs such as glucocorticoids downregulate β_2-AR expression in non-atrophied slow-twitch muscles but not in fast-twitch muscles. (**b**) Muscle disuse downregulates β_2-AR expression in atrophied slow-twitch muscle, whereas no changes or upregulation of receptor expression are observed in fast-twitch muscles. (**c**) β_2-AR stimulation using anabolic drugs downregulates β_2-AR expression in hypertrophied fast-twitch muscles but not in slow-twitch muscles. (**d**) Exercise training such as endurance training upregulates β_2-AR expression in exercise-recruited slow-twitch muscles, whereas no changes or downregulation are observed in fast-twitch muscles, although muscle mass is not altered. However, although exercise training such as isometric strength training induces muscle hypertrophy, there is no information regarding the effects of such exercise on β_2-AR expression. The differential effects of types of exercise training on physiological responses such as β_2-AR expression and muscle hypertrophy should be clarified in more detail and are currently being investigated by our group. Upward arrow (*open arrow*): upregulation of β_2-AR expression; downward arrow (*filled arrow*): downregulation of β_2-AR expression; lateral arrow (*shaded arrow*): no change

β_2-AR is composed of seven transmembrane α-helices forming three extracellular loops, including an NH_2 terminus, and three intracellular loops that include a COOH terminus (Johnson 2006). β_2-AR contains phosphorylation sites in the third intracellular loop and proximal cytoplasmic tail. The phosphorylation of these sites triggers the agonist-promoted desensitization, internalization, and degradation of the receptor (Krupnich and Benovic 1998). These regulatory mechanisms contribute to maintaining agonist-induced β_2-AR responsiveness under various conditions.

The adaptive responses of β_2-AR expression to anabolic and catabolic conditions in skeletal muscles are summarized in Fig. 18.1. Understanding the correlation between changes in muscle mass and β_2-AR expression in several anabolic or

catabolic conditions provides scientific evidence to eradicate sports doping and will identify novel approaches for attenuating muscle atrophy concomitant with disuse and various diseases. This chapter describes the effects of (1) pharmacological β_2-AR stimulation (sports doping), (2) muscle hypertrophy (exercise training), and (3) muscle atrophy (catabolic conditions and hormones) on β_2-AR expression in skeletal muscles.

18.2 Pharmacological Stimulation of β_2-AR

18.2.1 Muscle Hypertrophy and β_2-AR

In modern sports, many types of doping drugs have been used by athletes to improve athletic performance, despite the many negative reactions and side effects of these drugs (Clarkson and Thompson 1997). β_2-adrenergic agonists, such as clenbuterol, salbutamol, and fenoterol (Fig. 18.2), increase muscle mass and power (Akama and Abe 2013). Notably, a β_2-adrenergic agonist, clenbuterol [1-(4-amino-3,5-dichlorobenzyl)-2-(tert-butylamino) ethanol], is more frequently used as a non-steroidal anabolic drug for sports doping (Sato et al. 2008, 2010). According to recent World Anti-Doping Agency (WADA) documents, clenbuterol was the seventh most commonly used anabolic agent in 2009 (67 cases; 2.0 % of all anabolic agents discovered).

Numerous studies have shown that the administration of β_2-adrenergic agonists induces muscle hypertrophy in many species (Lynch and Ryall 2008). Experiments using mice lacking β_1-AR, β_2-AR, or both demonstrate that β_2-adrenergic agonist-induced functions such as muscle hypertrophy are mediated by β_2-AR (Hinkle et al. 2002). β_2-Adrenergic agonists promote muscle growth by increasing the rate of protein synthesis and/or decreasing protein degradation (Lynch and Ryall 2008). Furthermore, β_2-adrenergic agonists induce the slow-to-fast (myosin heavy chain [MHC]I/$\beta \rightarrow$ MHCIIa $\rightarrow$ MHCIId/x $\rightarrow$ MHCIIb) transformation of muscle fibers.

The β_2-AR signaling pathway involves the agonist-dependent activation of $G\alpha_s$, which in turn activates AC, resulting in increased cAMP production (Fig. 18.3). The transcription of many target genes is initiated by cAMP-activated PKA via the phosphorylation of cAMP response element (CRE) binding protein (CREB) or adaptor proteins such as the CREB-binding protein (CBP) and p300, subsequently promoting protein synthesis (Lynch and Ryall 2008). While β_2-AR-mediated signaling was traditionally believed to involve selective coupling to $G\alpha_s$, recent studies revealed that β_2-AR exhibits dual coupling to both $G\alpha_s$ and $G\alpha_i$ in skeletal muscles (Lynch and Ryall 2008). In addition to $G\alpha_s$, $G\alpha_i$-linked $G\alpha_i$ subunits play an active role in various cell signaling processes such as the phosphoinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR)/p70S6K, PI3K/Akt/forkhead box-O (FOXO), and mitogen-activated protein kinase (MAPK) pathways. These signaling pathways play important roles in β_2-adrenergic agonist-induced hypertrophy in skeletal muscles (Lynch and Ryall 2008).

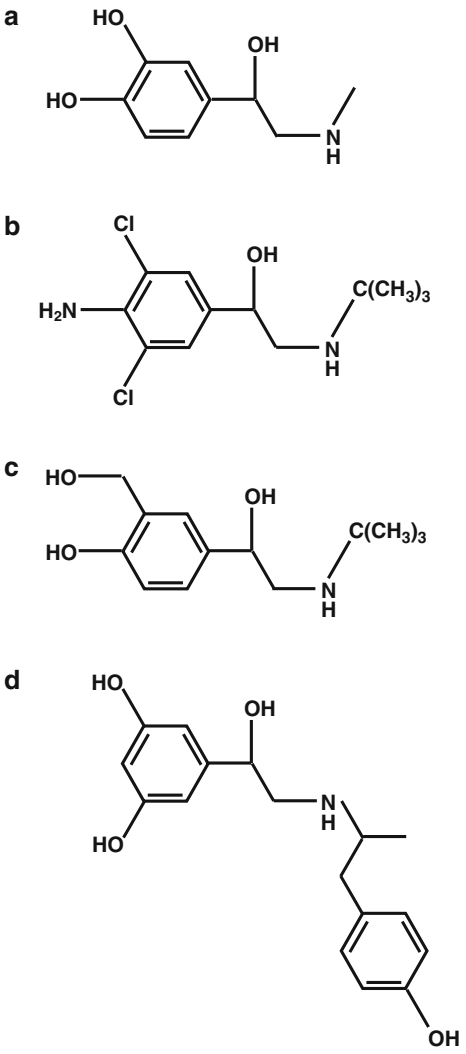

Fig. 18.2 Chemical structure of adrenaline and common synthetic β_2-agonists (Sato et al. 2012). (**a**) Adrenaline, 4-{1-hydroxy-2-(methylamino) ethyl} benzene-1, 2-diol. (**b**) Clenbuterol, 1-(4-amino-3, 5-dichlorobenzyl)-2-(tert-butylamino) ethanol. (**c**) Salbutamol, 4-{2-(tert-butylamino)-1-hydroxyethyl}-2-(hydroxymethyl) phenol. (**d**) Fenoterol, 5-(1-hydroxy-2-[{2-(4-hydroxyphenyl)-1-methylethyl}amino]ethyl) benzene-1, 3-diol

In addition to promoting protein synthesis, the hypertrophic response of skeletal muscles following β_2-adrenergic agonist administration is associated with decreased protein degradation. β_2-adrenergic agonists attenuate protein degradation predominantly via Ca^{2+}-dependent proteolysis and the ATP/ubiquitin-dependent pathway (Kline et al. 2007). However, little is known regarding the preventive effects of β_2-adrenergic agonists on the proteolysis system compared with the protein synthesis system.

Hypertrophic responses to β_2-adrenergic agonists are observed more frequently in fast-twitch muscle than in slow-twitch muscle. Our group previously showed that clenbuterol administration (1.0 $mg \cdot kg^{-1} \cdot day^{-1}$) to rats for 10 days increases the

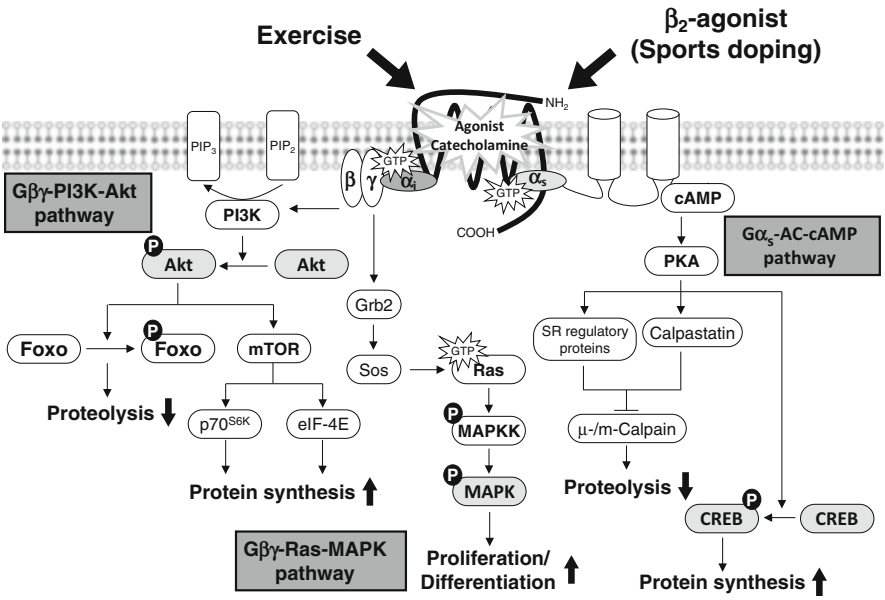

Fig. 18.3 The β_2-adrenergic receptor (β_2-AR) signaling pathway is involved in anabolic and metabolic adaptations to β_2-agonist treatment and exercise in skeletal muscles (Sato et al. 2012). The β_2-AR signaling pathway involves the agonist- or catecholamine-dependent activation of $G\alpha_s$, which in turn activates Adenyl Cyclase (AC), resulting in increased cyclic adenosine monophosphate (cAMP) production. Cyclic AMP-activated protein kinase A (PKA) initiates the transcription of many target genes via the phosphorylation of cAMP response element (CRE)-binding protein (CREB) or the adaptor proteins, which subsequently promote protein synthesis. The $G\alpha_s$-AC-cAMP pathway can also attenuate protein degradation via a Ca^{2+}-dependent pathway. In addition to $G\alpha_s$, the receptor-coupled $G\alpha_i$ dissociates from the heterodimeric $G\beta\gamma$, with the free $G\gamma\beta$ subunits mediating the activation of the mitogen-activated protein kinase (MAPK) and/or phosphoinositol 3-kinase (PI3K)-Akt/protein kinase B (PKB) pathways. Phosphorylation of Akt is known to have numerous downstream effects. The phosphorylation and subsequent nuclear exclusion of forkhead transcription factor (Foxo) prevents the transcription of atrophic genes such as MAFbx, MuRF, and genes involved in the inhibition of protein synthesis, such as eukaryotic initiation factor (eIF) 4-binding protein 1 (4EBP-1). Activation of mammalian target of rapamycin (mTOR) increases protein synthesis via the phosphorylation and activation of $p70^{S6K}$, the phosphorylation of 4EBP-1, and the subsequent activation of eIF-4E. Phosphorylation of MAPK activates cell proliferation and differentiation via the direct stimulation of downstream transcription factors such as myocyte enhancer factor 2 (MEF2) and activating transcription factor 2 (ATF2), which initiate the transcription of various genes, such as peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α)

mass of fast-twitch (extensor digitorum longus: EDL) muscle without altering slow-twitch (soleus) muscle (Sato et al. 2008, 2010); other groups also observed the same tendency (Kitaura et al. 2001; Stevens et al. 2000). However, the mechanisms of the fiber type-dependent effects of β_2-adrenergic agonists on muscle hypertrophy remain unclear.

Recent reports showed that β_2-AR activation increases the expression of the orphan nuclear receptor, NOR-1 (NR4A3), a negative regulatory factor of myostatin (a member of the transforming growth factor-β superfamily and a potent negative regulator of muscle mass), in fast-twitch muscles without altering that in slow-twitch muscles (Kawasaki et al. 2011; Pearen et al. 2008). Furthermore, Shi et al. (2007) showed that β_2-adrenergic agonist-induced fiber type-dependent hypertrophy might in part be due to MAPK pathways, including those of extracellular signal-regulated kinase (ERK) and p38 MAPK. Moreover, pharmacological inhibition of the PI3K/Akt/mTOR signaling pathway revealed that the attenuation of the anabolic response to clenbuterol is greater in fast-twitch muscles than in slow-twitch muscles (Kline et al. 2007). In addition to the protein synthesis system, Yimlamai et al. (2005) found that clenbuterol inhibits ubiquitination more strongly in fast-twitch muscles than in slow-twitch muscles. Thus, β_2-AR-mediated signaling pathways tend to promote muscle hypertrophy to a greater extent in fast-twitch muscle than in slow-twitch muscle.

18.2.2 Post-translational Regulation of β_2-AR

As shown in Table 18.1, some reports focus on the responses of β_2-AR expression to β_2-AR stimulation in skeletal muscles (Beitzel et al. 2007; Ryall et al. 2006; Sato et al. 2008, 2010). This is because β_2-AR functions such as muscle hypertrophy are maintained via the regulation of receptor density, by synthesis and downregulation, as well as receptor sensitivity, by receptor sensitization, desensitization, phosphorylation, and internalization (Krupnich and Benovic 1998; Pierce et al. 2002).

Desensitization of β_2-AR is associated with receptor phosphorylation. McCormick et al. (2010) showed that fast-twitch fibers mainly express non-phosphorylated β_2-AR, whereas slow-twitch fibers predominantly express phosphorylated β_2-AR. Furthermore, treating muscle fibers with β_2-adrenergic agonists (e.g., clenbuterol, formoterol, and salbutamol) increases the phosphorylation of β_2-AR in slow-twitch fibers but not in fast-twitch fibers (McCormick et al. 2010). However, receptor phosphorylation occurs via the actions of protein kinases (such as PKA) and/or GPCR kinase (GRK). Rat skeletal muscles contain predominantly GRK2 and GRK5; GRK is expressed to a greater extent in fast-twitch muscles than in slow-twitch muscles. These expression levels in each type of muscle fiber are not altered by β_2-adrenergic agonist administration (Jones et al. 2003). Thus, there is a negative correlation between the level of phosphorylated β_2-AR and that of receptor kinase. Therefore, further investigation is needed to reveal the detailed mechanism of β_2-AR phosphorylation.

Following β_2-AR phosphorylation, the receptor is internalized into the cytosol. The internalized β_2-AR is then degraded or dephosphorylated and subsequently recycled to the membrane (Krupnich and Benovic 1998; DeWire et al. 2007). Prolonged administration of β_2-adrenergic agonists leads to the downregulation of β_2-AR density in skeletal muscles (Huang et al. 2000). Such post-translational regulation is advantageous for maintaining the rate of muscle protein synthesis and/or degradation.

Table 18.1 Responses of β2-AR expression in skeletal muscles to anabolic and catabolic conditions (Sato et al. 2011a)

Conditions	Species	β_2-AR expression levels		Other findings	References
		Protein	mRNA		
β_2-AR stimulation					
Fenoterol (1.4 mg kg^{-1} day^{-1}, 4 weeks)	Rat	Increased (FT)	n.d.		Ryall et al. (2006)
		Not changed (ST)			
Clenbuterol (1.0 mg kg^{-1} day^{-1}, 10 days)	Rat	n.d.	Increased (FT)	Decreased β_1-AR mRNA level (LV)	Sato et al. (2008)
			Not changed (ST)	Decreased β_2-AR mRNA level (LV)	
Clenbuterol (1.0 mg kg^{-1} day^{-1}, 10 days)	Rat	n.d.	Decreased (FT)	Decreased GR mRNA level (FT)	Sato et al. (2010)
			Not changed (ST)	Decreased HuR mRNA level (FT)	
				Decreased AUF1 mRNA level (FT)	
				Decreased hnRNP A1 mRNA level (FT)	
Fenoterol (1.4 mg kg^{-1} day^{-1}, 2–7 days)	Rat	Not changed (FT, ST)	Decreased (FT, ST)	Remained $G\alpha_s$ content (FT, ST)	Beitzel et al. (2007)
				Remained AC activity (FT, ST)	
Clenbuterol (2.0 mg kg^{-1} day^{-1}, 18 days)	Rat	Decreased (FT+ST)	n.d.		Rothwell et al. (1987)

Clenbuterol (4.0 mg kg^{-1} of feed, 10 days)	Rat	Decreased (FT)	n.d.	Remained β_2-AR affinity (FT)	Huang et al. (2000)
Clenbuterol (0.2 mg kg^{-1} day^{-1}, 7 days)	Rat	Decreased (FT+ST)	n.d.		Sillence et al. (1991)
Clenbuterol (50 mM)	Mouse (ex vivo)	Phosphorylated	n.d.	Increased cAMP concentration (FT, ST)	McCormick et al. (2010)
Formoterol (100 mM)		Increased (ST)			
Salbutamol (500 mM)		Not changed (FT)			
Endurance training					
Treadmill (12 weeks)	Rat	Decreased (FT)	n.d.	Remained β_2-AR affinity	Nieto et al. (1997)
				Decreased AC activity	
				Decreased $G\alpha_s$ content	
Treadmill (18 weeks)	Rat	Not changed (FT)	n.d.	Increased AC activity (FT, ST)	Buckenmeyer et al. (1990)
		Increased (ST)		Remained β_2-AR density (acute)	
Catabolic conditions					
Dexamethasone (1.0 mg kg^{-1} day^{-1}, 10 days)	Rat	Not changed (FT, ST)	Not changed (FT)	Decreased GR mRNA level (FT, ST)	Sato et al. (2011b)
			Decreased (ST)	Decreased CREB mRNA level (ST)	
				Increased AUF1 mRNA level (FT)	

(continued)

Table 18.1 (continued)

Conditions	Species	β_2-AR expression levels		Other findings	References
		Protein	mRNA		
Dexamethasone (1.0 mg kg^{-1} day^{-1}, 10 days)	Rat	n.d.	Not changed (FT)	Decreased GR mRNA level (FT, ST)	Kawano et al. (2009)
			Decreased (ST)	Increased β_1-AR mRNA level (LV)	
Dexamethasone (0.2 mg kg^{-1} day^{-1}, 10 days)	Rat	Not changed (FT)	n.d.	Remained β_2-AR affinity (FT)	Huang et al. (2000)
Casted-immobilization (10 days)	Rat	Not changed (FT, ST)	Not changed (FT)	Decreased GR mRNA level (ST)	Sato et al. (2011c)
			Decreased (ST)	Decreased GR protein level (ST)	
Aging	Rat	Not changed (FT, ST)	n.d.		Ryall et al. (2006)
Injury (bupivacaine injection)	Rat	Increased (FT)	Increased (FT)	Increased $G\alpha_s$ contents (FT)	Beitzel et al. (2007)
				Decreased $G\alpha_s$ content (ST)	
		Decreased (ST)	Decreased (ST)	Increased AC activity (FT, ST)	

FT fast-twitch muscle, *ST* slow-twitch muscle, *LV* left ventricle muscle, *n.d.* indicates no data

18.2.3 Short-Term and Chronic Transcriptional Regulation of β_2-AR

β_2-AR synthesis, including transcription and the subsequent translation, is required to restore transmembrane receptor density. The process of β_2-AR synthesis can be separated into two pathways: (1) positive autoregulation of β_2-AR gene transcription via receptor-mediated elevation of cAMP concentration followed by the phosphorylation and activation of CREB and (2) transactivation of the β_2-AR gene via interactions between hormones and the nuclear receptor complex and response elements on the β_2-AR promoter region (Collins et al. 1990; Cornett et al. 1998). In particular, transcription of the β_2-AR gene and its subsequent mRNA expression via cAMP-mediated CRE activation increased in response to short-term β_2-adrenergic agonist exposure (Collins et al. 1990; Cornett et al. 1998). Moreover, treatment with glucocorticoids or thyroid hormone transactivates the β_2-AR gene both in vitro and in vivo (Bengstsson et al. 2000).

Our previous reports show that clenbuterol administration (1.0 mg kg^{-1} day^{-1}) for 10 days in rats decreases β_2-AR mRNA expression in the fast-twitch EDL muscle without altering that in the slow-twitch soleus muscle (Sato et al. 2008, 2010). Furthermore, the mRNA expression of glucocorticoid receptors (GRs) also decreases with clenbuterol treatment in the EDL muscle but not in the soleus muscle (Sato et al. 2010). Glucocorticoids and the GR complex activate the transcription of the β_2-AR gene via their interaction with glucocorticoid response elements (GREs) and consensus *cis*-acting DNA sequences (i.e., AGA ACA nnn TGT TCT) in the promoter region of the β_2-AR gene (Cornett et al. 1998), thus upregulating β_2-AR expression (Huang et al. 2000; Hadcock and Malbon 1998). These findings corroborate our results that there is a positive correlation between the expression levels of β_2-AR and GR in skeletal muscles. Beitzel et al. (2007) also report that administration of the β-adrenergic agonist, fenoterol (1.4 mg kg^{-1} day^{-1}, *i.p.*), for 5 days decreases β_2-AR mRNA expression in the EDL and soleus muscles. Thus, in contrast to the transactivation of the β_2-AR gene and the increase in the mRNA level in response to short-term agonist exposure, chronic β_2-adrenergic stimulation inhibits β_2-AR synthesis in skeletal muscles.

18.2.4 Post-transcriptional Regulation of β_2-AR

In addition to post-translational and transcriptional regulation, several groups focus on the post-transcriptional regulation of β_2-AR mRNA. β_2-AR mRNA contains an AU-rich element (ARE) within the 3′-untranslated region (3′-UTR) that can be recognized by several mRNA-binding proteins, including Hu antigen R (HuR), AU-rich element binding/degradation factor1 (AUF1), and heterogeneous nuclear ribonucleoprotein A1 (hnRNP A1) (Blaxall et al. 2000). These factors play a role in the

regulation of β_2-AR mRNA stability (Blaxall et al. 2000). Our study demonstrates that clenbuterol-induced stimulation of β_2-AR decreases the mRNA expression levels of these factors in the EDL but not in the soleus muscle (Sato et al, 2010), suggesting that the post-transcriptional process of β_2-AR synthesis requires the regulation of mRNA stability.

18.3 Exercise Training and β_2-AR

Strength resistance training increases muscle mass, fiber cross-sectional area, protein and RNA content, and the capacity to generate force (Baar and Esser 1999). In contrast to strength training, endurance training is characterized by increased mitochondrial mass, increased oxidative enzymes, decreased glycolytic enzymes, increased slow contractile and regulatory proteins, and decreased fast-fiber area (Pette and Heilmann 1997). These findings suggest that the functional roles of β_2-AR in skeletal muscles differ with the type of exercise training.

18.3.1 Strength Exercise Training and β_2-AR

Mounier et al. (2007) investigated changes in the weight of the EDL muscle induced by clenbuterol administration, strength training, and a combination of both. They found that the effects of strength training and clenbuterol on muscle hypertrophy were not additive in fast-twitch muscles. Their report also demonstrates that the strength training-induced enhancement of lactate dehydrogenase-specific activity is completely inhibited by clenbuterol administration, while the clenbuterol-induced decrease in monocarboxylate transporter1 mRNA expression is completely offset by strength training (Mounier et al. 2007). Thus, no synergistic effects are seen on muscle mass with a combination of strength training and β_2-AR stimulation. Furthermore, strength training counteracts molecular modifications such as glycolytic control induced by chronic clenbuterol administration in fast-twitch muscles to some extent. However, our evidence regarding the synergistic effects of strength training and β_2-AR stimulation is insufficient because experimental models of strength-trained animals are not fully established.

18.3.2 Endurance Exercise Training and β_2-AR

In contrast to strength training, β_2-AR stimulation affects endurance training-induced modulations such as contractile activity, muscle fiber type shift, metabolic enzyme activity, and insulin resistance. Lynch et al. (1996) showed that

low-intensity endurance training prevents clenbuterol-induced slow-to-fast (type I fiber → type II fiber) fiber type transformation in the EDL and soleus muscles, and thereby offsets the clenbuterol-induced decrease in Ca^{2+} sensitivity in fast-twitch fibers. These results suggest that endurance training-heightened muscle aerobic capacity is attenuated by β_2-AR stimulation-induced muscle fiber type transformations. Furthermore, pharmacological β-AR blockage diminishes the endurance training-induced increase in citrate synthase activity in the fast-twitch plantaris muscle (Powers et al. 1995). Moreover, clenbuterol administration prevents endurance training-induced improvement in insulin-stimulated glucose uptake and attenuates the increase in citrate synthase activity in the skeletal muscles of obese Zucker rats (Torgan et al. 1993). These findings demonstrate that the endurance training-induced increase in aerobic metabolism in skeletal muscles requires the moderate but not excessive stimulation of β_2-AR.

Recently, Miura et al. (2007) showed that an increase in peroxisome proliferator-activated receptor-γ coactivatior-1α (PGC-1α) mRNA in response to exercise is mediated by β_2-AR activation. Furthermore, the Ca^{2+}-signaling and p38 MAPK pathways, which are downstream of β_2-AR, are activated in skeletal muscles in response to exercise, which regulates PGC-1α expression. Since PGC-1α promotes mitochondrial biogenesis, the exercise-induced activation of β_2-AR may in part enhance aerobic capacity by increasing PGC-1α expression (Akimoto et al. 2005; Handschin et al. 2003). Thus, β_2-AR stimulation is essential for enhancing the effects of exercise training, such as fiber type shift as well as oxidative and anaerobic metabolism, on muscle functions.

18.3.3 Response of β_2-AR Expression to Exercise Training

As described above, the functional roles of β_2-AR during exercise training are physiologically important in skeletal muscles. Therefore, changes in the expression and sensitivity of β_2-AR should be important for the metabolic, anabolic, and catabolic adaptations of skeletal muscles during exercise training. Nevertheless, little information exists regarding the response of β_2-AR expression to exercise training in skeletal muscles. However, many studies have demonstrated the effects of exercise training on β_2-AR expression in several tissues and cell types such as myocardia, adipocytes, and macrophages (Barbier et al. 2004; Stones et al. 2008; Ogasawara et al. 2006; Kizaki et al. 2008). Barbier et al. (2004) demonstrated that exercise training induces changes in the distribution of β_1-, β_2-, and β_3-AR densities in the rat left ventricle. In adipocytes, the exercise-induced trafficking of β_2-AR into the cell membrane from the cytosol is coupled to adipocyte function to increase intracellular cAMP production (Ogasawara et al. 2006). Kizaki et al. (2008) also found a reduction in the expression of β_2-AR mRNA in macrophages and highlighted the significance of β_2-AR in the exercise training-induced improvement of the innate immune

function of macrophages. Thus, changes in β_2-AR expression play a role in physiological adaptations to exercise training in several tissues.

A few studies also report the effects of exercise training on β-AR in skeletal muscles (Sato et al. 2011a) (Table 18.1). Nieto et al. (1997) demonstrate that β-AR density and $G\alpha_s$ content in the fast-twitch gastrocnemius muscle are significantly lower in endurance-exercised rats than in controls. They also reveal that exercise reduces muscle AC activity, both receptor- and non-receptor-mediated (i.e., pharmacological stimulation of AC by forskolin). However, Buckenmeyer et al. (1990) reported that endurance training increases β-AR density in slow-twitch muscles that are primarily recruited during endurance training, whereas β-AR density is not altered in fast-twitch muscles. Their report also demonstrates that receptor-mediated AC activity in slow-twitch muscles is increased by endurance training, and non-receptor-mediated AC activity is increased by training in both fast- and slow-twitch muscles. In contrast to chronic endurance training, no effects of acute exercise on β-AR density and AC activity were observed in either type of muscle. Therefore, endurance exercise training-induced changes in β_2-AR expression and signaling in slow-twitch muscle contribute to the adaptation of metabolic and anabolic capacities during exercise.

In addition to these findings, we recently reported changes in intracellular β_2-AR signaling in skeletal muscles in response to β_2-adrenergic stimulation and exercise (Sato et al. 2013). As seen in Table 18.2, other groups have also studied the effects of β_2-adrenergic agonists and exercise on β_2-AR signaling in skeletal muscles, and these studies reveal the similarities and differences in the responses of β_2-AR signaling molecules to β_2-agonists and exercise (Gosmanov et al. 2002; Kline et al. 2007; Shi et al. 2007; Akimoto et al. 2005; Gonçalves et al. 2012; Sakamoto et al. 2003). These findings may highlight the fact that β_2-AR signaling plays a functional role in anabolic and metabolic adaptations to β_2-adrenergic agonists and exercise in skeletal muscles. The insights mentioned in these papers will provide scientific evidence for the eradication of β_2-adrenergic agonists as sports doping agents by furthering our knowledge of mechanisms of muscle hypertrophy.

18.4 Muscle Atrophy and β_2-AR

18.4.1 Preventive Roles of β_2-AR in Disuse-Induced Muscle Atrophy

Muscle wasting and weakness are common in physiological and pathological conditions such as aging, cancer cachexia, sepsis, other forms of catabolic stress, denervation, disuse (e.g., unloading, inactivity, and microgravity), burns, human immunodeficiency virus (HIV)-acquired immunodeficiency syndrome (AIDS), chronic kidney or heart failure, chronic obstructive pulmonary disease (COPD), and muscular dystrophies. For many of these conditions, the anabolic properties of

Table 18.2 Effects of β_2-agonists and exercise (mechanical loading) on the phosphorylation of β_2-adrenergic receptor signaling proteins in skeletal muscles (Sato et al. 2012)

Proteins	β_2-agonists		Exercise (mechanical loading)		References
	Fast-twitch muscles	Slow-twitch muscles	Fast-twitch muscles	Slow-twitch muscles	
CREB	Unresponsive	Unresponsive	Unresponsive	Unresponsive	Sato et al. (2013)
p38 MAPK	Unresponsive	Phosphorylated	Phosphorylated or unresponsive	Phosphorylated	Akimoto et al. (2005)
ERK1/2	Phosphorylated	Unresponsive	Phosphorylated	Phosphorylated	Gosmanov et al. (2002)
Akt	Phosphorylated or unresponsive	Phosphorylated or unresponsive	Phosphorylated or unresponsive	Phosphorylated or unresponsive	Sakamoto et al. (2003), Sato et al. (2013)

CREB Cyclic adenosine monophosphate response element-binding protein, *MAPK* Mitogen-activated protein kinase, *ERK1/2* Extracellular signal-regulated kinase 1/2, *Akt* Protein kinase B

β_2-adrenergic agonists provide therapeutic potential for attenuating or reversing muscle wasting, muscle fiber atrophy, and muscle weakness. These β_2-adrenergic agonists also have important clinical significance for enhancing muscle repair and restoring muscle function after muscle atrophy.

In particular, muscle disuse, which is mainly reflected by an increase in myofibrillar protein breakdown, causes a progressive decrease in muscle strength associated with decreased cross-sectional area of muscle fibers. Therefore, preventing disuse-induced muscle atrophy is a problem requiring urgent attention and β_2-AR is highlighted as a target of pharmacological stimulation. Since 2000, many groups have focused on the preventive effects of β_2-adrenergic agonists on disuse-induced muscle atrophy (Ryall et al. 2006; Yimlamai et al. 2005; Suzuki et al. 2014).

Yimlamai et al. (2005) demonstrated that clenbuterol attenuates hindlimb unweighting-induced atrophy and reduces ubiquitin conjugates only in fast-twitch plantaris and tibialis anterior muscles but not in the slow-twitch soleus muscle; this suggests that clenbuterol alleviates hindlimb unweighting-induced atrophy, particularly in fast-twitch muscles, at least in part through a muscle-specific inhibition of the ubiquitin-proteasome pathway. However, Stevens et al. (2000) reported that clenbuterol treatment accelerates hindlimb unweighting-induced slow-to-fast (MHCI/b → MHCIIa → MHCIId/x → MHCIIb) transformation in the soleus muscle. β_2-Adrenergic agonists also reverse muscle wasting and weakness in several conditions such as aging, muscular dystrophy, denervation, cancer cachexia, and myotoxic injury (Ryall et al. 2006; Beitzel et al. 2004).

18.4.2 Preventive Roles of β_2-AR in Catabolic Hormone-Induced Muscle Atrophy

Prolonged muscle disuse and/or unloading increases the secretion of glucocorticoids, which promotes the catabolism of muscle proteins via the ubiquitin-proteasome pathway (Smith et al. 2010; Zhao et al. 2009). Sepsis also elevates plasma glucocorticoids and adrenocorticotropic hormone (ACTH) levels (Sun et al. 2002). Therefore, several studies have focused on the counteractive effects of β_2-AR stimulation on glucocorticoid-induced muscle atrophy (Huang et al. 2000; Pellegrino et al. 2004). Huang et al. (2000) showed that clenbuterol almost prevents the decrease in the weight of gastrocnemius/plantaris muscle bundles induced by dexamethasone, a synthetic glucocorticoid. Pellegrino et al. (2004) demonstrated that concurrent treatment with clenbuterol and dexamethasone minimizes the MHC transformation induced by clenbuterol (slow-to-fast) or dexamethasone (fast-to-slow) alone. Thus, β_2-AR stimulation plays an inhibitory role in muscle atrophy and weakness induced by catabolic diseases, mechanical unloading, catabolic hormones, and pharmacological agents.

18.4.3 Response of β_2-AR Expression to Catabolic Hormones

Although the effectiveness of β_2-AR stimulation on muscle atrophy is well documented, catabolic condition-induced changes in the expression of β_2-AR in skeletal muscles are not fully understood. Understanding the response of β_2-AR expression to muscle atrophy is required to establish treatments for muscle atrophy.

Table 18.1 shows catabolic condition-induced changes in β_2-AR expression in skeletal muscles. Our group investigated whether catabolic hormones or agents alter β_2-AR expression in skeletal muscles (Kawano et al. 2009; Sato et al. 2011b). Dexamethasone administration (1.0 mg kg^{-1} day^{-1}) to rats for 10 days decreases the expression of β_2-AR mRNA in the soleus muscle without altering that in the EDL muscle, although the expression of β_2-AR protein in the EDL and soleus muscles is not altered (Kawano et al. 2009; Sato et al. 2011b). Dexamethasone also did not alter β_2-AR density in gastrocnemius/plantaris muscle bundles (Huang et al. 2000). These phenomena were specifically observed in skeletal muscles; meanwhile, glucocorticoids and the GR complex activate the transcription of the β_2-AR gene in the human hepatoma cell line HepG2 (Cornett et al. 1998), subsequently leading to the upregulation of β_2-AR levels in DDT_1 MF-2 smooth muscle cells and lung tissue (Hadcock and Malbon 1998; Huang et al. 2000). Furthermore, dexamethasone decreases the expression of GR mRNA in the soleus muscle (Kawano et al. 2009; Sato et al. 2011b). Dexamethasone also decreases and increases the expression of CREB mRNA, a transcription factor of the β_2-AR gene (Collins et al. 1990), in the soleus and EDL muscles, respectively (Sato et al. 2011b). These findings suggest that the dexamethasone-induced decrease in the expression of β_2-AR mRNA in the slow-twitch soleus muscle is associated with transcriptional regulation.

18.4.4 Response of β_2-AR Expression to Muscle Disuse

The effects of physiological and pathological catabolic condition-induced muscle atrophy on β_2-AR expression have also been studied (Ryall et al. 2006; Beitzel et al. 2007; Sato et al. 2011c, 2012) (Table 18.1). Our recent investigation demonstrated that casted immobilization (knee and foot arthrodesis) for 10 days induced marked atrophy in the soleus muscle, and decreased the expression of β_2-AR mRNA (Sato et al. 2011c). Decreased GR mRNA and protein expression were also detected in the soleus muscle (Sato et al. 2011c). These results suggest that casted immobilization decreases the expression of β_2-AR mRNA in slow-twitch muscles via the downregulation of GR levels and subsequent glucocorticoid signals. Ryall et al. (2006) showed aging-induced muscle wasting in the EDL and soleus muscles, although there were no age-associated changes in β_2-AR density in these muscles. Furthermore, in the regeneration process from muscle injury induced by bupivacaine injection, β_2-AR density and mRNA expression as well as $G\alpha_s$ content were

decreased in the soleus but increased in the EDL muscle (Beitzel et al. 2007). Thus, the effects of catabolic conditions such as disuse, aging, and injury on β_2-AR expression are different from and/or dependent on the conditions, especially in fast-twitch muscles, whereas decreasing tendencies are observed in slow-twitch muscles.

Both pharmacological and mechanical studies indicate that the preventive effects of β_2-AR stimulation on muscle atrophy and weakness are limited by decreased β_2-AR synthesis and subsequently decreased density. In order to use β_2-adrenergic agonists as therapeutic agents for muscle wasting, further studies are necessary to obtain detailed evidence regarding the responses of β_2-AR expression and function to muscle atrophy.

18.5 Conclusions

In this chapter, we have discussed the adaptive responses of β_2-AR expression in skeletal muscles to β_2-adrenergic agonist treatment, exercise training, muscle disuse, and glucocorticoid treatment. This chapter also outlines the functional roles of β_2-AR in skeletal muscles. Skeletal muscle partly requires β_2-AR activation for hypertrophy, regeneration, and atrophy prevention; however, its functions and responsiveness must be adaptively regulated by the receptor itself via downregulation, synthesis, and desensitization. New insight in the form of scientific evidence is needed to eradicate sports doping and to identify new therapeutic targets for attenuating muscle atrophy induced by physiological and pathological conditions.

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Part III
Physical Activity, Exercise, Nutrition, Aging, and Health

Chapter 19
The Role of Exercise and Nutrition in Lifestyle-Related Disease

Toshio Moritani

Abstract Daily energy intake per person in Japan reached a peak of 2,226 Kcal in 1975 and dropped dramatically to 1,902 Kcal in 2004, nearly identical to the value during the immediate post-World War II period. However, since 1975 obesity has sharply increased despite this dramatic decline in energy intake. This may be, in part, the result of a "relative energy surplus" caused by a decline in energy expenditure due to modern industrialization that far exceeds the decreased energy intake. Bray (J Nutr 121:1146–1162, 1991) has proposed the "MONA LISA" (Most Obesities kNown Are Low In Sympathetic Activity) hypothesis, suggesting that obesity is associated with a relative or absolute reduction in the activity of the thermogenic component of the sympathetic nervous system. It is now well recognized that "middle age obesity" is strongly associated with both aging and depressed autonomic nervous system (ANS) activity, particularly the sympathetic thermogenic responses to a high-fat diet and an irregular food intake pattern. Our series of studies have suggested the decline in ANS activity that regulates fat metabolism and appetite control is potentially reversible by regular exercise training in middle-aged individuals and obese children with depressed ANS activity. In other words, habitual exercise plays a vital role in enhancing not only fat and glucose metabolism, but also in preventing obesity and enhancing appetite control. Recent studies have clearly indicated that exercising obese individuals have a much lower mortality rate and incidence of disease than lean individuals with little or no exercise. A possible explanation could be that exercise effects immune functions and myocytokines, preventing and improving lifestyle-related diseases. Finally, our recent studies on the effect of functional muscle electrical stimulation on glucose utilization during hyperinsulinemic-euglycemic clamp will be discussed together with the most recent topics on brain derived neurotrophic factors (BDNFs) that appear to influence energy metabolism, appetite, and aspects of neurocognitive function. These data

Electronic supplementary material The online version of this chapter (doi: 10.1007/978-4-431-55333-5_19) contains supplementary material, which is available to authorized users.

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_19

strongly suggest that a lack of exercise or a sedentary lifestyle combined with an unhealthy diet may lead to accelerated ageing, diseases of the body and brain, and an overall decline in the quality of life.

Keywords Lifestyle-related disease • Obesity • Autonomic nervous system • Brain-derived neurotrophic factor (BDNF)

19.1 Etiology of Obesity and Metabolic Syndrome

Daily energy intake per person in Japan reached a peak value of 2,226 Kcal in 1975 and dropped dramatically to 1,902 Kcal in 2004, which is nearly identical to the energy intake immediately after World War II, according to the Ministry of Health, Labor and Welfare in Japan. However, obesity in Japan has sharply increased despite this dramatic decline in energy intake. This may be, in part, the result of a "relative energy surplus" caused by a decline in energy expenditure due to modern industrialization that far exceeds the decreased energy intake.

Obesity, a common and important health hazard, is associated with an increased incidence of hypertension, congestive heart failure, diabetes, and cardiac sudden death, as well as an overall increase in mortality rate. The causes of most cases of human obesity are unknown. Recent identification of obese genes (leptin, uncoupling protein [UCP] families, and the Trp64Arg polymorphism of the β3-adrenergic receptor) has increased our understanding of the pathophysiology of obesity and related diseases (Lönnqvist et al. 1995; Sakane et al. 1997). Figure 19.1 schematically summarizes the current hypothesis explaining the major role of autonomic nervous system (ANS) activity and its principal components for regulating our body weight.

Bray (1991) has proposed the MONA LISA (Most Obesities kNown Are Low In Sympathetic Activity) hypothesis, suggesting that obesity is associated with a relative or absolute reduction in the activity of the thermogenic component of the sympathetic nervous system. Since the β3-adrenergic receptor plays a significant role in the control of lipolysis and thermogenesis in brown adipose tissue (Yoneshiro et al. 2011) through ANS activity (Fig. 19.1), we first determined the prevalence of the polymorphism in 204 subjects (Shihara et al. 1999). Results indicated that the subjects with the β3-adrenergic receptor variant, even the heterozygotes, demonstrated significantly lower resting ANS activity than normal subjects, whereas the clinical characteristics did not differ between groups. We further tested 243 postmenopausal women (55.4 ± 0.4 years) who visited a climacteric clinic. Body composition, blood pressure, glucose, and lipid profiles were determined. Menopausal women with reduced sympatho-vagal activities have significantly higher body fat content, blood pressure, and blood lipid concentrations, suggesting that such autonomic depression could be a crucial risk factor in accelerating the undermining of postmenopausal women's health and, ultimately, quality of life (Kimura et al. 2006).

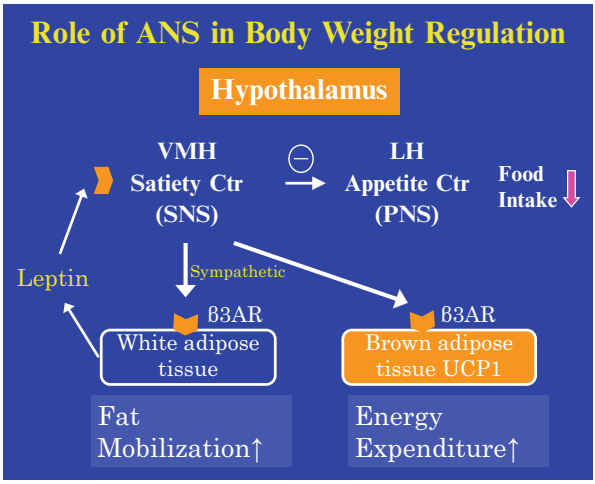

Fig. 19.1 Schematic diagram showing the role of the autonomic nervous system (ANS) and its interaction with white adipose and brown adipose tissues for regulating body weight (Moritani et al. 2005). *VMH* ventromedial hypothalamus, *LH* lateral hypothalamus, *SNS* sympathetic nervous system, *PNS* parasympathetic nervous system, *B3AR* β3 adrenergic receptor

It is not uncommon for people to spend one-half of their waking day sitting, with relatively idle muscles. Hamilton et al. (2007) have argued that sitting time and non-exercise activity thermogenesis (NEAT) have been linked in epidemiological studies to rates of metabolic syndrome, type 2 diabetes, obesity, and cardiovascular disease (CVD). A longitudinal study by Hancox et al. (2004) included approximately 1,000 randomly-selected individuals born in Dunedin, New Zealand, in 1972–73, and assessed them at regular intervals up to age 26. They used regression analysis to investigate the associations between earlier television viewing and body-mass index, cardiorespiratory fitness, serum cholesterol, smoking status, and blood pressure at age 26. Television viewing in childhood and adolescence is associated with overweight condition, poor fitness, smoking, and raised cholesterol in adulthood. These data strongly suggest that excessive TV viewing might have long-lasting adverse effects on health (Fig. 19.2).

Furthermore, even when adults meet physical activity guidelines, sitting for prolonged periods can compromise metabolic health. Objective measurement studies show deleterious associations between television-watching time and metabolic health, and breaking up sedentary time is beneficial. Greater sitting time, TV time, and time spent in automobiles increase premature mortality risk. Figure 19.3a shows an accumulated moderate- to vigorous-intensity physical activity time of 31 min per day for a week in average for one subject; however, this person spends 71 % of his or her waking hours in sedentary time. Thus, it is possible for individuals to be physically active in bouts, yet highly sedentary overall. Figure 19.3b demonstrates that the person in the right-hand panel (the ‘Breaker’) interrupts his or her sedentary time far more frequently than the person whose data are shown in the left panel (the

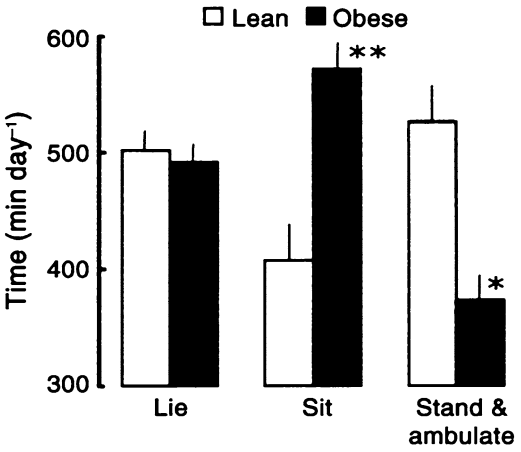

Fig. 19.2 Time spent in different postures by 10 obese and 10 lean sedentary subjects as determined by a triaxial accelerometer (Levine et al. 2005)

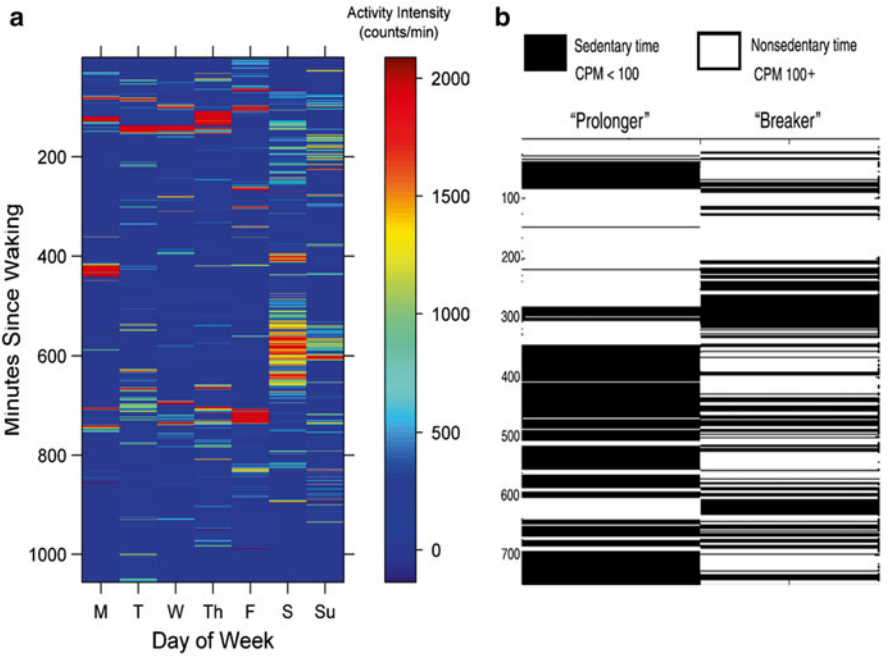

Fig. 19.3 Being physically active, but also highly sedentary: 1 week of accelerometer count data showing, on average, 31 min of moderate- to vigorous-intensity activity time and 71 % of sedentary activity during waking hours (**a**). Breaks in sedentary time: same amount of sedentary time, but differing distribution of activity (*CPM* counts per minute): 'Prolonger' vs. 'Breaker' (Owen et al. 2010) (**b**). A prolonger spends prolonged periods of sedentary time with occasional breaks for activity, whereas a breaker who accumulates the same total amount of sedentary time breaks that time up with many periods of light activity

'Prolonger'). Independent of total sedentary time, moderate- to vigorous-intensity activity time, and mean intensity of activity, Healy et al. (2008) found that having a higher number of breaks in sedentary time was beneficially associated with waist circumference, body mass index, triglycerides, and 2-h plasma glucose.

There is a growing understanding that too much sitting is a real and substantial risk to health. One of the intriguing findings from these accelerometer measurement studies is that breaks in sedentary time were shown to have beneficial associations with favorable metabolic biomarkers (Healy et al. 2008; Levine et al. 2005; Owen et al. 2010), due possibly to challenging and enhancing the ANS that regulates body weight and appetite (Amano et al. 2001; Lönnqvist et al. 1995; Yoneshiro et al. 2011). Thus, NEAT is likely to serve as a crucial thermoregulatory switch governing the storage or dissipation of excess energy. Determining the physiological regulation of NEAT may lead to a better understanding of the pathophysiology and improved prevention and treatment of obesity. Our exercise intervention study has also demonstrated a strong possibility that ANS activity can be enhanced by exercise training among previously obese menopausal women with reduced ANS activity (Amano et al. 2001).

19.2 Outbreak of Diabetes in Japan

In 2003, there were 7.4 million diabetics and 8.8 million diabetic candidates in Japan, nearly a 31-fold increase from 1955. The 10.7 million diabetic patients in 2011, a nearly 43-fold increase from 1955, cannot be explained by genetics. The so-called "Deadly Quartet" of obesity, diabetes, hyperlipidemia, and hypertension are caused by adipokines secreted from visceral fat. A recent 15-year-long longitudinal study with 800 Japanese volunteers above age 40 has revealed a 4.6-fold higher incidence of Alzheimer's disease and a 3.1-fold increase in cancer death among the participants who were diabetic at the time of the initial medical screening.

As far as the pathogenesis of diabetes is concerned, Stuart et al. (1988) demonstrated that the limited physical activity dictated by bed rest for as little as seven days is associated with substantial resistance to insulin's effects on glucose metabolism. Further, the data suggest that these effects occur primarily in skeletal muscle with little change in insulin action on the liver. Thus we should consider the strong possibility that the primary cause of diabetes is inactivity-induced muscle metabolic disorder. Exercise can directly activate glucose uptake in skeletal muscle by inducing translocation of glucose transporter type 4 (GLUT-4) to the cell surface via an insulin-independent mechanism. In fact, muscle-contraction-stimulated GLUT-4 translocation is not impaired in insulin-resistant conditions such as type 2 diabetes and obesity (Hayashi et al. 1998) (Fig. 19.4).

A recent study also indicates that a defect in the ability to oxidize lipid in skeletal muscle is evident with obesity, which is corrected with exercise training but persists after weight loss without exercise (Berggren et al. 2009). In this study, there was no

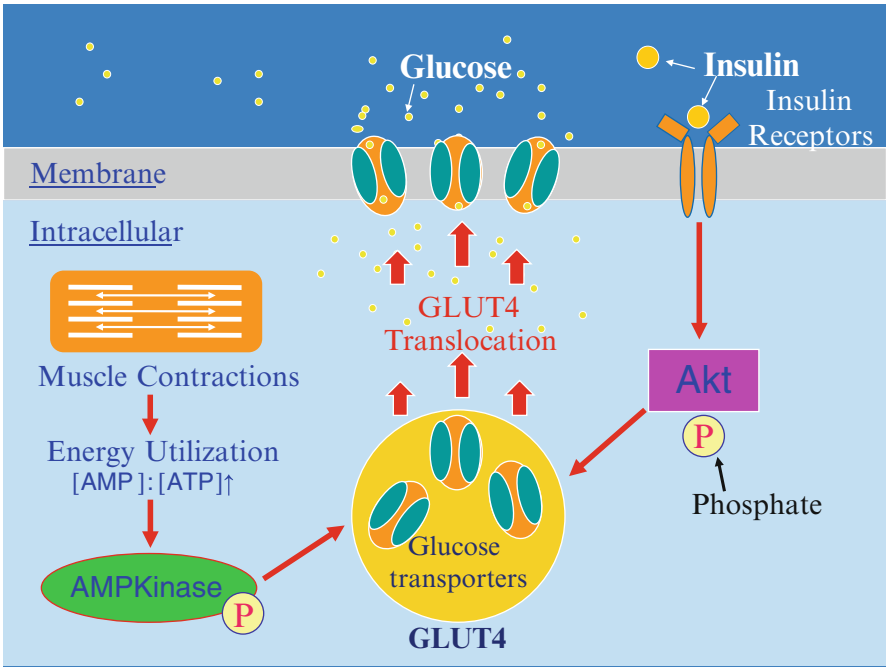

Fig. 19.4 Schematic diagram demonstrating the biochemical signals for inducing glucose transport and utilization in the muscle. Exercise increases glucose uptake by the translocation of GLUT-4 glucose transporters, similar to the action of insulin, but through independent mechanisms (Hayashi et al. 1998). *AMP* adenosine monophosphate, *ATP* adenosine tri-phosphate, *Akt* protein kinase B

difference in muscle fatty acid oxidation (FAO) between the extremely obese and weight loss groups, but FAO in these two groups was nearly 45 % depressed compared with the lean subjects. Muscle FAO also did not change in extremely obese women before and 1 year after a 55-kg weight loss. In contrast, ten consecutive days of exercise training significantly increased FAO in the skeletal muscle of lean (1.7-fold), obese (1.8-fold), and previously extremely obese subjects after weight loss (2.6-fold). Since this study with muscle biopsy eliminates the influence of ANS activity and circulating hormones, the results highlight the vital role of exercise on muscle fat oxidation capacity (Berggren et al. 2009).

19.3 Metabolic and Appetite Response to Fat, Protein, and Carbohydrate: New Evidence

There is no immediate increase in fat oxidation after nearly 1,000 Kcal of excess fat intake from baseline. Because fat intake does not promote fat oxidation, excess dietary fat is almost entirely stored in adipose tissue (Jéquier and Tappy 1999).

Lipid utilization decreases while carbohydrate (CHO) oxidation increases in response to a 9-day overfeeding period with a mixed diet until CHO balance is achieved. These results confirm that high-fat diets are more obesity-producing than high-CHO diets. Protein and CHO balances are achieved in both conditions. In the hypercaloric condition, fat oxidation is inhibited and large amounts of the ingested lipid is stored. The conversion of CHO into fat is an energy-requiring process, which converts nearly 25 % of the energy content of ingested CHO into heat. Deposition of dietary triglycerides into adipose tissue requires very little energy (0–2 %). During CHO overfeeding, hepatic denovo lipogenesis does not exceed more than 10 g fatty acids per day (Jéquier and Tappy 1999). Recent studies (Brinkworth et al. 2009) have also demonstrated that over the course of 1 year there was a favorable effect of an energy-restricted high-CHO, low-fat diet compared with an isocaloric high-fat, low-CHO diet on mood state and affect in overweight and obese individuals.

Our understanding of how neurohormonal gut–brain signaling regulates energy homeostasis has advanced significantly in recent years (Martins et al. 2007; Wren and Bloom 2007). Ghrelin is an orexigenic (appetite-stimulating) peptide produced by the stomach, which appears to act as a meal initiator. Satiety signals derived from the intestine and pancreas include peptide YY (PYY), pancreatic polypeptide (PP), glucagon-like peptide 1 (GLP-1), oxyntomodulin, and cholecystokinin. Recent research suggests that gut hormones can be manipulated to regulate energy balance in humans, and that obese subjects retain sensitivity to the actions of gut hormones. Postprandially, plasma ghrelin is suppressed in proportion to calories ingested, when macronutrient content and volume are kept constant. Interestingly, fat appears to suppress ghrelin less potently per calorie than carbohydrate or protein. This may, in part, explain the reduced satiety and enhanced weight gain associated with high-fat diets.

In line with this finding, it has been clearly demonstrated that consuming a low-CHO (approximately 47 % energy) diet is associated with greater likelihood of being overweight or obese among healthy, free-living adults. The lowest risk of obesity may be obtained by consuming 47–64 % energy from CHO (Merchant et al. 2009). Gut-hormone-based therapies may thus provide an effective and well-tolerated treatment for obesity.

Interestingly, Martins et al. (2007) investigated the acute effects of exercise on the postprandial levels of appetite-related hormones and metabolites, energy intake (EI), and subjective measures of appetite. Ghrelin, PYY, GLP-1, and PP were measured in the fasting state and postprandially in 12 healthy, normal-weight volunteers using a randomized crossover design. One hour after a standardized breakfast, subjects either cycled for 60 min at 65 % of their maximal heart rate or rested. Exercise significantly increased mean PYY, GLP-1, and PP levels, and this effect was maintained during the post-exercise period for GLP-1 and PP. No significant effect of exercise was observed on postprandial levels of ghrelin.

In conclusion, acute exercise, of moderate intensity, temporarily decreased hunger sensations and was able to produce a short-term negative energy balance. This impact on appetite and subsequent energy homeostasis was not explained by

changes in postprandial levels of ghrelin; however, exercise-induced anorexia may potentially be linked to increased PYY, GLP-1, and PP levels (Martins et al. 2007).

19.4 Exercise and Cognitive Function

Synaptic plasticity and behaviors are likely dependent on the capacity of neurons to meet the energy demands imposed by neuronal activity. In an area critical for learning and memory, the hippocampus, exercise modified aspects of energy metabolism by decreasing oxidative stress and increasing the levels of cytochrome c oxidase-II, a specific component of the mitochondrial machinery (Gomez-Pinilla et al. 2008). While exercise significantly increased the mRNA levels of brain-derived neurotrophic factor (BDNF) in the hippocampus as compared to the sedentary condition, pharmacological treatment fully blocked the exercise-induced effect on BDNF mRNA, effectively reducing BDNF mRNA levels to those found in the sedentary condition. One week of voluntary exercise that enhanced learning and memory performance elevated the expression of molecular systems involved in the metabolism of energy (adenosine monophosphate [AMP]-activated protein kinase [AMPK], ubiquitous mitochondrial creatine kinase [uMtCK], and uncoupling protein 2) and molecules that work at the interface of energy and synaptic plasticity (BDNF, insulin-like growth factor 1 [IGF-1] and ghrelin) (Gomez-Pinilla et al. 2008). These findings suggest that the effects of exercise on synaptic plasticity and cognitive function involve elements of energy metabolism, and that BDNF seems to work at the interface between the two processes as a metabotrophin.

The circulating BDNF is reduced in patients with major depression and type 2 diabetes. Because acute exercise increases BDNF production in the hippocampus and cerebral cortex, Seifert et al. (2010) hypothesized that endurance training would enhance the release of BDNF from the human brain as detected in arterial and internal jugular venous blood samples. In a randomized controlled study, 12 healthy sedentary males carried out 3 months of endurance training ($N=7$) or served as controls ($N=5$). Results indicated that 3 months of endurance training significantly enhanced the resting release of BDNF ($P<0.05$); no significant change occurred in the control subjects. Exercise promotes cardiovascular and musculoskeletal health. This study shows that, in addition, regular physical activity may be important for maintenance and improvement of brain health and, therefore, supports exercise as a coadjuvant to the treatment of various neurological diseases, including Alzheimer's disease, major depression, and type 2 diabetes (Seifert et al. 2010).

The hippocampus shrinks in late adulthood, leading to impaired memory and increased risk for dementia. Hippocampal and medial temporal lobe volumes are larger in more fit adults, and physical activity training increases hippocampal perfusion, but the extent to which aerobic exercise training can modify hippocampal volume in late adulthood remains unknown. Recent results from an exercise intervention study by Erickson et al. (2011) show, in a randomized controlled trial with 120 older adults (mean age 67.6 ± 5.8 years), that aerobic exercise training increases

the size of the anterior hippocampus, leading to improvements in spatial memory. This study clearly demonstrated that exercise training increased hippocampal volume by 2 %, effectively reversing age-related volume loss by 1–2 years. In sum, the hippocampus remains plastic in late adulthood and 1 year of aerobic exercise was sufficient to enhance hippocampal volume. Increased hippocampal volume translates to improved memory function and higher serum BDNF (Erickson et al. 2011). These results demonstrate that higher fitness levels are protective against loss of hippocampal volume and consequent impaired memory and dementia risk.

19.5 Electrical Muscle Stimulation (EMS) for Enhancement of Muscle Metabolism

Regular exercise results in numerous health benefits, including a reduced risk of coronary heart disease and developing type 2 diabetes. Exercise increases glucose uptake by the translocation of GLUT-4 glucose transporters, similar to the action of insulin, but through independent mechanisms (Hayashi et al. 1998). However, there are individuals who are restricted from voluntary physical activity and in a bedridden state due to chronic illness, spinal cord injury, and other forms of disability. Unlike the orderly recruitment of motor units during low-intensity voluntary exercise in which type I slow-twitch fibers are utilized first, during EMS, fast-twitch motor units with glycolytic fibers are activated first because of their larger axons which have much lower electrical resistance for a given externally-applied electrical current (Hamada et al. 2004b). It is thus reasonable to assume that EMS may be a better approach to enhance the glucose transport activity in skeletal muscle, without requiring vigorous voluntary exercise that ensures the activation of type II fibers with subsequent enhancement of postexercise glucose uptake, particularly for those individuals who are unable to exercise. Figure 19.5 and Video **19.1** demonstrate a typical setting of our EMS procedures for metabolic enhancement (exponentially rising stimulus pulse with 250 μs duration, 4 Hz continuous stimulation).

Our results (Hamada et al. 2004a) indicated that oxygen uptake was significantly increased by approximately 2-fold in response to EMS. Muscle glucose uptake determined by glucose infusion rate (GIR) in hyperinsulinemic-euglycemic clamp was significantly increased and lasted more than 2 h in response to electrically-induced contractions (Hamada et al. 2004a) . We have recently examined whether belt-type surface electrical muscle stimulation (B-SES) attenuates postprandial hyperglycemia in type two diabetes (Miyamoto et al. 2012). Eleven patients with type 2 diabetes participated in two experimental sessions; one was a 30-min B-SES 30 min after breakfast (EMS trial) and the other was a complete rest after breakfast (Control trial). In each trial, blood was sampled before and at 30, 60, 90, and 120 min after the meal. Postprandial glucose level was significantly attenuated in the EMS trial at 60, 90, and 120 min after a meal ($p < 0.05$). The C-peptide concentration was also significantly lowered in the EMS trial ($p < 0.01$). On the other hand,

Fig. 19.5 Video demonstration of our belt-type surface electrical muscle stimulation (B-SES) procedures for metabolic enhancement

there was no significant increase in creatine phosphokinase (CPK) concentration in either trial.

These data provide the first evidence indicating that a new exercise method, EMS, is effective for treating postprandial hyperglycemia in individuals with type 2 diabetes, especially those who cannot perform adequate voluntary exercise because of excessive obesity, orthopedic diseases, or severe diabetic complications. Thus, EMS may become a useful modality for enhancing energy and glucose metabolism in skeletal muscle through insulin-independent mechanisms in patients with diabetes and/or patients with chronic progressive muscle atrophy (Fig. 19.6).

Figure 19.7 and Video **19.2** shows a demonstration of our EMS procedures for producing muscle hypertrophy. EMS implemented during the early post-surgical rehabilitation stage is effective in maintaining and increasing muscle thickness and strength in the operated limb. Following anterior cruciate ligament (ACL) reconstruction, restricted weight bearing and immobilization results in thigh and calf muscle atrophy and weakness. We have therefore assessed the effect of EMS on prevention of muscle atrophy in patients during the early rehabilitation stage after ACL reconstruction (Hasegawa et al. 2011). Twenty patients with acute ACL tears were randomly divided into two groups. The control group (CON group) participated in the usual rehabilitation program only. In addition to this protocol, the electrical muscle stimulation group (EMS group) received EMS training using a 20 Hz exponential pulse wave form for 20 min, 5 times/week from the 2nd post-operative day to 4 weeks after the surgery. Muscle thickness of the vastus lateralis and the calf had increased significantly at 4 weeks after surgery in the EMS group, while it decreased significantly in the CON group. The decline of knee extension strength was significantly less in the EMS group than in the CON group at 4 weeks after the surgery, and the EMS group showed greater recovery of knee extension strength at

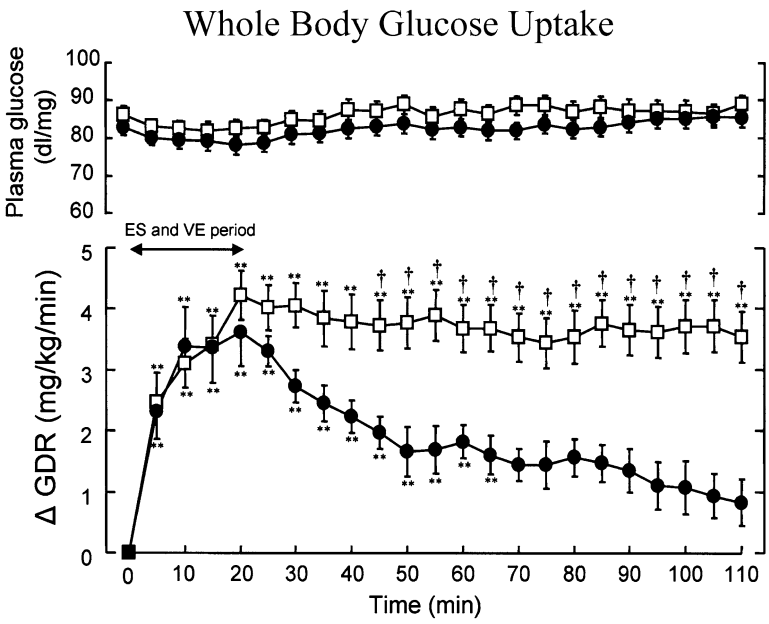

Fig. 19.6 Time course of changes in plasma glucose (**a**) and glucose disposal rate (GDR; **b**) during steady-state euglycemic clamp in both Electrical Stimulation (ES: *open bars*) and Voluntary Exercise (VE: *solid bars*) conditions (Hamada et al. 2004a)

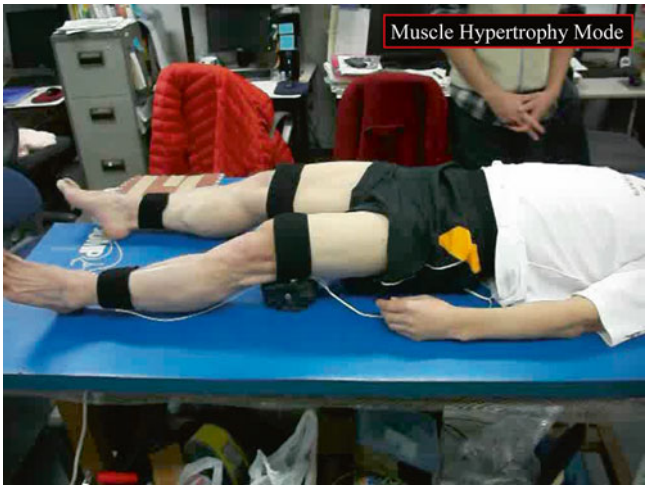

Fig. 19.7 Video demonstration of our belt-type surface electrical muscle stimulation (B-SES) procedure for producing muscle hypertrophy

3 months after surgery. EMS implemented during the early post-surgical rehabilitation stage is effective in maintaining and increasing muscle thickness and strength in the operated limb.

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Chapter 20
Vasopressin V1a Receptor Gene and Voluntary Exercise in Humans and Mice

Shizue Masuki, Eri Sumiyoshi, and Hiroshi Nose

Abstract Exercise training protects against age- and lifestyle-related diseases. We recently reported that middle-aged and older Japanese men carrying the TT genotype of the single nucleotide rs1042615 polymorphism in the vasopressin V1a receptor had significantly higher body mass index and diastolic blood pressure than those who did not. However, these higher values decreased to levels comparable to those of men carrying other genotypes following 5 months of interval walking training (IWT), suggesting that they might have been physically inactive before starting IWT. Therefore, we postulated that TT men would have lower adherence to long-term exercise programs. To assess this, middle-aged and older men underwent IWT for 29 months. We found that adherence to the exercise program was markedly decreased in TT men compared with men of other genotypes during the training period.

To elucidate the mechanism, we assessed whether voluntary locomotion was impaired in mice genetically deficient in V1a receptors (V1a KO). We found that voluntary locomotion in wild-type mice occurred at higher probability after cerebral activation, while in V1a KO mice the probability was markedly reduced with no suppression of baroreflex control of heart rate during cerebral activation. Moreover, these findings in V1a KO mice were confirmed after local infusion of a V1a receptor antagonist into the nucleus tractus solitarii of wild-type mice. Thus, central V1a receptors play an important role in facilitating voluntary exercise. This finding might help to explain the lower adherence to a long-term IWT program in TT men.

Keywords Exercise training • Genetics • Vasopressin • Baroreceptor reflex

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_20

20.1 Introduction

The rapid growth in the elderly population in many countries has highlighted the importance of exercise training for decreasing the likelihood of age- and lifestyle-related diseases, promoting independence, and enhancing the quality of life (Blair et al. 1989; Higashi et al. 1999; Manson et al. 2002; Schjerve et al. 2008; Turcotte and Fisher 2008; Walker et al. 2009). However, few studies have assessed how gene polymorphisms affect interindividual variation in response to exercise training in a large population of middle-aged and older people, although several studies have reported genes and genetic variation associated with health-related fitness phenotypes (Bray et al. 2009). This lack might be due to the fact that there have been no uniformly and broadly-available exercise training regimens calibrated to individual physical fitness with few limitations on time and place. Without such a regimen, it might have been difficult to distinguish whether genetics or training regimen differences might be the cause of interindividual variation in the effects of exercise training. In this chapter, we will present an example of an exercise training regimen that could enable us to successfully determine how gene polymorphism affects physiological responses to exercise training. We will also present genetic and pharmacological animal models to clarify the mechanism by which genetic factors affect physiological responses in humans.

20.2 Interval Walking Training

Recently, we have developed an exercise training regimen fitted to individual physical fitness that is broadly available to middle-aged and older people by combining interval walking training (IWT) and an information technology network system to track exercise intensity in individuals (Nemoto et al. 2007; Nose et al. 2009). Because the IWT regimen is so simple and because training achievements can be measured precisely by triaxial accelerometry (Yamazaki et al. 2009), this program has enabled us to locate polymorphisms that cause interindividual variations in the lifestyle-related risk factor responses to exercise training in a large population of subjects.

20.3 Short-Term IWT and a V1a Receptor Polymorphism

Using this system, we assessed whether the single nucleotide rs1042615 polymorphism of the vasopressin V1a receptor altered the indices of lifestyle-related diseases in middle-aged and older people (64 ± 7 (SD) years) and, if so, whether it also altered the effects of IWT (Masuki et al. 2010). CC, CT, and TT rs1042615 carriers (42, 118, and 64 men, respectively; 113, 263, and 154 women, respectively) performed IWT. We included ≥ 5 sets of 3-min slow walking at 40 % peak aerobic

capacity for walking (VO_{2peak}) followed by 3-min fast walking at ≥70 % VO_{2peak} per day for ≥4 days per week for 5 months. Before IWT, the men's body mass index (BMI) and diastolic blood pressure (DBP) were 25.1 ± 0.3 (SE) kg/m^2 and 84 ± 1 mmHg, respectively, in TT, higher than the 23.6 ± 0.4 kg/m^2 and 78 ± 1 mmHg in CC, respectively ($P < 0.01$) (Fig. 20.1); however, the differences disappeared after IWT despite similar training achievement between groups ($P > 0.6$). After IWT, BMI and DBP decreased in TT (−0.9 ± 0.1 kg/m^2 and −5 ± 1 mmHg, respectively) more than in CC (−0.5 ± 0.1 kg/m^2 and 1 ± 1 mmHg, respectively; $P < 0.05$), with a greater decrease in low-density lipoprotein (LDL) cholesterol in TT than in CC carriers ($P < 0.01$) (Fig. 20.2). The decreases in DBP and LDL cholesterol remained greater in TT carriers even after adjustment for their pretraining values. On the other

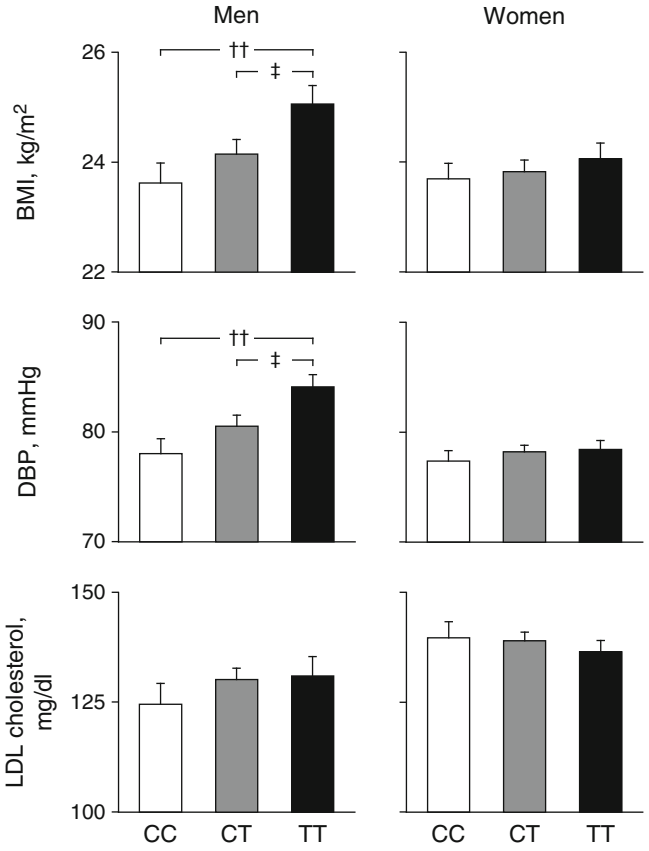

Fig. 20.1 Body mass index (BMI), diastolic blood pressure (DBP), and low-density lipoprotein (LDL) cholesterol before interval walking training in 3 groups; CC (men = 42, women = 113), CT (men = 118, women = 263), and TT (men = 64, women = 154) for BMI and DBP; CC (men = 38, women = 96), CT (men = 107, women = 234), and TT (men = 55, women = 133) for LDL cholesterol. ††Significant differences from CC group, $P < 0.01$. ‡Significant differences from CT group, $P < 0.05$ (Figure from Masuki et al. 2010)

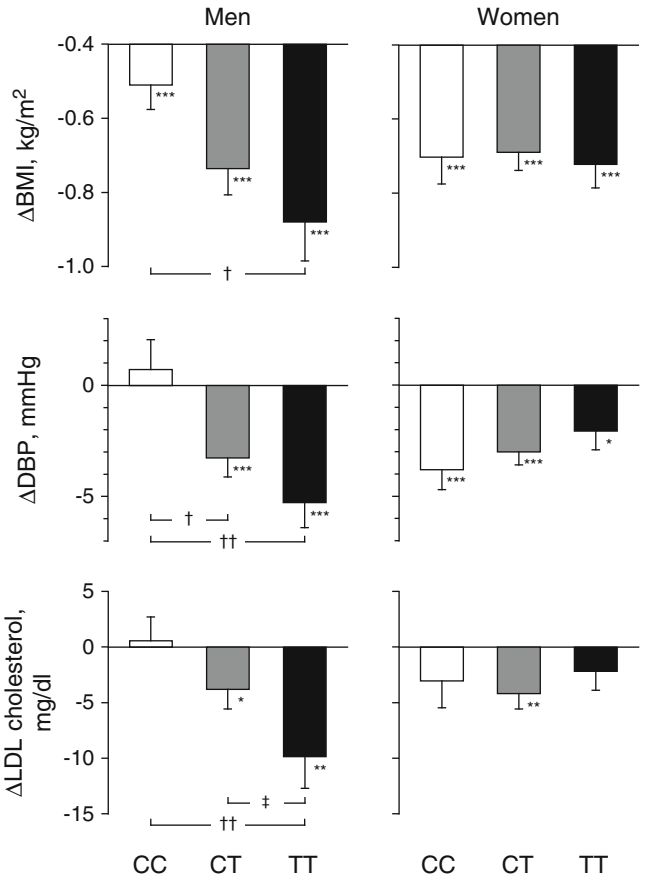

Fig. 20.2 Changes in BMI, DBP, and LDL cholesterol after interval walking training in CC, CT, and TT groups. Significant differences from pretraining values, *P<0.05, **P<0.01, and ***P<0.001. †Significant differences from CC group, P<0.05. The number of subjects and other symbols are the same as in Fig. 20.1 (Figure from Masuki et al. 2010)

hand, for women, these parameters before IWT and their changes after IWT were similar among CC, CT, and TT carriers. These results suggested that BMI and DBP before IWT and the sensitivity of DBP and LDL cholesterol responses to IWT were higher in middle-aged and older male carriers of the TT rs1042615 polymorphism of the V1a receptor, whereas women did not show any of these responses.

20.4 Long-Term IWT and the V1a Receptor Polymorphism

Considering the fact that the originally higher BMI and DBP in TT men decreased to levels comparable to those of men carrying other genotypes after 5-month IWT, what might explain the higher values in TT men before IWT? One possibility is that

TT men might have been physically inactive before starting IWT. Therefore, we hypothesized that TT men would have lower adherence to a *long-term* exercise training program.

To assess this, subjects (65 ± 7 (SD) years) with CC, CT, and TT rs1042615 genotypes (30, 88, and 49 men and 86, 189, and 104 women, respectively) performed IWT for 29 months (Masuki et al. 2011). We prescribed ≥5 sets of 3-min slow walking at 40 % VO_{2peak} followed by 3 min of fast walking at ≥70 % VO_{2peak}/day, ≥4 days/week. We found that monthly adherence to the exercise program (4 days/week) gradually decreased to 47 % by the 29th month in all initially-enrolled men and women; however, the decrease was greater in TT men than in men with other genotypes ($P<0.0001$). Moreover, in men who completed 29 months of IWT, TT men exhibited energy expenditure during fast walking (EE_{fast})/week similar to that of men carrying other genotypes until the 17th mo; however, EE_{fast}/week in TT men decreased thereafter (vs. the 1st mo, $P<0.001$). In contrast, EE_{fast}/week in men carrying other genotypes remained unchanged ($P>0.3$). Therefore, compared to the other genotypes, EE_{fast}/week in TT men was 38 % lower after the 18th mo ($P<0.0001$). This lower EE_{fast}/week in TT men than in men of other genotypes was attributed to 24 % fewer walking days ($P<0.0001$) and 25 % lower EE_{fast}/walking day ($P<0.005$). Depressive and orthopedic symptoms were similar between groups throughout IWT ($P>0.2$). On the other hand, for women, these measurements were similar between groups. Thus, TT men, but not women, exhibited lower adherence to the long-term IWT program.

Regarding the mechanism behind the greater reduction in EE_{fast} per week for TT men, we excluded the effects of orthopedic disorders, depressive symptoms, and smoking status (King et al. 1995; Rhodes et al. 1999). We hypothesized that inter-individual variation in pressor response at the onset of voluntary locomotion, which might be related to the V1a receptor polymorphism (Donaldson and Young 2008; Walum et al. 2008), could be a factor influencing EE_{fast} per week.

20.5 Arterial Pressure Regulation at the Onset of Voluntary Exercise

Arterial blood pressure rises at the onset of voluntary exercise, which is probably advantageous for increasing blood flow to contracting muscles. Since arterial blood pressure at rest is controlled at a lower level than during exercise by the baroreflex control system but it increases rapidly at the onset of exercise, this system is thought to be important to increase pressure to meet the subsequent intensity of exercise and to facilitate exercise. For example, we demonstrated that voluntary locomotion in mice was limited by a rapid fall in arterial pressure due to enhanced muscular vasodilation when baroreflex control was blocked by carotid sinus denervation or the administration of α-adrenergic blockade (Fig. 20.3) (Masuki and Nose 2003). From these results, we speculated that arterial pressure might not increase at the onset of exercise in TT men, perhaps due to impaired V1a receptor function. Therefore, in the next section, we will discuss arterial pressure regulation at the onset of exercise using animal models with impaired V1a receptor function.

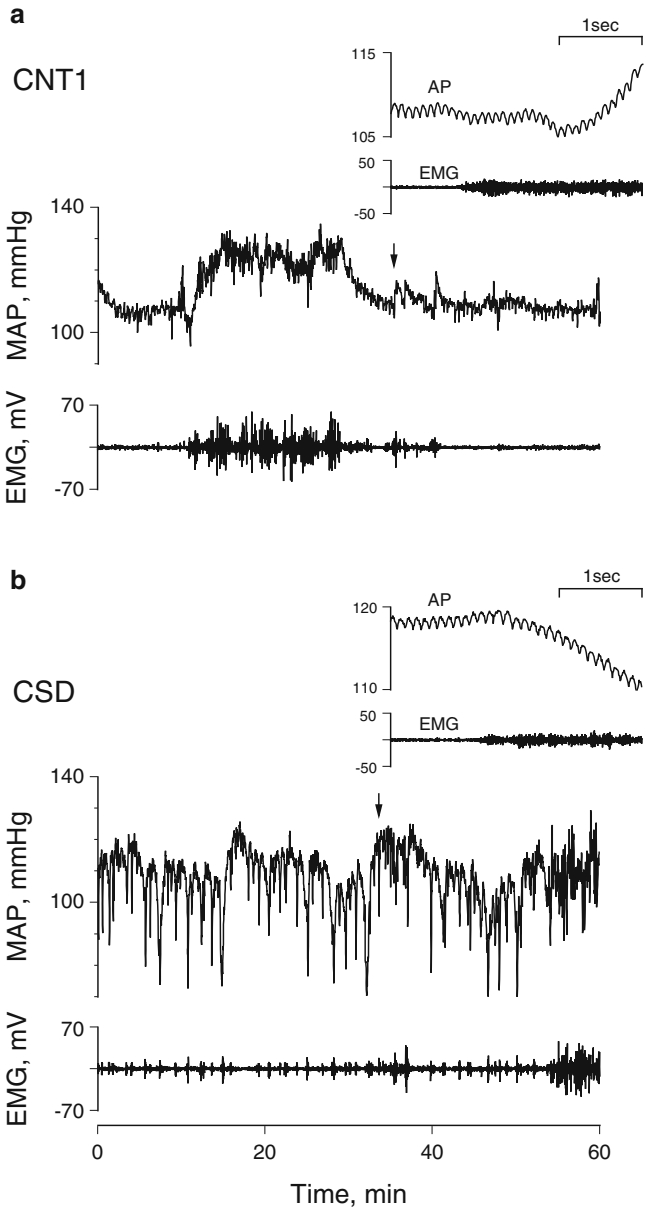

Fig. 20.3 Typical examples of mean arterial pressure (MAP) and electromyogram (EMG) for a control mouse (CNT1, **a**) and a carotid-sinus-denervated mouse (CSD, **b**) in the free-moving state for 60 min. Arterial pressure (AP) and EMG during the time intervals indicated by the *arrows* in the lower figures are presented on an enlarged time scale in the upper *right side* of each panel (Figure from Masuki and Nose 2003)

20.6 Arterial Pressure Regulation at the Onset of Exercise in Mice with Impaired V1a Receptor Function

Arterial pressure regulation is achieved through the baroreflexes, which alter the efferent signals to the heart and the peripheral vessels based on the afferent signals from the peripheral baroreceptors. In the cardiovascular center of the medulla, the feedback gain of baroreflexes is further modulated by signals from the higher brain regions (Rowell et al. 1996). Vasopressin V1a receptors have been reported to be richly expressed in the nucleus tractus solitarii (NTS) of the medulla (Koshimizu et al. 2006) and to regulate the activity of NTS neurons receiving baroreceptor input (Bailey et al. 2006); therefore, it is plausible that V1a receptors in the medulla might act as mediators that receive signals from the higher brain regions and modulate baroreflex control of heart rate (HR). If this is true, V1a receptors might significantly contribute to the start of voluntary locomotion via this pathway.

Previously, we reported that increased cerebral activity suppressed baroreflex control of HR and this was related to the start of voluntary locomotion with a rapid increase in arterial pressure in wild-type mice (Masuki and Nose 2009). Based on these results and also on the results from TT men, we hypothesized that the suppression of baroreflex control of HR after voluntary cerebral activation would be impaired in V1a receptor knockout (V1a KO) mice, and be accompanied by a marked reduction in probability of locomotion after cerebral activation. In addition, we hypothesized that if V1a receptors in the NTS mediated these responses, the findings in V1a KO mice would be confirmed after local infusion of a V1a receptor antagonist into the NTS of wild-type mice.

To assess this, we measured mean arterial pressure (MAP, arterial catheter), HR, and electroencephalogram (EEG) in free-moving male V1a KO (n = 8) and wild-type mice (WT, n = 8) (Masuki et al. 2013). Baroreflex sensitivity (ΔHR/ΔMAP) was determined from HR response (ΔHR) to a spontaneous change in MAP (ΔMAP) every 4 s during the total resting period which was ~8.7 h of the 12-h measuring period in both groups. ΔHR/ΔMAP was determined during the periods when the cross-correlation function (R(t)) between ΔHR and ΔMAP was significant. Cerebral activity was determined every 4 s from the power density ratio of the θ to δ wave band (θ/δ) on the EEG. We found that spontaneous change in θ/δ synchronized with R(t) in both groups (Fig. 20.4); however, a significant correlation occurred during 62 ± 3 % of the total resting period in WT mice, but during only 38 ± 4 % of the total resting period in V1a KO mice (Fig. 20.5a). When R(t) and ΔHR/ΔMAP were divided into 6 bins according to the level of θ/δ, both were positively correlated with θ/δ in WT mice, while neither was correlated in V1a KO mice (Fig. 20.5b). Moreover, the probability that mice started to move after an increase in θ/δ was 61 ± 5 % in WT mice but only 24 ± 4 % in V1a KO mice, markedly lower than in WT mice with no suppression of the baroreflex control of HR (Figs. 20.5c, d). In addition, these findings in V1a KO mice were confirmed after local infusion of the V1a receptor antagonist into the NTS of wild-type mice (V1a BLK, n = 8).

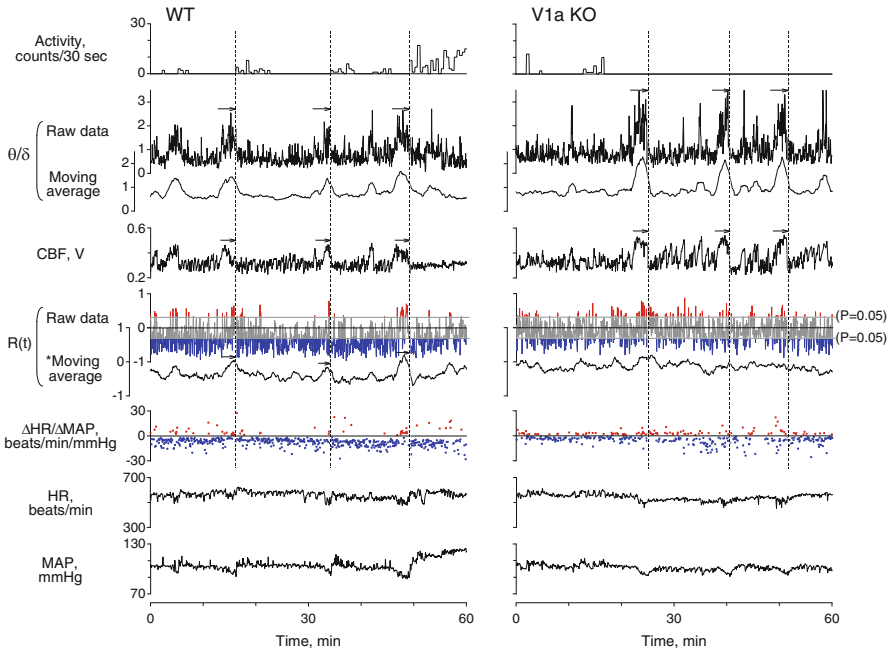

Fig. 20.4 Typical examples of measurements of a wild-type control (WT) and a V1a receptor knockout (V1a KO) mouse in the free-moving state for 60 min. *Top* to *bottom*: activity counts, ratio of θ to δ wave band in EEG (θ/δ), cerebral blood flow (CBF), cross-correlation function (R(t)) between ΔMAP and ΔHR, ΔHR/ΔMAP, HR, and MAP. *R(t) was transformed to $Z_{R(t)}$. θ/δ and $Z_{R(t)}$ determined every 4 s were averaged for a period from $t-40$ to $t+40$ s (21 values) while moving t by 4 s increments. These values were used to determine the average correlation coefficient and the correlation period (Fig. 20.5a) and the probability of locomotion after voluntary cerebral activation during the resting period (Fig. 20.5c) (Figure from Masuki et al. 2013)

Fig. 20.5 (continued) analyses. Total measuring period for each mouse was 720 min. *Values were averaged after z transformation. ***Significant difference from WT mice, $P<0.001$ (**b**) CBF, $Z_{R(t)}$, and ΔHR/ΔMAP in response to graded levels of θ/δ. Data used for the analyses were the same as in Fig. 20.5a. CBF was expressed as % of the value at the lowest θ/δ. ΔHR/ΔMAP was determined when R(t) between ΔHR and ΔMAP was significant regardless of negative or positive. *Significant differences from values at the lowest θ/δ, $P<0.05$ (**c**) The probability of locomotion within 40 s after an increase in θ/δ. ***Significant difference from WT mice, $P<0.001$ (**d**) CBF, $Z_{R(t)}$, ΔHR/ΔMAP, HR, MAP, and activity counts before and after an increase in θ/δ. Because locomotion, when it occurred, started 12 s on average after an increase in θ/δ, the time of 12 s after the increase was regarded as "0 s", and variables were presented in the range of ±240 s from 0 s. Data were derived according to 2 criteria: (1) θ/δ increased to a threshold of 2 SD during the total resting period; (2) the increase was preceded by a >240 s resting period. CBF was similarly expressed as in Fig. 20.5b. *Because some ΔHR/ΔMAP were lacking when R(t) was not significant, they were interpolated from the next values and means and SE for 8 mice in each group was calculated as for other variables. *Red* portions indicate significant differences from values at −240 to −200 s (Figure from Masuki et al. 2013)

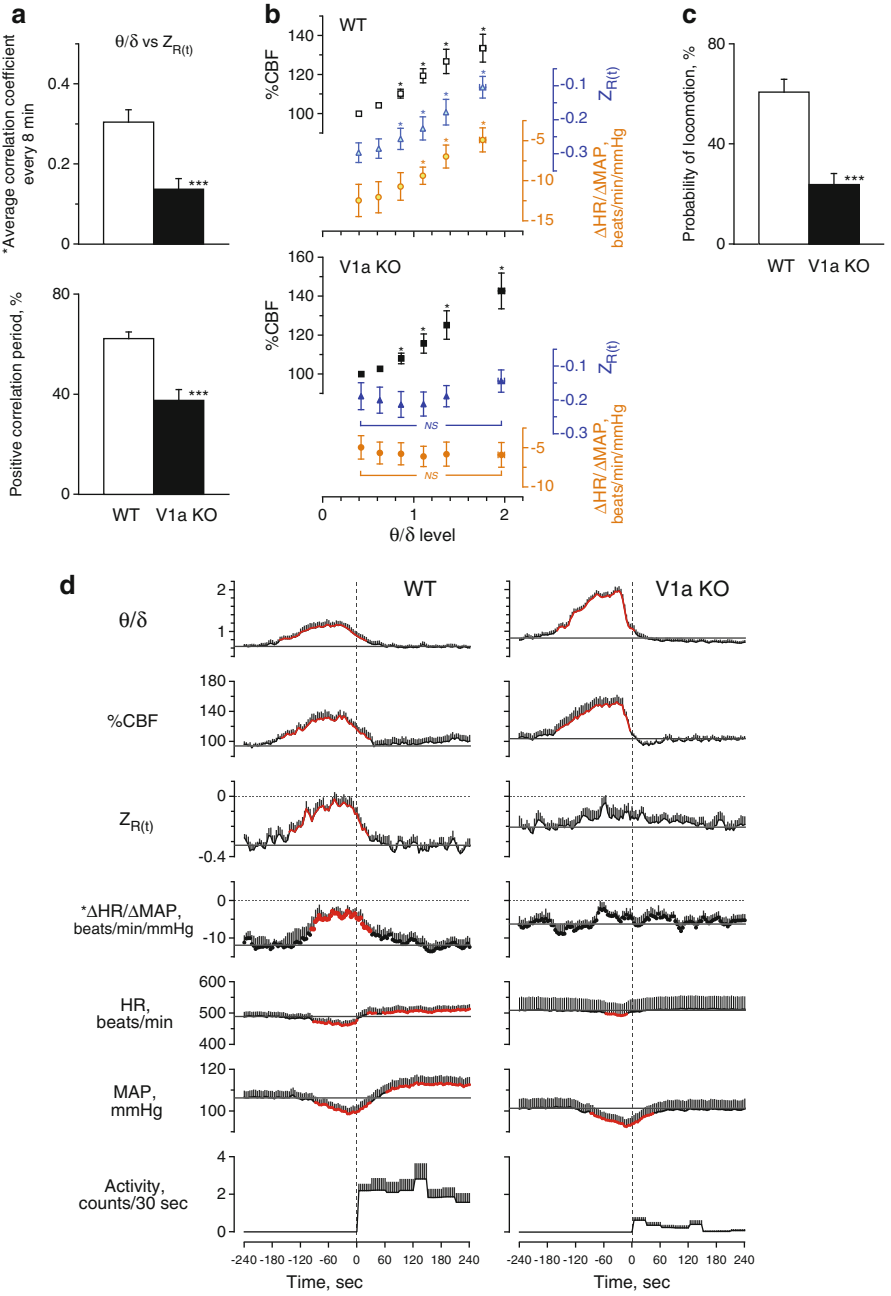

Fig. 20.5 θ/δ, CBF, $Z_{R(t)}$, and ΔHR/ΔMAP in free-moving wild-type control (WT) and V1a receptor knockout (V1a KO) mice. Means and SE bars are presented for 8 WT and 8 V1a KO mice (**a**) The average correlation coefficient between θ/δ and $Z_{R(t)}$ determined every 8 min during the resting period (*upper*). The positive correlation period between θ/δ and $Z_{R(t)}$, presented as % of the resting period (*lower*). Data during the resting period for ~520 min in each mouse were used for the

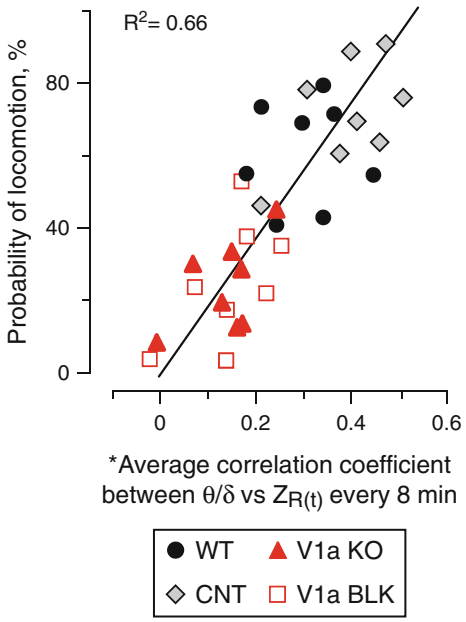

Fig. 20.6 Relationship between the average correlation coefficient of θ/δ with $Z_{R(t)}$ every 8 min vs. the probability of locomotion after an increase in θ/δ in wild-type control (WT) and V1a receptor knockout mice (V1a KO), and after local infusion of vehicle control (CNT) or a V1a receptor antagonist (V1a BLK) into the nucleus tractus solitarii of wild-type mice on individual values measured in 32 mice (8 mice×4 groups). *Values were averaged after z transformation. We found a significant and high correlation between them ($R^2=0.66$, $P<0.001$), indicating that the probability of locomotion after cerebral activation is reduced when linkage between cerebral activity and baroreflex control of HR is impaired (Figure from Masuki et al. 2013)

To better understand the relationship between the suppression of baroreflex control of HR after cerebral activation and the probability of voluntary locomotion, we plotted these data for WT, V1a KO, and V1a BLK mice. As shown in Fig. 20.6, the probability of voluntary locomotion was highly correlated with the suppression of baroreflex control of HR after cerebral activation. Thus, central V1a receptors might play an important role in facilitating voluntary locomotion after cerebral activation by suppressing the baroreflex control of HR.

20.7 Summary

We developed a uniform and broadly-available exercise training regimen by combining IWT and an information technology system to precisely track training achievements. Using this system, we demonstrated that the V1a receptor polymorphism altered both short- and long-term effects of IWT in middle-aged and older

people. Because animal models suggested that mice with impaired V1a receptor function had markedly lower probability of locomotion after cerebral activation, the blunted sensitivity of the V1a receptor might be involved in lower adherence to a long-term IWT program in humans. These findings might help the development of customized exercise programs that could increase the adherence of at-risk individuals.

Acknowledgements This research was supported by grants from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (18689009 and 21790224), from the Japan Society for the Promotion of Science (17209007, 21650168, and 24689014), from the Uehara Memorial Foundation, and from the Ministry of Health, Labor and Welfare of Japan (H17-Chohju-Ippan-016). This research was also supported by the Shinshu University Partnership Project between Shinshu University, Jukunen Taiikudaigaku Research Center, the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and Matsumoto City.

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Chapter 21
The Role of Physical Activity in the Prevention of Atherosclerosis: Focus on Oxidative Stress and Oxidised Low-Density Lipoprotein

Masashi Miyashita, Masaki Takahashi, and Jong-Hwan Park

Abstract Oxidative stress and inflammatory conditions are associated with an increased risk of atherosclerosis and cardiovascular disease. A large body of evidence supports the notion that higher intensity and/or longer duration exercise training can reduce many cardiovascular disease risk factors including oxidative stress and oxidised low-density lipoprotein. Although physical activity guidelines suggest that adults should engage in at least 150 min of physical activity each week, estimates in many countries suggest that many individuals do not exercise adequately as per guidelines. It is important to determine the minimum level of physical activity required to reduce the risks of cardiovascular disease and atherosclerosis. Thus, the authors conducted a series of investigations to examine the influence of daily physical activity or low-volume exercise training on cardiovascular disease risk factors including oxidative stress markers and oxidised low-density lipoprotein concentration in older adults. We demonstrate that daily physical activity and a low-volume walking program (<150 min/week) improved oxidative stress status in older adults. The implications of the research findings may encourage more people to incorporate a small amount of physical activity into their lives, and translate to prevention of cardiovascular disease and atherosclerosis in the long term.

Keywords Low-volume exercise training • Aging • Oxidative stress • Atherosclerosis

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_21

21.1 Introduction

Chronic oxidative stress is associated with the development of several diseases, such as atherosclerosis, cardiovascular disease, cancer, and diabetes (Strobel et al. 2011; Abramson et al. 2005; Patel et al. 2011). Oxidative stress in the vascular wall induces the oxidation of low-density lipoprotein (LDL) and the expression of inflammatory mediators (Kondo et al. 2009). These changes may be a fundamental causal pathway leading directly or indirectly to loss of elasticity in the arterial wall, and thus may contribute to the initiation of atherosclerosis. Oxidative stress and oxidised LDL increase as we age, and are associated with a decreased antioxidant capacity to limit and repair oxidative damage (Harman 1956; Sohal and Weindruch 1996; Ashok and Ali 1999). Oxidative stress is thought to be a key mechanism in the aging process, and we previously showed that the levels of oxidative stress markers and inflammation mediators are higher in middle-aged and older adults than in young adults (Takahashi et al. 2011). These processes are probably related to a sedentary lifestyle and an age-related decline in the production of endogenous antioxidants (Kondo et al. 2009; Frisard et al. 2007). It is well established that exercise training can cause a reduction in blood oxidative stress markers in human (Miyazaki et al. 2001; Fatouros et al. 2004). Therefore, it is important to ameliorate oxidative stress by increasing physical activity in older adults.

21.2 Daily Physical Activity and Oxidative Stress

Physical activity is one strategy that has been demonstrated to be effective in the reduction of atherosclerosis and cardiovascular disease risk factors including oxidative stress and oxidised LDL (Finaud et al. 2006; Vinagre et al. 2007; Ziegler et al. 2006), but little is known regarding the effect of daily physical activity on oxidative stress status and oxidised LDL concentrations in older adults. The authors have reported that daily physical activity may have a protective effect against oxidative stress by increasing total antioxidant capacity, especially in postmenopausal women (Takahashi et al. 2013b). Premenopausal women have a higher estrogen concentration than men do, and this may affect the oxidative stress defense system because of the antioxidant capacity of estrogen (Kendall and Eston 2002; Shwaery et al. 1997), although other studies have found that the level of lipid peroxidation and protein and DNA oxidation markers were lower in premenopausal women than in men (Nakano et al. 2003). Postmenopausal women do not experience the protective antioxidant benefits and anti-inflammatory effects of estrogen, and are therefore likely to show increased oxidative stress (Karolkiewicz et al. 2009). Our findings imply that daily physical activity is important to reduce the potential risk of atherosclerosis and cardiovascular disease in postmenopausal women Fig. 21.1.

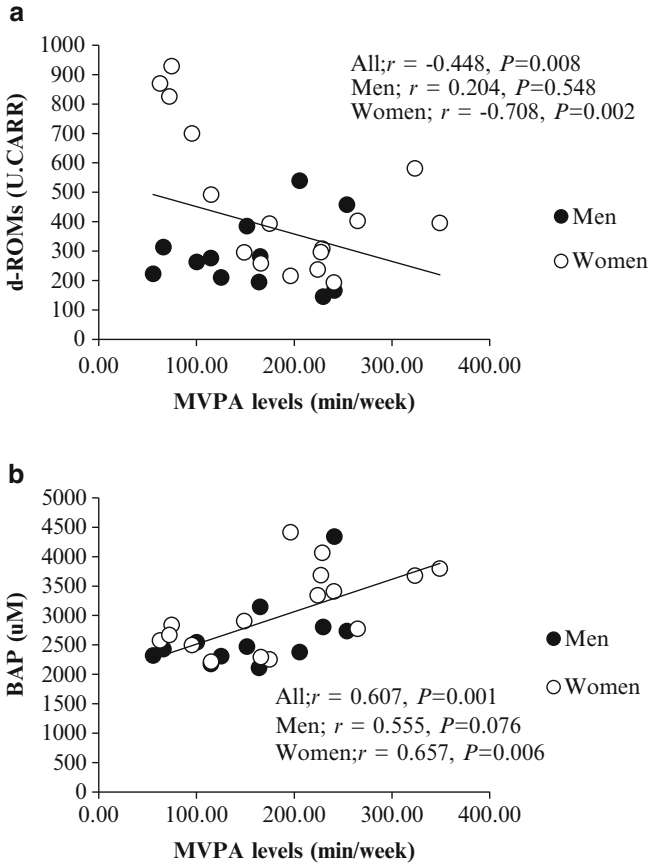

Fig. 21.1 The relationship across all participants between moderate-to-vigorous physical activity (MVPA) levels and fasting plasma concentrations of derivatives of reactive oxygen metabolites (d-ROMs) (**a**) and biological antioxidant potential (BAP) (**b**) in men (n = 12) and women (n = 17) (Masaki Takahashi et al. 2013b)

Notably, we have also reported that concentrations of fasting plasma oxidised LDL were negatively correlated with the amount of physical activity (Park et al. 2011). This finding indicates that regular physical activity may play a protective role in the oxidation of LDL in older adults. Most previous studies were conducted under laboratory conditions with participants exercising for a designated period of time as part of the experimental conditions (Ziegler et al. 2006; Vinagre et al. 2007). From the viewpoint of aging and especially postmenopausal aging, it is important to decrease risk factors of atherosclerosis and cardiovascular disease by increasing daily physical activity Fig. 21.2.

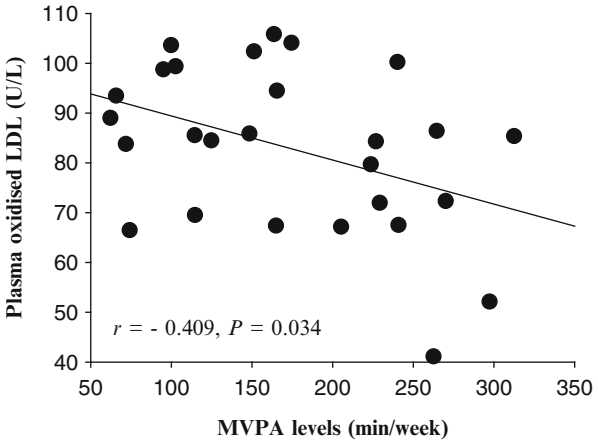

Fig. 21.2 The relationship between moderate-to-vigorous physical activity (MVPA) levels and fasting plasma oxidised low-density lipoprotein (LDL) concentrations in older adults (n = 27). (Jong-hwan Park et al. 2011)

21.3 Importance of Low-Volume Physical Activity

The American College of Sports Medicine (ACSM) and the World Health Organization's 2010 Global Recommendations on Physical Activity for Health showed that physical activity and public health recommendations for older adults (150 min of moderate-intensity aerobic activity and muscle-strengthening activities) can prevent general chronic disease (Haskell et al. 2007). Although meeting the current physical activity recommendation is associated with a reduced risk of metabolic syndrome, hypertension, and cardiovascular diseases, less than one-half of the adult population in East Asian countries, including Japan, failed to meet the public health guidelines for physical activity (Wai et al. 2008). Indeed, less than one-fourth of the older adult population (≥60 years) regularly engage in physical activity (defined as performing ≥30 min of physical activity at least 2 days each week, continuing for at least 1 year) in Japan (Ministry of Health, Labour and Welfare, Japan, 2011). In addition, a recent cohort study demonstrated that approximately 90 min/week (15 min/day) of physical activity is sufficient to reduce mortality and extend life expectancy among Taiwanese men and women (Wen et al. 2011). However, no studies to date have examined the effects of a low-volume exercise program on cardiovascular risk markers in older adults. Thus, determining the minimum level of physical activity required to reduce risks of atherosclerosis and cardiovascular disease could have public health implications.

21.4 Low-Volume Exercise Training and Oxidative Stress

Previous studies have focused on the influence of higher intensity, longer duration exercise training (≧150 min/week) on oxidative stress and antioxidant capacity (Finaud et al. 2006). These reports indicate that endurance training attenuates resting oxidative stress by increasing antioxidant capacity (Fatouros et al. 2004; Miyazaki et al. 2001). It remains unclear whether physical activity below the current minimum recommendation is effective for reducing resting oxidative stress and therefore lowering the risks of developing oxidative-stress-related disease in older adults. However, some epidemiological and exercise intervention studies have reported that low-intensity exercise reduces the risk of coronary heart disease (Jakicic et al. 2003; Nakanishi et al. 2000). We have reported that 12 weeks of a supervised walking program involving <150 min exercise per week improved oxidative stress in older adults (Takahashi et al. 2013a). Our current findings will be of interest to sedentary older adults because even low-volume exercise (100 min/week; average walking time, 49.4 ± 8.8 min per session) was effective in reducing resting oxidative stress in older adults. This is important if a recommendation for low-volume exercise is more likely to be followed by sedentary/working populations who have low fitness levels and/or limited time to commit to longer bouts of activity. In addition, walking is a free form of exercise that can be engaged in as part of everyday life and is achievable by virtually all older adults, even those who are not physically fit (Morris and Hardman 1997; Simpson et al. 2003). Some studies have shown that individuals are more likely to adhere to low-to-moderate intensity exercise than to vigorous-intensity exercise (Kahn et al. 2002; Rhodes et al. 2009; Rose and Parfitt 2008). Thus, our current findings might encourage more people to incorporate low intensity exercise and a small amount of physical activity into their daily life.

One possible mechanism to explain the reduction in the resting oxidative stress marker after exercise training may be increased enzymatic and non-enzymatic antioxidants in several tissues (Takahashi et al. 2013a). We have reported that low-volume exercise training caused elevated plasma antioxidant capacity in older adults. This elevation is transient, however, since detraining leads to a prompt elevation in oxidative stress. In fact, we have confirmed that exercise training cessation abolished these adaptations (unpublished data). Thus, exercise needs to be performed frequently for continued benefit Fig. 21.3.

21.5 Combined Exercise Training and Vitamin E Supplementation

A number of studies have investigated the effects of exercise training combined with vitamin E supplementation on oxidative stress markers (Jessup et al. 2003; Rokitzki et al. 1994). α-Tocopherol is biologically and chemically the most potent

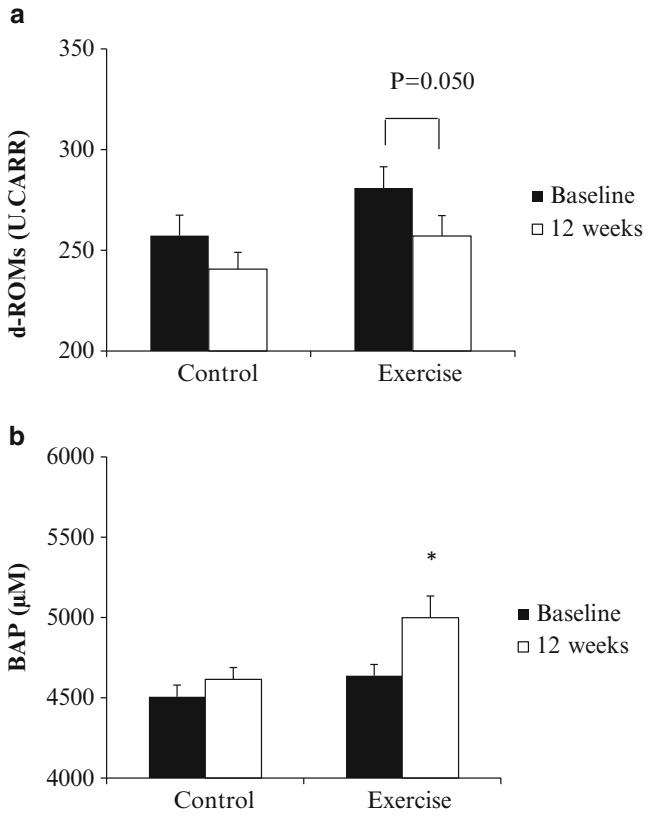

Fig. 21.3 Serum derivatives of reactive oxygen metabolites (d-ROMs) (**a**) and concentrations of biological antioxidant potential (BAP) (**b**) measured at baseline and 12 weeks in the control and exercise groups. Data represent mean ± SE values. * Significantly different from the baseline value in the same group ($P < 0.05$). (Masaki Takahashi et al. 2013a)

form of vitamin E, and it is a major free-radical-trapping antioxidant in the blood that influences LDL (Traber and Atkinson 2007; Meagher et al. 2001). Therefore, it is a more sought-after lipid-soluble antioxidant, compared to γ-tocopherol, retinal, and carotenoids. Notably, a growing body of evidence has reported the detrimental effects of antioxidant supplementation on health and on the performance benefits of exercise training (Gomez-Cabrera et al. 2008; Ristow et al. 2009). Although reactive oxygen species (ROS) have harmful functions, they are also essential to immune function and cell signaling (Thomas 2000). Some studies have suggested that high doses of antioxidants blunt the positive effects of exercise training and interfere with the roles of ROS, such as vasodilation and insulin signaling (Gomez-Cabrera et al. 2008; Strobel et al. 2011; Ristow et al. 2009). However, the effects of combined exercise training and recommended daily doses of vitamin E supplementation on oxidative stress status and oxidised LDL in older adults are unclear. Thus, the

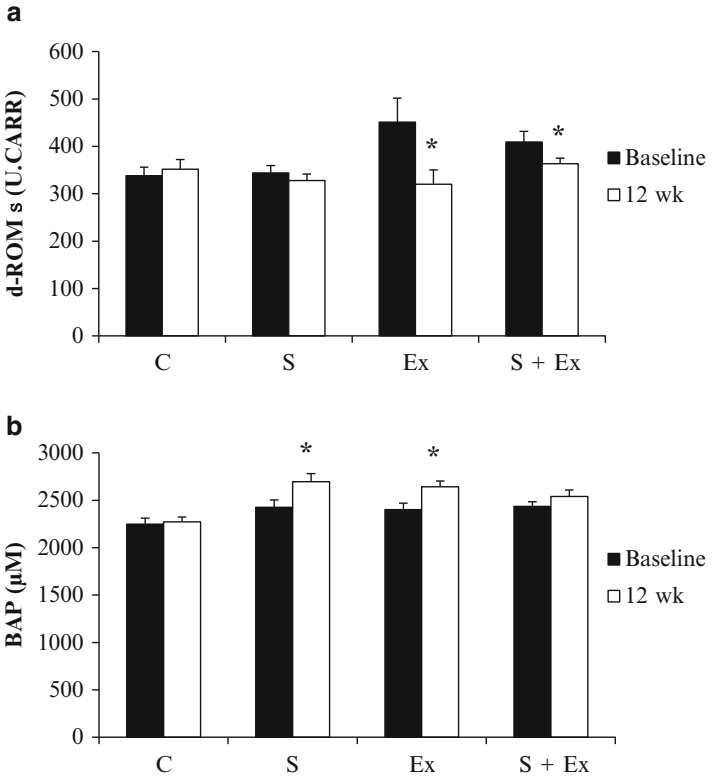

Fig. 21.4 Serum derivatives of reactive oxygen metabolites (d-ROMs) (**a**) and concentrations of biological antioxidant potential (BAP) (**b**) measured at baseline and 12 weeks in the control (C), vitamin E (S), exercise (Ex), and vitamin E and exercise (S + Ex) groups. Data are presented as means ± SE. *Significantly different from the baseline value in the same group ($P < 0.05$). (Masaki Takahashi et al. 2013c)

authors examined the effects of a 12-week low-volume walking program, below the current recommended amount of exercise (<150 min/week), plus vitamin E supplementation on oxidative stress markers and oxidised LDL in older adults (Takahashi et al. 2013c; Park et al. 2013). The evidence from our studies is consistent, and demonstrates that a 12-week low-volume walking program at an intensity below the current recommended amount of exercise for older adults (<150 min/week) is effective for lowering serum oxidative stress markers, and elevating enzymatic and non-enzymatic antioxidant capacities in older adults. In addition, a 12-week regimen of vitamin E supplementation decreases the concentrations of serum oxidative stress markers and increases serum or plasma enzymatic and non-enzymatic antioxidant capacity. However, our studies indicate that the effects of this exercise regimen plus vitamin E supplementation showed no additive effects on the improvement of oxidative stress status in older adults Fig. 21.4.

21.6 Summary and Conclusions

Elevated oxidative stress and oxidised LDL are associated with the development of several diseases, such as atherosclerosis, cardiovascular disease, cancer, and diabetes (Abramson et al. 2005; Patel et al. 2011; Itabe and Ueda 2007). Physical activity is one strategy for reducing oxidative stress and oxidised LDL (Finaud et al. 2006; Vinagre et al. 2007; Ziegler et al. 2006). On the other hand, it is important to note that it is difficult to achieve compliance with recommendations of moderate-to-high-intensity, moderate-to-high-volume physical activity in older adults. In addition, the optimal amount of exercise for achieving health benefits is still unknown, and may be lower than the currently recommended level of 150 min/week of moderate-intensity exercise. To develop effective physical activity strategies to reduce atherosclerosis and cardiovascular disease risks in older adults, it is important to further identify the effects of lower amounts of daily moderate-intensity physical activity (such as walking) on markers of cardiovascular disease risks. We have reported, in a cross-sectional study, that daily physical activity plays a role in preventing or alleviating oxidative stress and oxidation of LDL. Moreover, our data demonstrated that low-volume physical activity, below the current recommended amount of exercise (<150 min/week), may be effective for reducing oxidative stress in older adults, indicating that a small volume of physical activity could have important public health implications including the prevention of atherosclerosis and cardiovascular disease.

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Chapter 22
Association Between Exercise and Diet on Maintaining Bone Health in Postmenopausal Women and Female Athletes

Yoshiko Ishimi, Kaoru Yanaka, and Mitsuru Higuchi

Abstract Prevention is the most important measure that can be taken to avoid osteoporosis, because bone mass, once it is lost, cannot be recovered. Both men and women reach their maximum bone mass when they are in their 20s and 30s; bone mass is maintained or may even increase slightly as people reach their 40s, and gradually decreases thereafter. In particular, bone mass dramatically decreases in postmenopausal women because of a decrease in serum estrogen level. Bone mass is influenced by genetic and environmental factors such as mechanical loading, nutrition, and lifestyle, along with gender, age, and metabolic factors. Among these factors, mechanical loading, i.e. exercise, and nutrition seem to be important in maintaining bone health, and lifestyle choices, including following a regular exercise program and consuming a diet rich in minerals and vitamins, when maintained throughout life, can be expected to preserve bone health. In contrast, excessive exercise with energy restriction induces osteoporosis in female athletes. This section will discuss the importance of appropriate exercise and diet on bone health in women, and some insights gained from studies using a rat model.

Keywords Exercise • Diet • Postmenopausal women • Female athlete • Bone health • Osteoporosis

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_22

22.1 Introduction

Prevention of osteoporosis is a key health issue in Japan, where the number of people with osteoporosis was estimated to be approximately 12.8 million in 2011. Bone mass reaches a maximum when both men and women are 20–30 years old; this level is maintained or slightly increased as people move into their 40s, after which it gradually decreases (Fig. 22.1). Bone mass dramatically decreases in postmenopausal women and, as a result, women with osteoporosis outnumber men with the condition by a ratio of 3 to 1. The main cause of osteoporosis is thought to be estrogen deficiency; however, both routine exercise and a diet rich in minerals and vitamins throughout life are important in preventing osteoporosis.

In contrast, in some athletic women, excessive exercise training may be accompanied by disordered eating, amenorrhea, and osteoporosis, which together constitute a syndrome known as the "female athlete triad" (FAT). This syndrome was first described in 1992 (Nattiv et al. 1994), and the American College of Sports Medicine position stand on the subject of FAT was published in 1997 (Otis et al. 1997). When fourth replacement the position stand on the triad, osteoporosis was specified by the World Health Organization (WHO) (Kanis et al. 1994) as a criteria for diagnosing FAT in female athletes. The disorders that constitute FAT, whether alone or in combination, pose significant health risks to physically-active girls and women. The interrelated conditions and the range from healthy to unhealthy conditions among athletes were described as 3 interrelated spectra (Otis et al. 1997). The pathophysiological mechanisms underlying the loss of bone mass in female athletes are decreased energy availability and hypothalamic-controlled amenorrhea

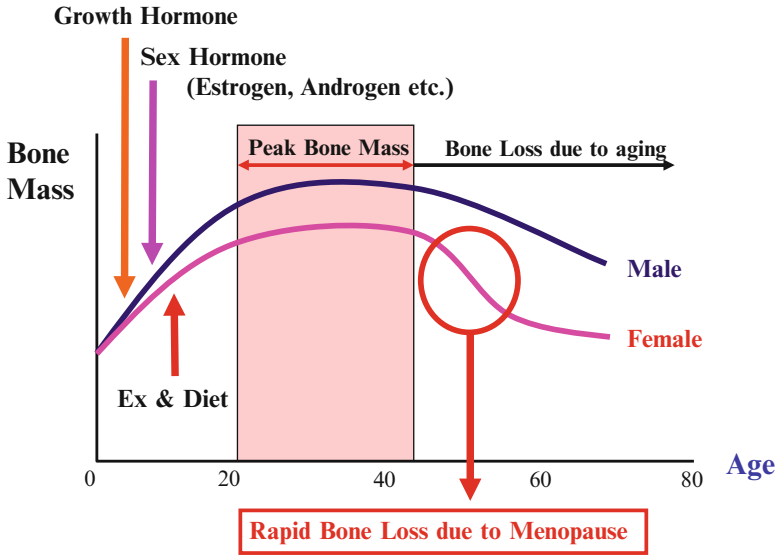

Fig. 22.1 Relationship between aging and bone mass

(Lambrinoudaki and Papadimitriou 2010). The importance of adequate energy intake for bone metabolism is well established. Energy restriction in humans and animals has been reported to induce bone loss that accompanies body weight reduction (Cifuentes et al. 2004; Colman et al. 2011; Hawkins et al. 2010; Ricci et al. 2001; Talbott et al. 1998). Several mechanisms have been proposed to explain the bone loss caused by low energy intake, including a reduced mechanical load, altered hormone levels, and reduced intake of effective bone-forming nutrients such as calcium and vitamin D. In addition, reduced energy intake with or without excessive exercise training is strongly associated with reproductive dysfunction (Caston et al. 1995; Chatterton et al. 1990; Loucks 1994; Loucks and Thuma 2003; Loucks 2006; Williams et al. 1995, 2001a, b). It has been reported that exercise training can delay the normal process of ovulation or cause changes in gonadotropin secretion from the anterior pituitary (Caston et al. 1995; Chatterton et al. 1990; Williams et al. 1995, 2001a, b). Williams et al. (2001b) provided strong evidence that energy availability plays an important role in the development of exercise-induced amenorrhea and reported that the exercise-induced suppression of reproductive functions could be reversed by supplemental energy intake.

Exercise has a positive effect on bone metabolism, but not if an energy shortage exists. DiMarco et al. (2007) tried to establish an animal model of FAT to examine the long-term effects of energy restriction on estrous cycling, bone mineral content (BMC), and serum estradiol and leptin levels in voluntarily wheel-running female rats. They reported that rats on a restricted diet exhibited a lower concentration of serum estradiol, leptin, and femoral BMC than the ad libitum-fed controls. However, the bone mineral density (BMD) of the femur was not affected. Thus, the aim of the present study was to establish an animal model of osteoporosis for female athletes that included altered reproductive hormone levels. The study was designed to investigate the effects of long-term energy restriction with voluntary wheel running on the BMD and assess the levels of 17β-estradiol (E_2) and luteinizing hormone (LH) in the plasma of female rats with intact ovaries. In addition, we analyzed the distal femur to evaluate effects on bone morphology.

In this review, the scientific evidence focusing on osteoporosis prevention in postmenopausal women and the establishment of an animal model of female athlete osteoporosis will be discussed.

22.2 Osteoporosis

The National Institutes of Health (NIH) Consensus Conference adopted the definition of osteoporosis as a skeletal disorder that is characterized by compromised bone strength leading to a predisposition for and an increased risk of fracture (Conference Report 2004). On the basis of this definition, Yoshimura et al. (Yoshimura et al. 2009) estimated that the prevalence of osteoporosis in Japan reached 12.8 million people in 2011. The prevalence rate increases with age, and the rate is higher in women than in men because of female estrogen deficiencies later in life (Riggs et al. 2002).

In skeletal tissues, bone formation and resorption both play a role in bone remodeling. In postmenopausal bone tissue, high bone turnover is observed because the bone resorption rate is higher than the bone formation rate, thereby causing a decrease in bone mass. This phenomenon is attributable to estrogen deficiency; estrogen protects bone resorption by osteoclast.

22.3 Effect of Exercise on Bone Mass

It has been reported that bone loss occurs in patients under conditions of long-term bed rest and in astronauts in a zero-gravity environment. Therefore, mechanical stress is an important factor in maintaining healthy bone mass. Additionally, many cohort studies and meta-analyses have shown that the risk of bone fractures decreases as the amount of physical activity increases (Moayyeri 2008). This effect is probably age-dependent. However, appropriate physical activity during the growing stages is very important for osteoporosis prevention because this results in a higher peak bone mass. In addition, it has been reported that mechanical stress acts to oppose bone loss in postmenopausal women (Wu et al. 2000). This evidence shows that mechanical stress is an important factor in maintaining adequate bone mass. Table 22.1

Table 22.1 Intervention studies of exercise effects on bone mineral density in postmenopausal women (Orimo 2011)

Exercise	Strength	Number of times	Frequency	Term	Result	Evidence level[a]
Heel up (at home)		50 times	Every day + 1/week	1 year	○	II
Weight-bearing exercise (Walking etc.), Aerobics, Stretching		60 min	3 times/week	1 year	△	IV
Resistance training	RM	8 × 3 sets or 20 × 3 sets		1 year	△	II
Hip flection	5 kg	60 times		2 year	○	III
Aerobics and step exercise			2 times/week	1.5, 8 month personal	○	II
Resistance training of back muscles	30 % of 1RM	10 × 3 sets	5 times/week	2 year	After 10 year ○	II
Jump aerobics and step exercise		45 min	3 times/week	1 year	×	II
Tai Chi		45 min	5 times/week	1 year	○	II

RM Repetition maximum, ○: effective, △: partially effective, ×: not effective
[a]Evidence level I: Meta analysis/Systematic review, II: more than one randomized control trial, III: not a randomized control trial, IV: observational study

summarizes the results from interventional studies focusing on the effect of exercise on postmenopausal women. Seven of the 8 trials reported demonstrated a positive effect of regular exercise on bone mass in postmenopausal women (Orimo 2011).

Recker et al. (2004) reported that bone turnover was 2 and 3 times faster at 1 and 13 years, respectively, after menopause than in the pre-menopausal state. For this reason, some have speculated that the effectiveness of exercise on bone mass in menopausal women may depend on the bone turnover rate. Moderate exercise is recommended for middle-aged and elderly people because it is beneficial for maintaining bone mass but also carries a lower risk of injury than higher-intensity activities. Low-intensity exercises, such as walking, are appropriate and effective in older populations. Swimming is also a good exercise choice, and has recently been shown to be beneficial for maintaining bone mass in middle aged women (Wu et al. 2000). Conversely, excessive exercise may lower estrogen levels, which, in turn, can lead to low mineral densities in young female athletes (Rauh et al. 2010). Because stopping exercise also terminates its benefits on bone mass, it is desirable to continue regular exercise routines for as long as possible.

22.4 Effects of Nutrition on Bone Mass

Skeletal tissue consists of bone matrix protein (e.g., collagen) and minerals (e.g., calcium and phosphorus). Therefore, it is obvious that calcium is an important nutrient for the prevention of osteoporosis. Calcium accounts for 1–2 % of the total body weight, and more than 99 % of the body's calcium is found in the skeletal tissue and in the teeth. The recommended daily allowance (RDA) of calcium, based on the estimated average requirement in the Dietary Reference Intakes (DRIs) for Japanese (2015), is 800 mg/day for adult men and 650 mg/day for adult women (Table 22.2) (Ministry of Health, Labour and Welfare in Japan 2014). Although some reports have shown no relationship between calcium intake and BMD in postmenopausal women (Sasaki 2002), it is widely accepted that sufficient calcium intake throughout life leads to better bone health and prevents osteoporosis.

Vitamin D stimulates calcium absorption in the intestine and induces calcium re-absorption in the distal tubules of the kidneys. It has also been reported that a

Table 22.2 Recommended Dietary Allowance for calcium from DRIs for Japanese (2015) (Ministry of Health, Labour and Welfare in Japan 2014)

Age	Male (mg/d)	Female (mg/d)
12 ~ 14	1,000	800
15 ~ 17	800	650
18 ~ 29	800	650
30 ~ 49	650	650
50 ~ 69	700	650
≥70	700	650

DRIs Dietary reference intakes

Table 22.3 Recommended intake of calcium and vitamins from the Guideline for Prevention and Treatment of Osteoporosis 2011 (Orimo 2011)

Nutrients	Intake	Source
Calcium	700 ~ 800 mg/d	Dairy products, soy, fish etc.[a]
Vitamin D	400 ~ 800 Unit/d (10 ~ 20 μg/d)	Fish, mushrooms
Vitamin K	250 ~ 300 μg/d	Fermented soybeans, vegetables
Protein (reference values)	Female 50 g/d, Male 60 g/d	Meat, fish, eggs, beans

[a]Care should be taken when calcium supplement or calcium medication are provided

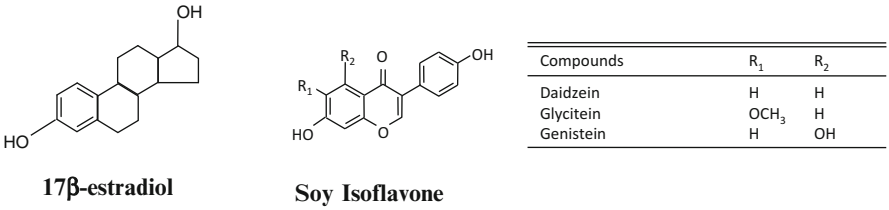

Fig. 22.2 Structures of estradiol and soy isoflavones

combination of calcium and vitamin D supplementation increases BMD in postmenopausal women (Tang et al. 2007; Shea et al. 2002). Vitamin K also plays an important role in bone formation. It stimulates γ-carboxylation of osteocalcin, which leads to enhanced bone mineralization. Thus, adequate vitamin and mineral intake is important for the preservation of bone health. The recommended intake values of nutrients related to bone metabolism, as reported by the Japan Osteoporosis Society, are shown in Table 22.3 (Orimo 2011). Protein also plays an important role in preserving bone quality. Smoking and excessive intake of sodium, phosphorus, caffeine, and alcohol are detrimental to bone health and should be avoided.

22.5 Effects of Functional Constituents in Food on Bone Health

The chemical structure of soybean isoflavones is similar to that of estrogen, and isoflavones have a weak affinity for estrogen receptors. This suggests that isoflavones may exhibit estrogenic actions in various tissues (Fig. 22.2) (Kuiper et al. 1998), and they have received considerable attention because of their potential to prevent bone loss in postmenopausal women, as well as in osteoporotic animal models (Wu et al. 2006; Ishimi et al. 1999). Although there have been several randomized controlled trials that demonstrated no relationship between isoflavone intake and bone mass in Caucasian women with high calcium and vitamin D intake, recent meta-analyses have shown beneficial effects of isoflavone on postmenopausal bone metabolism (Taku et al. 2010). The Consumer Affairs Agency of the Japanese government has declared isoflavones to be a principle ingredient on the list of Foods

for Specified Health Uses (FOSHU). Milk Basic Proteins (MBPs) are also on the FOSHU list because they increase BMD by stimulating bone formation, while suppressing bone resorption in healthy men and women (Aoe et al. 2001).

22.6 Cooperative Effects of Exercise and Diet

There is a shortage in calcium intake by Japanese individuals, especially by adult men and women. Elderly people, in particular, require more vitamins that play an important role in bone metabolism, such as vitamins D and K. Since the incidence of osteoporosis is increasing each year, and fractures are the third-highest cause for becoming bedridden, the maintenance of healthy bones is an important factor in extending a person's healthy lifespan. Therefore, we examined the synergistic effects of exercise and soy isoflavones, the latter of which have shown weak estrogenic effects on bone metabolism in postmenopausal Japanese women.

We assigned 136 subjects (average age, 55 years), who had undergone menopause within 5 years of natural menopause, to 4 groups: placebo only; placebo and walking (3 times/week at 6 km/h); isoflavone dietary supplementation only (75 mg conjugates/day, equivalent to 47 mg of aglycone, Fujicco Co. Ltd., Kobe, Japan); and isoflavone dietary supplementation plus walking. BMD of the lumbar spine, left hip, and whole body were assessed by dual-energy X-ray absorptiometry (DXA), using the Hologic QDR-4500 (Hologic Inc., Waltham, MA), at baseline and at 1 year. There was no difference in height, weight, body mass index (BMI), and baseline physical activity among the 4 groups. This was also true 1 year after interventions began. Average daily intake of isoflavones from soy foods was approximately 28 mg per day in all 4 groups both at baseline and after 1 year. There were no significant differences in daily intake of isoflavones and other nutrients from the regular diet among the groups at baseline, or between baseline and 1 year in each group. With regard to the % change in BMD, walking was shown to have a significant effect on preservation of BMD in the hip region after 1 year (Wu et al. 2006). Interestingly, both interventions showed significant effects on the preservation of BMD in Ward's triangle of the hip after 1 year (Fig. 22.3).

As an additional benefit, the walking groups showed a significant reduction in body fat percentage in the whole body, trunk region, and legs between 3 and 12 months. Serum high density lipoprotein- (HDL)-cholesterol concentration also significantly increased from baseline by 7.78 % and 8.78 % in the walking group and the isoflavone-plus-walking group, respectively. These results suggest that walking exercise prevents both increased body fat and bone loss in postmenopausal women.

The Exercise and Physical Activity Guide for Health Promotion 2013, which is provided by The Ministry of Health, Labor and Welfare in Japan, recommends 4 metabolic effects of training (METs)·h/week of exercise to prevent noncommunicable diseases (Ministry of Health, Labour and Welfare of Japan 2013). In our study, it was found that 9 METs·h/week (4 METs×3/4 h×3 times/week) are necessary for prevention of fat mass increases and bone mass decreases in postmenopausal Japanese women.

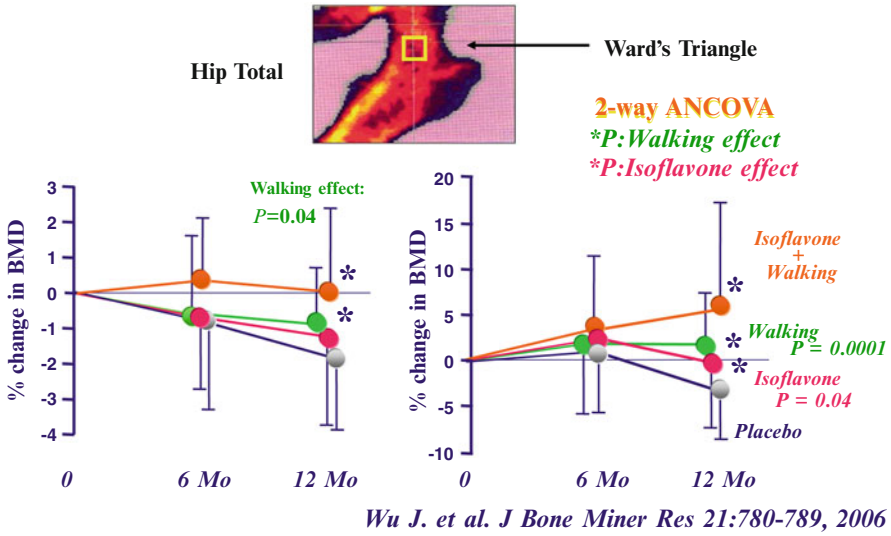

Fig. 22.3 Cooperative effects of exercise and isoflavone intake on bone mineral density in postmenopausal Japanese women (From Wu et al. (2006))

22.7 Establishing an Animal Model for Female Athletes with Osteoporosis

Female athlete triad (FAT) is a syndrome that leads to disordered eating, amenorrhea, and osteoporosis. The pathophysiologic mechanisms that lead to reduced bone mass in female athletes seem to be low energy and functional hypothalamic amenorrhea. The aim of the study was to establish an animal model of FAT which reproduces the osteoporosis seen in female athletes in order to clarify the detailed mechanism of FAT.

22.7.1 Materials and Methods

Experimental Protocol

Fourteen female 8-week-old Sprague Dawley rats were randomly divided into 2 groups: a running group with free access to running wheels all the time (RUN group, n = 8) and a sedentary group (SED group, n = 6). Food and water were available to all rats during the initial 10-week baseline period. After 10 weeks, when rats were 127 days old, the RUN rats were randomly divided into 2 sub-groups, the running ad libitum-fed group (RC group, n = 4) and the running restricted-fed group (RR group, n = 4). The baseline dietary intake of the RR group was calculated by

measuring the average food intake of individual rats for 2 weeks before the start of the restriction period. From 17 weeks of age, the rats in the RR group were fed 70 % of their baseline food intake. The rats were fed an AIN-93G and AIN-93 M diet with corn oil during the baseline period and restriction period, respectively (Reeves et al. 1993). Body weight and food intake were measured every third or fourth day during the initial baseline period, and every second day during the restriction period. Running distance was recorded 5 times per week. After 23 weeks, estrous cycles were monitored by daily vaginal smear patterns obtained for 2 weeks before dissection. Vaginal smear patterns were recorded. Blood was collected by exsanguination (bleeding out) via cardiac puncture. Plasma samples were collected by centrifugation and stored at −80 °C until the assay was performed. The right femur was used for BMD measurements, and the left femur for histomorphometric analysis. All procedures were performed in accordance with the Guidelines for the Care and Use of Laboratory Animals of National Institute of Health and Nutrition in Japan

Bone Analysis

During the study, the BMD of the right femur of each rat was measured by dual-energy X-ray absorptiometry (DXA) using a PIXImus densitometer (CE Lunar, Madison, WI, USA). At the end of the study, the BMD of the excised right femur of each rat was measured by DXA using a densitometer adapted for animal research (model DCS-600R; Aloka, Tokyo, Japan). BMD was calculated according to the BMC of the measured area. For analyzing femoral BMD and BMC the femurs were divided into three regions, roximal femur, middle femur, and distal femur, to assess the regional differences in the femurs.

Histomorphometry of Bone

The left femur of each rat was fixed and the undecalcified bone was embedded in methyl methacrylate. The following parameters were evaluated with a semiautomatic image analyzing system linked to a light microscope: bone volume/total volume (BV/TV), trabecular number (Tb.N), trabecular separation (Tb.Sp), osteoblast number/tissue volume (N.Ob/TV), osteoclast number/tissue volume (N.Oc/TV) osteoid volume/osteoid surface (OV/OS), and osteoid thickness (O.Th). Histomorphometric analyses were performed by staff at the Ito Bone Histomorphometry Institute (Niigata, Japan).

Plasma Biomarkers

Concentrations of E_2, LH, and osteocalcin were measured using an enzyme-linked immunosorbent assay (ELISA) kit.

Statistical Analyses

Data are presented as mean ± standard deviation (SD). The effects of energy restriction on body weight and food intake were analyzed by a one-way repeated-measures analysis of variance (ANOVA) at individual time points. Running distance was analyzed using the Student's *t*-test to determine the effects of ad libitum and restricted food intake on wheel running volume every 10 days throughout the experimental periods. The femoral BMD was analyzed by one-way ANOVA adjusted for animal body weight. The femoral BMC, all parameters of histomorphometric analysis, and plasma biochemical results were analyzed using one-way ANOVA with Scheffe's post hoc testing. All analyses were conducted using StatView software (StatView 4.0, Abacus Concepts).

22.7.2 Results

Body Weight, Food Intake, and Running Distance

Figure 22.4a demonstrates the longitudinal change in body weight. Body weight gradually increased in all groups until the rats were 130 days old. The body weight was significantly higher in the RC group than in the SED group when the rats were 10, 11, 14, 17, and 19 weeks old ($p<0.05$). In the baseline period, body weight was significantly higher in the RR group than in the SED group at 10 and 11 weeks of age ($p<0.05$). During the restricted period, at 20–32 weeks of age, body weight was significantly lower in the RR group than in the RC and SED groups ($p<0.05$).

Food intake was significantly higher in the RC group than in the SED group at 10–17 weeks of age during the baseline period ($p<0.05$) (Fig. 22.4b). Food intake during the baseline period was significantly higher in the RR group than in the SED group at 11, 14, and 16 weeks of age. During the restricted period, food intake was significantly lower in the RR group than in the other 2 groups ($p<0.05$), and it was significantly higher in the RC group than in the SED group after the baseline period ($p<0.05$).

Running Distance

Figure 22.5 shows the running distance calculated over a period of 10 days in each of the running groups throughout the experimental periods. The running distance was significantly shorter in the RR group than in the RC group at 110–119 days of age ($p<0.05$). No significant differences were observed between the RR and RC groups in the experimental period.

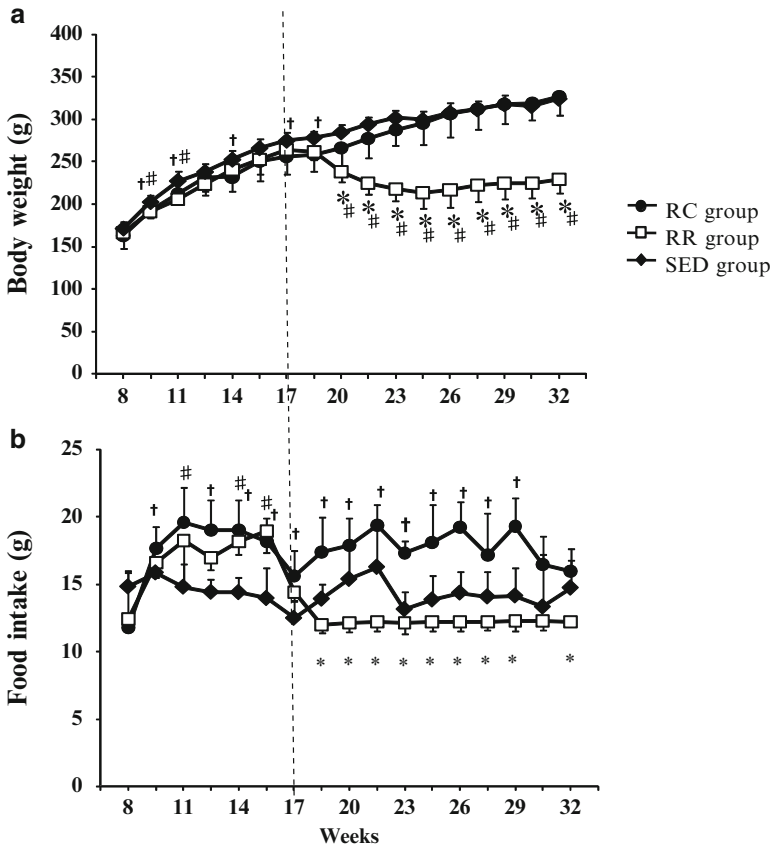

Fig. 22.4 Time course of change in (**a**) body weight, and (**b**) food intake during the experimental period in the wheel-running ad libitum-fed (RC) group, wheel-running restricted-fed (RR) group, and sedentary control (SED) group of rats

Femoral BMD

Figure 22.6 shows the time course of whole femur BMD change in SED, RC, and RR groups. The BMD of the RR group was significantly different from those of the SED and RC groups at 32 weeks. The effects of energy restriction along with voluntary wheel running on the femoral BMD are shown in Fig. 22.7. After adjustment for individual animal body weight, the BMDs of the resected whole femur and its proximal regions were significantly lower in the RR group than in the RC and SED groups ($p < 0.05$). The BMDs of the middle and distal regions in the RR group were significantly lower than in the SED group ($p < 0.05$). No differences were observed between the RC and SED groups in the whole BMD or in the BMD of the various regions of the femur. There were no differences in bone area among the groups for the three divided regions of the femur (data not shown).

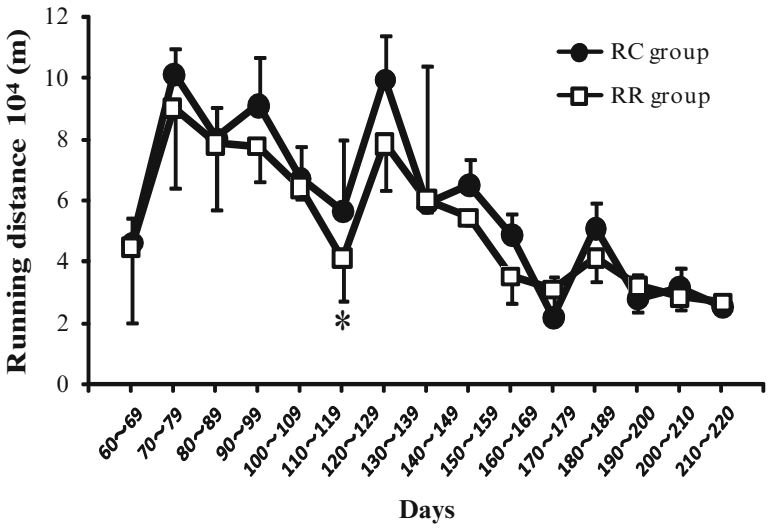

Fig. 22.5 Running distance for rats included in the wheel running group. (●) Running, ad libitum-fed (RC) and (□) running, restricted-fed (RR) groups throughout the duration of the experiment

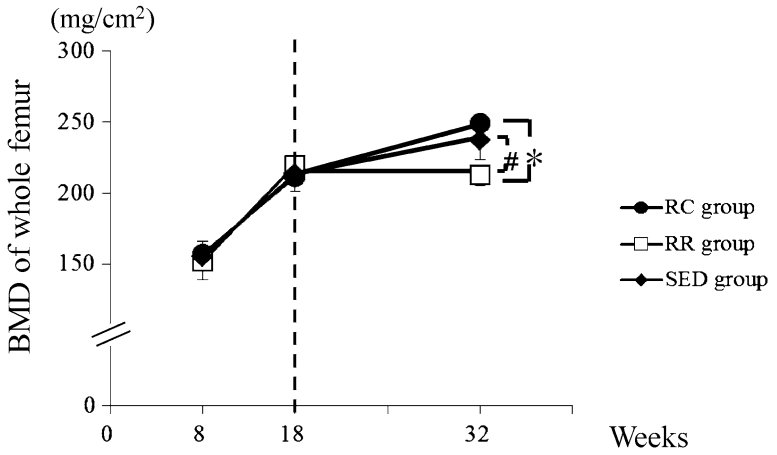

Fig. 22.6 Time course of change in femur bone mineral density. (●) Wheel-running, ad libitum-fed (RC), (□) wheel-running, restricted-fed (RR), and (◆) sedentary control (SED) groups of rats. #Significantly different from SED group, * Significantly different from RC group. $P<0.05$, by one-way analysis of variance (ANOVA)

Femoral BMC

Figure 22.8 shows the effects of energy restriction along with voluntary wheel running on the femoral BMC. The results are consistent with the results of weight-adjusted BMD (Fig. 22.7).

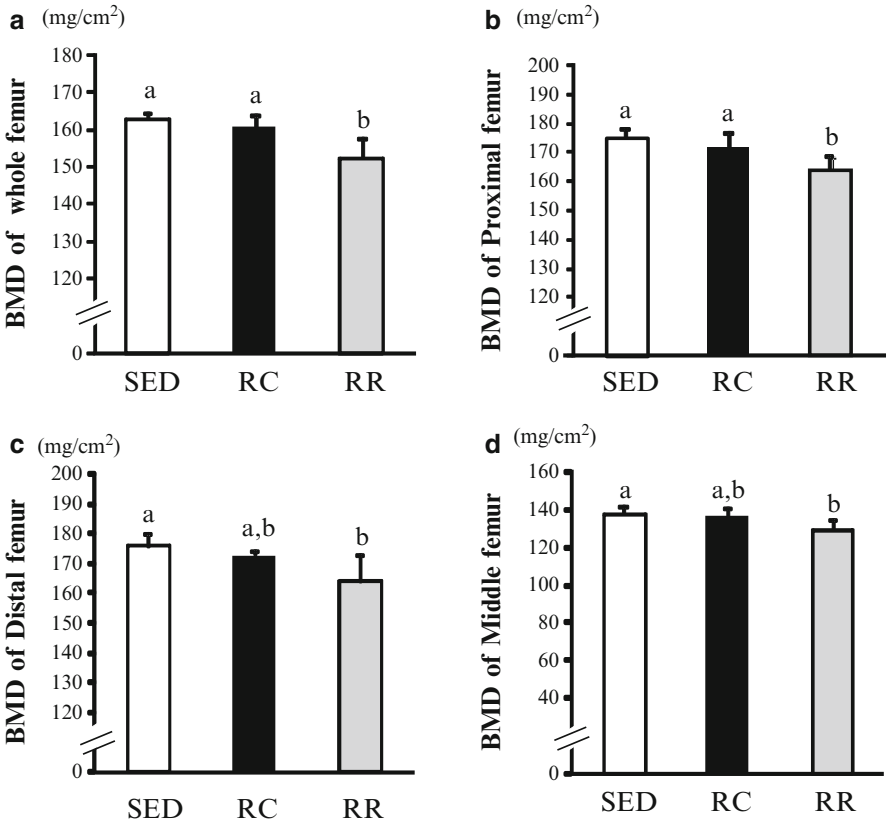

Fig. 22.7 Effects of energy restriction with voluntary exercise on bone mineral density of the femur: (**a**) whole femur, (**b**) proximal femur, (**c**) middle femur, and (**d**) distal femur

Histomorphometry of the Femur

The effects of energy restriction with voluntary wheel running on the structure of the distal region of the femur are shown in Table 22.4. BV/TV and Tb.N in the RR group were significantly lower than those in the SED group ($p<0.05$). Tb.Sp in the RR group was significantly higher than that in the SED group ($p<0.05$). There were no differences in BV/TV, Tb.N, and Tb.Sp between the RC and RR groups. N.Oc/TV in the RR group was significantly lower than in the RC and SED groups ($p<0.05$), whereas N.Ob/TV did not differ among the groups. OV/OS and O.Th. were significantly higher in the RR group than in the SED group ($p<0.05$). No differences in the OV/OS or O.Th. were observed between the RC and SED groups. Sections of distal femur trabecular bone are shown in Fig. 22.9 (×100). The bone volume in the RR group seems to be low compared with that of the SED group.

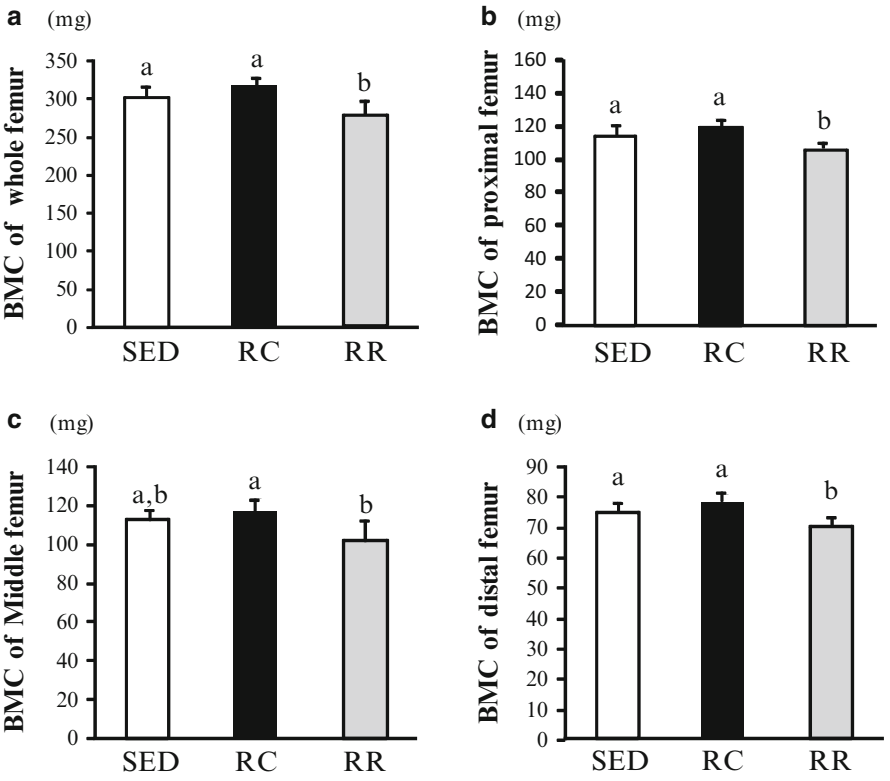

Fig. 22.8 Effects of energy restriction with voluntary exercise on bone mineral content of the femur: (**a**) whole femur, (**b**) proximal femur, (**c**) middle femur, and (**d**) distal femur

Table 22.4 Histomorphometry of trabecular bone in distal femur (Yanaka et al. 2012)

Bone variable	SED	RC	RR	*P* value
BV/TV, %	24.9 ± 2.3^{a}	20.6 ± 4.7^{ab}	13.9 ± 8.3^{b}	< 0.05
Tb.N, N/mm	4.5 ± 0.6^{a}	3.9 ± 1.0^{ab}	2.5 ± 1.0^{b}	< 0.05
Tb.Sp, μm	169.8 ± 28.2^{b}	220.2 ± 80.8^{ab}	399.2 ± 202.4^{a}	< 0.05
N.Oc/TV, N/mm^2	50.1 ± 11.6^{a}	34.8 ± 12.4^{a}	18.8 ± 2.9^{b}	< 0.05
N.Ob/TV, N/mm^2	38.2 ± 5.7	38.3 ± 22.2	60.2 ± 45.3	NS
OV/OS, μ/m	2.8 ± 0.1^{b}	$3.0. \pm 0.3^{ab}$	$3.3. \pm 0.4^{a}$	< 0.05
O.Th, μ/m	2.7 ± 0.1^{b}	$3.0. \pm 0.3^{ab}$	3.2 ± 0.4^{a}	< 0.05

The means without common letter are different at $P < 0.05$ by 1-way ANOVA
BV/TV bone volume/total volume, *Tb.N* trabecular number, *Tb.Sp* trabecular separation, *N.Oc/TV* osteoclast number/tissue volume, *N.Ob/TV* osteoblast number/tissue volume, *OV/OS* osteoid volume/osteoid surface, *O.Th* osteoid thickness

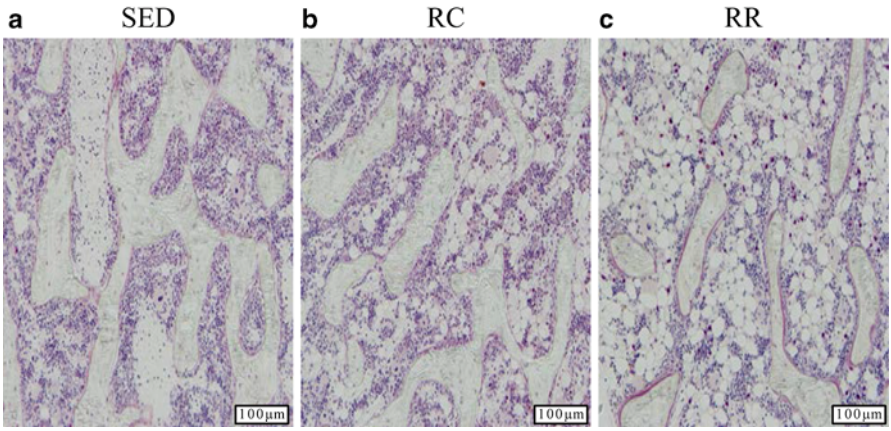

Fig. 22.9 Photograph of a femur from a rat in each group: (**a**) SED group, (**b**) RC group, (**c**) RR group. The RR group showed lower trabecular numbers and significantly increased osteoid surface area compared to the SED group. Scale bar = 100 μm

Table 22.5 Plasma concentration of E_2, LH, and OC in rats (Yanaka et al. 2012)

	SED	RC	RR	*p* value
E_2 (pg/mL)	46.3 ± 10.3^a	33.9 ± 6.3	33.6 ± 8.6^b	< 0.05
LH (ng/mL)	2.4 ± 1.4^a	2.2 ± 1.2^a	0.5 ± 0.4^b	< 0.05
OC (ng/mL)	57.1 ± 9.2	58.4 ± 3.0	55.7 ± 8.2	NS

E_2 estradiol, *LH* luteinizing hormone, *OC* osteocalcin, *SED* sedentary control, *RC* wheel-running ad libitum-fed, *RR* wheel-running restricted-fed

Biochemical Analysis of Plasma

The plasma E_2, LH, and osteocalcin concentrations are shown in Table 22.5. Plasma E_2 concentrations were significantly lower in the RR group than in the SED group ($p < 0.05$). Furthermore, E_2 concentrations tended to be lower in the RC group than in the SED group ($p = 0.054$). LH concentrations were significantly lower in the RR group than in the RC and SED groups ($p < 0.05$). No differences were observed in osteocalcin concentrations among the groups.

22.7.3 Discussion

In the present study, we investigated the effects of long-term energy restriction with voluntary wheel running on bone and reproductive functions in female rats with intact ovaries in order to establish an animal model of FAT. We found that energy

restriction combined with voluntary exercise decreased femoral BMD and altered the E_2 and LH plasma concentrations in female rats with intact ovaries. In addition, morphological evaluation of the femur revealed bone deterioration in the RR group compared to the RC and SED groups. Although we were unable to determine whether bone loss was caused by the reduced energy intake or voluntary wheel running in this study, these findings suggest that long-term energy restriction with voluntary wheel running exercise caused low bone mass with an altered hypothalamic-pituitary-ovarian (HPO) axis (Yanaka et al. 2012).

22.8 Overall Conclusions

In order to maintain quality of life and extend a person's health expectancy, it is important to prevent osteoporosis. Proper amounts of exercise, in conjunction with a diet rich in calcium, vitamins, and protein, and adequate exposure to sunlight throughout a person's life can reduce the prevalence of osteoporosis. It is most effective for young boys and girls to adopt such a lifestyle before reaching the age of peak bone mass. In contrast, the possibility exists that long-term energy restriction with excess exercise induces bone loss through impaired reproductive function in females. The intake of foods recommended in the FOSHU list is one good approach to helping preserve bone mass in postmenopausal women. It will be necessary to examine the effects of these FOSHU-recommended foods on a FAT animal model in a future study (Ishimi and Yanaka 2012).

Acknowledgements This study was supported in part by the Global Center of Excellence (GCOE) Program of the Japanese Ministry of Education, Culture, Sports and Technology for Waseda University.

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Chapter 23
Pain Management Among Elderly People with Knee Pain

Yuichiro Nakaso, Ai Shibata, Kaori Ishii, and Koichiro Oka

Abstract Knee pain is one of the common symptoms experienced by elderly people. Knee pain problem is a complex issue which contains physical and psychological aspects. For example, knee pain is associated with muscle weakness, mobility limitation, cognitive difficulties, behavioral abnormalities, and emotional upheavals. Recently, non-pharmacological treatment (e.g., exercise therapy, cognitive behavioral therapy) to improve physical and psychological outcomes has been used to cope with knee pain. The aim of this review is to introduce the key studies on non-pharmacological treatment for knee pain. Some studies showed that exercise therapy was effective for alleviating knee pain and improving physical function and that cognitive behavioral therapy improved psychological parameters. Moreover, combined exercise and cognitive behavioral therapy intervention may be more effective for pain management elderly people with knee pain than non-combined therapy. However there is a lack of evidence indicating the efficacy of such combined intervention, further research is needed.

Keywords Chronic pain • Musculoskeletal pain • Older adults • Exercise • Cognitive behavioral therapy

23.1 Introduction

Because aging populations are rapidly growing in many industrialized nations, aging well is of utmost concern. The World Health Organization published the report *Active Ageing: A Policy Framework* that has brought active ageing to the forefront of international public health awareness (World Health Organization 2002).

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_23

Knee pain is one of the most common symptoms experienced by elderly people (Hadler 1992). The National Health and Aging Trends Study reported that the prevalence of knee pain was 24.8 % among community-dwelling elderly people (Patel et al. 2013). In Japan, the prevalence of knee pain with knee osteoarthritis (OA) was 24.1 % in men and 37.6 % in women among elderly people which is over 65 years old (Muraki et al. 2009). Knee pain was reported to be associated with mobility limitations, future loss of independent ability to carry out activities of daily living (Nishiwaki et al. 2011), decrease in physical activity level (Wallis et al. 2013), and lower quality of life (Hirano et al. 2014) among older adults. Accordingly, there is a need to cope with knee pain to enable active and successful aging. However, the knee pain problem is a complex issue which contains not only physical, but also psychological aspects.

Pharmacological treatment has long been used for knee pain. This treatment is beneficial but may have side effects and presents a risk of over use. Moreover, it often fails to relieve knee pain because the problem has psychological as well as physical aspects. Recently, the use of non-pharmacological treatment (e.g., exercise therapy, cognitive behavioral therapy) to improve physical and psychological outcomes without side effects has been explored to cope with knee pain (Wang et al. 2012; Dixon et al. 2007).

Thus, the present article reviews the knee pain problem and non-pharmacological approaches to its alleviation among elderly people. The first section has briefly summarized physical and psychological problems among the elderly with knee pain. The second section will review interventions to cope with knee pain and associated other problems among the elderly.

23.2 Physical and Psychological Problems Among Elderly People with Knee Pain

Elderly people with knee pain may experience many other problems, which can be physical (lower extremity muscle weakness, mobility limitation) or psychological (cognitive difficulties, behavioral abnormalities, emotional upheavals). These problems are all affected by physical activity level and, in turn, they affect the quality of life among the elderly.

23.2.1 Physical Aspects

Elderly people with knee pain may have accompanying physical problems. First, knee pain is associated with muscle weakness. One longitudinal study (Glass et al. 2013) reported that among community-dwelling middle-aged or older adults with OA, quadriceps weakness was associated with an increased risk of knee pain

worsening over 5 years in women, although not in men. Second, knee pain could be a risk factor for future functional decline in the ability to successfully accomplish the activities of daily living. Nishiwaki et al. (2011) showed that older adults with constant knee pain were at higher risk of future dependence on others in order to conduct normal activities (transferring, bathing, dressing) that are related to mobility.

23.2.2 Psychological Aspects

To understand knee pain, the psychological accompaniments (e.g. cognitive, behavioral, and emotional variables) must be understood. An individual's confidence that they can cope with their pain is an important positive cognitive characteristic. Self-efficacy to cope with their pain and other symptoms could encourage an individual's attempts to manage their pain (Somers et al. 2012). On the other hand, a person who believes that they are not able to cope with their pain can feel helpless. One longitudinal study explored the prognostic value of coping strategies in a community setting (Alschuler et al. 2013). The result showed that pain was worse for participants who did not believe that they could cope with their pain. Second, the pain-coping behaviors (e.g. medication, resting, exercise) that are utilized are important. One population-based study reported that passive pain-coping behaviors such as medication and resting were more often used than active pain-coping strategies such as exercise (Blyth et al. 2005). Moreover, passive pain-coping behavior was associated with pain-related disability. Third, people with knee pain may have emotional problem. A systematic review showed a deleterious relationship between knee pain and depression (Phyomaung et al. 2014). Although assessments for depression were performed using various methods, this review reported that there was a significant association of knee pain with depression. Therefore, appropriate pain-coping skills are needed to change cognitive, behavioral, and emotional variables.

23.3 Interventions to Cope with Knee Pain

23.3.1 Exercise Therapy

The key objective of exercise therapy is to relieve knee pain and improve physical function. There are many types of exercise (e.g. strengthening exercise, aerobic exercise, aquatic exercise, proprioception exercise, Tai Chi). Several systematic reviews and meta-analyses (Fransen and McConnell 2009, Wang et al. 2012) have consistently shown exercise to be beneficial for older adults with knee pain.

One meta-analysis reported that land-based exercise was effective for alleviating knee pain (Standardized Mean Difference (SMD), 0.40 [95 %CI, 0.30 to 0.50]) and

improving physical function (SMD, 0.37 [95 % CI, 0.25 to 0.49]) (Fransen and McConnell 2009). Another meta-analysis revealed that strengthening exercise (SMD, −0.68 [95 %CI, −1.23 to −0.14]), aerobic exercise (SMD, −0.21 [95 %CI, −0.35 to −0.08]), and proprioception exercise (SMD, −0.71 [95 %CI, −1.31 to −0.11]) improved knee pain whereas aquatic exercise and Tai Chi did not (Wang et al. 2012). Thus, there is substantial evidence that exercise therapy is an effective therapy for knee pain in elderly people.

23.3.2 Cognitive Behavioral Therapy (Pain-Coping Skills Training)

Cognitive behavioral therapy (CBT) uses many techniques to change ways of thinking, modify beliefs and attitudes, increase control over pain, and change how an individual interprets and copes with pain (Abdulla et al. 2013). CBT-based pain-coping skills training (PCST) has three principle components (Keefe et al. 1990a). First, people with knee pain need to understand the rationale upon which pain-coping skills are based. For example, gate control theory is used to show that pain is a complex experience impacting thoughts, behaviors, and emotions. Secondly, cognitive and behavioral coping skills are learned in a training session and become familiar through regular home practice. Such skills include relaxation, imaging, distraction, activity-rest cycling, pleasant activity scheduling, and cognitive restructuring (Keefe et al. 1990a). Finally, these coping skills must be applied to a pain-related situation. One early randomized study reported that pain-coping skills training affected both pain and psychological disability (Keefe et al. 1990a, b).

Knee pain is not just an individual problem; it impacts spouses (Manne and Zautra 1990). Thus, interest has been growing in spouse-assisted PCST in which spouses participate in treatment. Spouse Assisted Coping Skills Training (SA-CST) has several characteristics which are not included in PCST (Keefe et al. 1996). First, behavioral rehearsal is used to teach couples an effective way to communicate about pain. Second, spouses involved in SA-CST help their partners to deal with those daily activities which are restricted by pain. Third, couples are trained to use mutual goal-setting. Finally, couples are taught strategies that will enable them to use pain-coping skills. SA-CST has been shown to be effective for alleviating pain, physical disability, psychological disability, and self-efficacy to cope with their pain (Keefe et al. 1996, 1999, 2004). There has been only one meta-analysis of psychological interventions that included CBT (Dixon et al. 2007). This review showed that psychological interventions had effects on pain (effect size: ES = 0.177), anxiety (ES = 0.282), depression (ES = 0.208), psychological disability (ES = 0.249), and the ability to cope with pain (ES = 0.184).

23.3.3 Combined Interventions Using Exercise Therapy and CBT

Even though both exercise therapy and CBT are beneficial for reducing knee pain, exercise therapy has less effect on psychological parameters and CBT has less effect on physical function. Thus, a combination of these two approaches might be more effective than either approach in isolation on both knee pain and improved psychological and physiological health outcomes. Recently, a randomized controlled study found that SA-CST and exercise training affect an individual's ability to cope with their pain, physical fitness, and muscle strength compared with standard care condition.

The effects of a rehabilitation program that integrates exercise, self-management, and active coping strategies were examined (Hunt et al. 2013; Hurley et al. 2007a, b, 2012; Jessep et al. 2009). The aim of this program was to change behavior by challenging inappropriate beliefs, encouraging exercise, and enabling self-management. This program included three group intervention components. First, simple exercises supported by physical therapists that were personalized to and progressed according to the ability of each participant were performed. Second, participants discussed topics such as importance of exercise, activity pacing, drug management, and management pain flare with each other and were taught active coping strategies, problem solving, and planning skills. Third, participants were taught home exercise and their adherence to the exercise program was monitored.

Hurley et al. (2007a, b, 2012) reported that the Enabling Self-management and Coping with Arthritic knee Pain through Exercise (ESCAPE)-knee pain program positively affected physical function. Although improvements in physical function declined over time, the ESCAPE-knee pain program improved physical function significantly more than did a usual primary care program (whatever intervention a participant's primary care physician considered to be required and appropriate) according to 30 months follow-up data (Hurley et al. 2012). Additionally, the ESCAPE-knee pain program group intervention was more cost-effective than the ESCAPE-knee pain program individual intervention or the usual care condition (Hurley et al. 2007b). Jessep et al. (2009) compared the effects of the ESCAPE-knee pain program with outpatient physiotherapy. The ESCAPE-knee pain program is more cost-effective than outpatient physiotherapy for community-based intervention.

23.4 Future Direction

In the present article, the complex problems that arise among elderly people with knee pain, and the use of non-pharmacological interventions to cope with knee pain, were reviewed. Elderly people with knee pain may suffer not only from

uncomfortable pain but also from other physical and psychological problems. Therefore, non-pharmacological interventions (e.g. exercise therapy, CBT) which target improving both physical and psychological problems are needed. Ample evidence shows the separate effects of exercise therapy and of CBT. However, there is a lack of evidence indicating the efficacy of combined exercise therapy plus CBT intervention. Such a combined intervention may be more effective in supporting active and successful aging in elderly people with knee pain than is either intervention alone. Further research to examine the efficacy of combined intervention on knee pain and related health outcomes is needed.

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Chapter 24
Effective Exercise Programs Among Frail Elderly People

Shuichi P. Obuchi, Hisashi Kawai, and Seigo Mitsutake

Abstract In Japan, frail elderly people are defined as having a maximum walking speed of less than 80 m per minute or possessing at least one failure in terms of instrumental activities of daily living. Comprehensive geriatric training (CGT) was developed to improve the physical functions of frail elderly people. CGT includes conditioning training, progressive resistance training, and balance training for frail elderly individuals in an effective exercise program. The CGT program promotes the health of frail elderly people by improving physical functions and enhancing the ability for self-management.

Keywords Frail elderly people • Comprehensive geriatric training (CGT) • Preventive long-term care

24.1 Frail Elderly People

24.1.1 Definition of Frail Elderly People

We define frail elderly people as those whose maximum walking speed is one standard deviation slower than that of average elderly people (80 m/min) or who have at least one failure in terms of instrumental activities of daily living (IADL) (Suzuki and Obuchi 2006). Sarcopenia is a syndrome characterized by progressive, generalized loss of skeletal muscle mass and strength together with a risk of adverse outcomes, such as physical disability, poor quality of life, and death (Delmonico et al. 2007; Goodpaster et al. 2006). The European Working Group on Sarcopenia in Older People (EWGSOP) has proposed an algorithm based on gait speed measurement as a way to begin practical sarcopenia case screening (Cruz-Jentoft et al. 2010). A cut-off point of >48 m/min has been used to identify the risk of sarcopenia (Abellan et al. 2009). The EWGSOP considers sarcopenia to be common among frail older people.

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_24

The target with sarcopenia screening using EWGSOP guidelines is, however, different from the target required for preventive long-term care in Japan. Frail elderly people diagnosed with sarcopenia using EWGSOP guidelines receive long-term care and are regarded as patients with a disease condition in Japan. "Frailty" is considered an antonym for "intact" in Europe and the United States. Unlike in the West, in Japan's super-aged society, "frail elderly people" refers to the intermediate stage between robust elderly people and those in need of care. Therefore, it is necessary to define frail elderly people as those who are weak but are able to live alone.

Under EWGSOP guidelines, gait speed is measured as the time taken to walk 4 m from a standstill. Because a distance of 3 m or more is required to accelerate to a standard walking speed, the method of measuring walking speed with EWGSOP assesses only the acceleration in the initial phase of walking. In the West, this method thus presents problems in assessing frail elderly people. Consequently, frail elderly people in Japan are screened using both maximum walking speed and IADL assessed by TMIG-Index (Suzuki and Obuchi 2006).

24.1.2 Features of Frail Elderly People

The definition of frail elderly people in both Japan and the West relies on reduced walking ability. Reduced mobility results in higher mortality as well as greater need for long-term care. The lower limbs of frail elderly people are weak; however, exercise programs for such individuals are usually conducted without taking into consideration the frail musculature of the legs. For example, exercises carried out in an upright position, such as squats, have been considered appropriate for frail elderly people. Because the extension strength of the knee is low among frail elderly people, exercises conducted in a standing position result in overload of the legs. Table 24.1 presents a comparison between two groups of community-dwelling elderly people classified in terms of maximum walking speed: ≥80 m/min group and <80 m/min group (Obuchi 2013). The mean length of time that individuals in the <80 m/min group required to complete the Timed Up & Go (TUG) test (Shumway-Cook et al. 2001) was more than twice that required by the ≥80 m/min group (Table 24.1). Furthermore, the knee extension torque of the <80 m/min group

Table 24.1 Comparison of physical functions between the two groups

	≥80 m/min group			<80 m/min group		
	Mean	SD	N	Mean	SD	N
5-m normal walking speed (m/min)	83.4	12.5	742	51.1	10.7	45
5-m maximum walking speed (m/min)	120.0	19.9	743	64.9	11.7	47
Knee extension torque (Newtons)	76.4	26.4	734	49.0	17.7	43
TUG (s)	5.3	1.1	737	11.1	4.5	43
One leg standing time (s)	44.2	21.6	742	16.2	19.3	46

TUG Timed Up & Go test

was only 49 newtons (N), which is less than one standard deviation of the average in the ≥80 m/min group. Therefore, it is clear that standing exercises lead to overload of the legs among frail elderly people.

In day-care centers, sitting exercises, such as balloon volleyball and gymnastics using towels, have been used for frail older people. However, sitting exercises do not improve walking ability because the load in a sitting position is too small to promote strength in the legs.

24.1.3 Specific Exercise Guidance for Frail Elderly People

It is well known that particular types of exercise movement have specific effects. For example, if the purpose of training is to improve endurance, endurance will improve; if the purpose of training is to strengthen muscles, muscular strength will improve. Therefore, to enhance the movement ability of frail elderly people, it is necessary to focus on exercises to enhance specific mobile capabilities. In particular, to improve the walking ability of frail elderly people, it is essential to promote strength training of antigravity muscles. Further, Kinugasa et al. (1994) demonstrated that because the balance function decreases sooner than other functions, it is necessary to enhance the training balance function at an early stage among older people. The one-leg standing time of the <80 m/min group was one-third or less that of the ≥80 m/min group (Table 24.1).

In addition, when providing exercise guidance for frail elderly people, it is necessary to take pain into consideration. Using the data from the same community-dwelling elderly people as in Table 24.1. Table 24.2 presents a comparison of pain in the knee and lower back among frail elderly and healthy elderly people (Obuchi. 2013). The occurrence of pain in the lower back and knee among frail elderly people was significantly statistically higher (being found in about 68 % of cases) than in healthy elderly individuals. With exercise guidance, it is thus necessary to consider how the elderly will respond to pain and amelioration of pain.

Table 24.2 Comparison of lower back pain and knee pain between the two groups

		≥80 m/min group		<80 m/min group	
		N	%	N	%
Lower back	No pain	445	60.0	15	31.9
	Pain	297	40.0	32	68.1
Knee	No pain	493	66.4	15	31.9
	Pain	250	33.6	32	68.1

24.2 Comprehensive Geriatric Training

24.2.1 What Is Comprehensive Geriatric Training?

The purpose of comprehensive geriatric training (CGT) is improvement of physical functions among frail elderly people. CGT consists of conditioning training, progressive resistance training, and balance training. This exercise program was constructed using the guidelines of the American College of Sports Medicine as well as the results of research (Chodzko-Zajko et al. 1998; Evans 1999; Gillespie et al. 2001). In Japan, a number of studies have demonstrated the effect of CGT in improving the physical functions of older people (Arai et al. 2006, Arai et al. 2009; Inaba et al. 2006). CGT is usually conducted by an interdisciplinary team comprising both medical and fitness staff. The medical staff are responsible for carrying out medical management, developing appropriate emergency response plans, and training other staff members.

24.2.2 Characteristics of the CGT Program

The characteristics of the CGT program are indicated in Fig. 24.1. Every session begins with a 10–15-min warm-up period consisting of gentle stretching and light exercise, and it ends with a 10-min cool-down period of stretching. The frail elderly

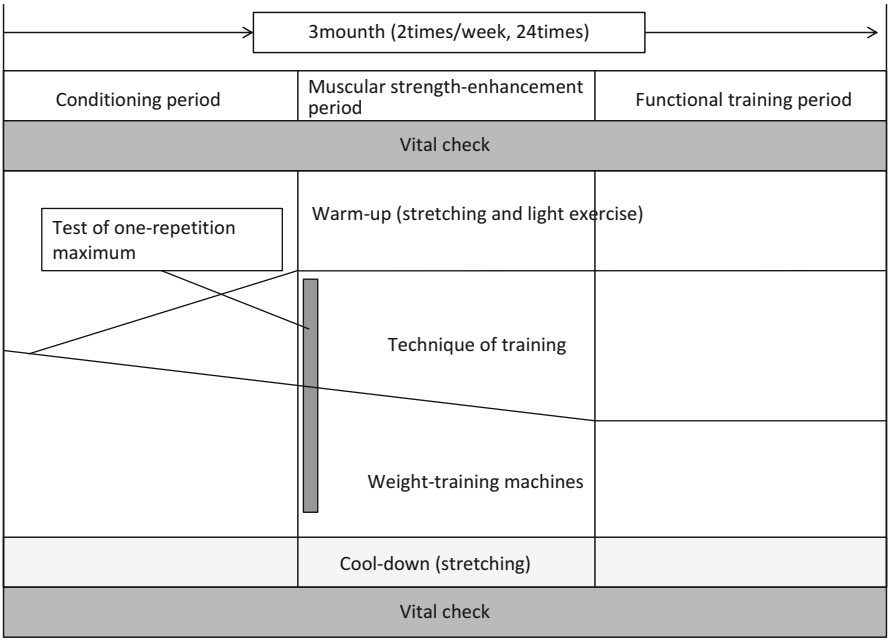

Fig. 24.1 The three periods of CGT (Obuchi and Satake 2006)

subjects devote much of their physical conditioning time to stretching exercises. This period also involves exercises with weight-training machines, and the subjects become familiar with low-intensity, repetitive training.

At the beginning of the muscular-strength-enhancement period, the one-repetition maximum of the participant is measured directly if the participant is able to perform machine training adequately. One-repetition maximum is defined as the maximum weight that can be lifted through a full range of motion with proper form. The participants conduct the exercises using four weight-training machines (leg press, leg extension, hip abduction, and rowing; Fig. 24.2).

At the beginning of the strengthening phase, the intensities are set at 60 % or more of the individual's one-repetition maximum for two or three sets of 10 repetitions. To avoid pain in the joints and muscular soreness, we apply these intensities at the beginning of the strength-enhancement period. We believe that if such precautions are not undertaken, there is a great likelihood of participants dropping out of the program. Participants who are unable to lift the weights adequately continue with conditioning training. If some participants have specific physical problems, such as pain in the joints or joint immobilization, the physical therapist deals with those problems on an individual basis. The resistance is increased if the subjects

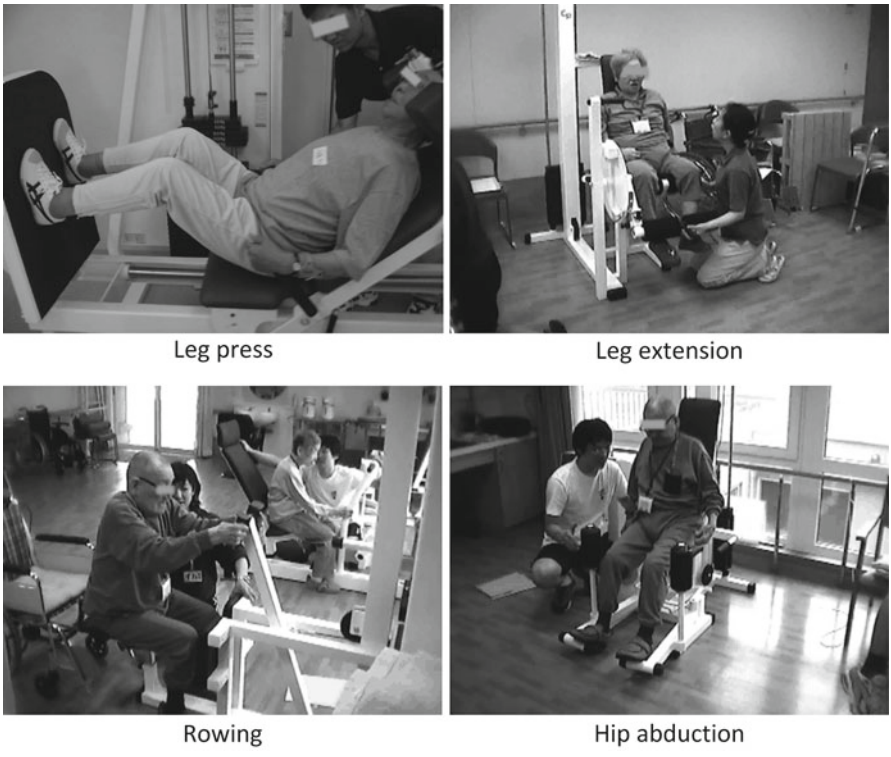

Fig. 24.2 Weight-training machines

are able to effortlessly complete three sets of 10 repetitions. A rest period of about 2 min is given between the sessions of machine training. The subjects also undergo balance training during this strengthening phase.

During the functional training period, in addition to the high-intensity resistance training described above, the program includes intensive balance training and functional training exercises, which progressively increase in difficulty based on set criteria and according to an individual's ability. We also introduce functional training that requires more dynamic, rapid movement of the center of gravity. For example, the target in the early phase of the functional training period is to achieve a stable standing position with a narrow base of support against small perturbations. In the beginning we emphasize correct trunk and lower-body alignment in a standing position with a wide lower-extremity stance. The base of support is gradually reduced with narrowing of the distance between the legs. Participants who are unable to stand stably and maintain correct alignment are allowed to use simple stabilizing equipment, such as a chair or parallel bars. The training involves the participants being asked to stand on one foot or to raise their heels or toes while standing without the use of stabilizing equipment. We do not use specialized devices to create the perturbations in the functional training period. The small perturbations used in this study were achieved by having the participants raise their arms by themselves, twist their trunks, catch or throw an object, be pushed by the therapist, and other such actions. In addition, a soft foam surface, which made it difficult to control swaying of the body mass, was introduced to the base of support.

In the next phase of the functional training period, the subjects tried to move their center of gravity and base of support rapidly and over a wide range by coordinating the lower extremities and trunk. In the final phase of the functional training period, the participants performed high-level functional tasks, such as walking sideways while bending the knees, and jumping and landing on the floor.

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Chapter 25
Rowing: A Favorable Tool to Promote Elderly Health Which Offers Both Aerobic and Resistance Exercise

Meiko Asaka and Mitsuru Higuchi

Abstract Aerobic exercise is recommended for the prevention of lifestyle-related diseases, while resistance exercise is recommended for the prevention of osteoporosis and sarcopenia. Both types of exercise are important in helping elderly people to maintain quality of life. Rowing is one of the oldest sports in the world and it offers a combination of both aerobic and resistance exercise. Because rowing is practiced on a seat, less impact is placed upon the knee joints, making it safe for elderly people even if they are categorized as overweight or obese. Elderly rowers have higher cardiorespiratory fitness (CRF) and a lower risk of coronary heart diseases compared with age-matched untrained people. The bone mineral density and muscle size in rowers are also greater than in untrained people. After 6-month exercise training in elderly men using a rowing ergometer, CRF and muscle size increased and the risk of lifestyle-related diseases also improved. An indoor rowing ergometer has been developed which offers a safe and easy tool for exercise in elderly people, even those who are wheelchair-bound. Therefore, rowing could offer a beneficial combination of aerobic and resistance exercises for achieving an active life in the elderly population.

Keywords Rowing • Elderly people • Physical fitness • Lifestyle-related diseases • Sarcopenia

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Electronic supplementary material The online version of this chapter (doi: 10.1007/978-4-431-55333-5_25) contains supplementary material, which is available to authorized users.

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_25

25.1 Introduction

Japan is now one of the healthiest countries in the world in terms of both life expectancy and health-adjusted life expectancy (HALE). Because of the rapidly growing life expectancy of the Japanese people, the population of elderly people over 65 years old has been dramatically increasing and Japan has already reached the stage of being considered a super aging society, which means that 21 % or more of the population are 65 years or older, with a low birth rate. According to the Ministry of Health, Labour and Welfare of Japan, there exists almost a 10 year gap between life expectancy and HALE, implying that elderly people, on average, live in an unhealthy state for the last 10 years of their lives. Living in an unhealthy state (such as suffering from lifestyle-related diseases, being required to enter long-term care, and so on) causes declines in quality of life (QOL) and increased medical cost. Thus, the current urgent task is to prolong healthy life expectancy including active aging, that is, continued exercise activities with aging, and consequent maintenance of functional capacity and muscle strength.

It is well known that exercise is the one of the most effective ways to maintain functional capacity and muscle strength. Recently, various exercise methods for elderly people have been developed and studied. Rowing is one such activity and is one of the oldest sports in the world. A great number of people over a wide range of ages participate in rowing. Especially in European countries, rowing is very popular because there are many rivers, lakes, and canals, and rowing was a way of transportation in the past. Many rowing regattas have been held in Europe and North America. In the modern Olympic games dating from 1896, rowing is included as a sporting event. Pierre de Coubertin, who is the founder of the modern Olympic Games, was himself a rower and recommended rowing for health in his brochure entitled “La cure d'aviron (Health through rowing)”. Nowadays, elderly people enjoy rowing as a recreational sport. Rowing is less likely to inflict serious injury to the knee area because the body mass is supported by the seat of the boat or ergometer, making rowing a safe exercise for elderly people. Some elderly rowing teams participate in masters rowing competitions. Rowing is generally considered to be a water sport, but the recent development of a rowing machine has enabled the same rowing exercise to be conducted indoors. Indoor rowing championships are held every year throughout the world, and may include a 95–99-years-old category. Astronauts in space have also performed rowing exercise to maintain cardiorespiratory fitness and to prevent muscle and bone loss because rowing includes elements of both aerobic and resistance exercises.

Thus, rowing is an effective and safe tool that elderly people can use to maintain functional capacity and muscle strength. In the following section, we will introduce the effects of rowing exercise on health, focusing on elderly people.

25.2 Rowing as an Aerobic Exercise

Aerobic exercise is recommended for the prevention of obesity and lifestyle-related diseases. During the last few years, metabolic syndrome has been receiving attention in Japan just as in other countries. Metabolic syndrome, which is defined as a cluster of abnormalities comprising two or more risk factors such as blood lipid abnormality, high blood pressure, and high fasting blood glucose, in addition to abdominal fat obesity, is associated with increased risk of coronary heart disease (CHD) and diabetes. Many studies have explored the question of how to prevent metabolic syndrome and it is well known that aerobic fitness, also termed cardiorespiratory fitness (CRF), is an independent predictor of metabolic syndrome. Aoyama et al. (2009) reported that women have generally lower metabolic syndrome risk than men and high CRF is associated with a lower risk of metabolic syndrome while low CRF is associated with a higher risk in both men and women. There is an age-related decline in CRF. The decline of CRF assessed by maximal oxygen uptake (VO_2max) generally begins between 25 and 30 years of age, and declines by approximately 10 % per decade in healthy sedentary people (Holloszy 1995). VO_2max decreases with physical inactivity and increases in response to regularly performed vigorous exercise.

In the Position Stand of the American College of Sports Medicine (1998), any activity such as aerobic exercise that uses large muscle groups continuously, rhythmically, and aerobically, is recommended for developing and maintaining CRF. Rowing is included as one example of such activity. It is known that rowers have high CRF; male elite rowers have a VO_2max of up to 6.5 L/min and female elite rowers have a VO_2max of up to about 4.4 L/min (Secher and Volianitis 2007). In our studies, we measured the VO_2max of elderly male rowers (Fig. 25.1a). Elderly male rowers rowed on water or using an ergometer once or twice per week. Although elderly male rowers have a lower VO_2max than young male rowers, elderly male rowers have a VO_2max that is higher than that of age-matched untrained men, and similar to that of young untrained men (Fig. 25.1b) (Kawano et al. 2012; Yoshiga et al. 2002a).

Next, we evaluated the risk of lipid abnormality in rowers. Both low density lipoprotein (LDL) and high density lipoprotein (HDL) are cholesterol-rich lipoproteins. Higher LDL and lower HDL blood cholesterol indicate coronary heart disease and atherosclerosis. Lower HDL cholesterol is one indicator of metabolic syndrome. Elderly male rowers have lower risk factors for CHD as assessed by HDL cholesterol, LDL cholesterol, and the ratios of LDL-cholesterol/HDL-cholesterol and total-cholesterol/HDL-cholesterol than do either young or elderly untrained men (Fig. 25.2) (Kawano et al. 2012; Sanada et al. 2009; Yoshiga et al. 2002a).

Aerobic exercise also exerts favorable effects on measurements of vascular function such as arterial stiffening (Tanaka et al. 2000). Increased arterial stiffness with age is a key risk factor for cardiovascular diseases such as hypertension and

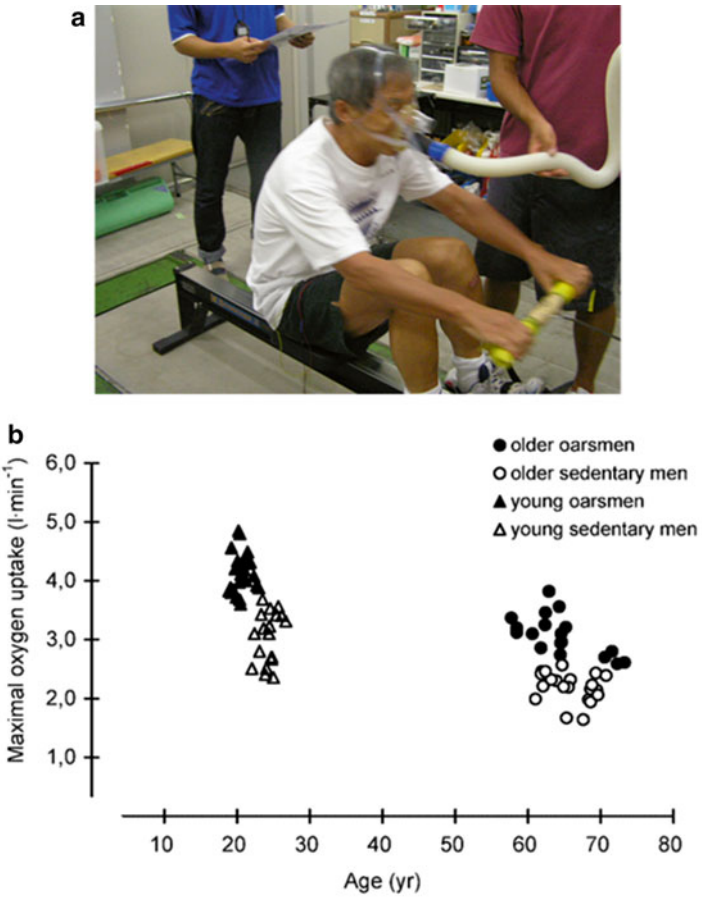

Fig. 25.1 (**a**) Measurement of maximal oxygen uptake (VO_2max) in elderly rowers using a rowing ergometer. (**b**) VO_2max in rowers and non-rowers as a function of age (Figure from Yoshiga et al. (2002a))

arteriosclerosis (Laurent et al. 2001). On the other hand, resistance exercise increases arterial stiffness (Kawano et al. 2006; Miyachi et al. 2004). However, combined aerobic and resistance exercise does not change arterial stiffness (Kawano et al. 2006). As has been mentioned, rowing is an aerobic exercise, but it is also considered to be a resistance exercise. Thus, our interest was in whether rowing prevents the process of arterial stiffening via resistance exercise or improves arterial stiffness via aerobic exercise. Previous studies have suggested that rowers have lower arterial stiffness than age-matched untrained controls independent of age (Cook et al. 2006; Sanada et al. 2009).

These results indicate that rowing is good for maintaining or increasing CRF and preventing metabolic syndrome and lifestyle-related diseases.

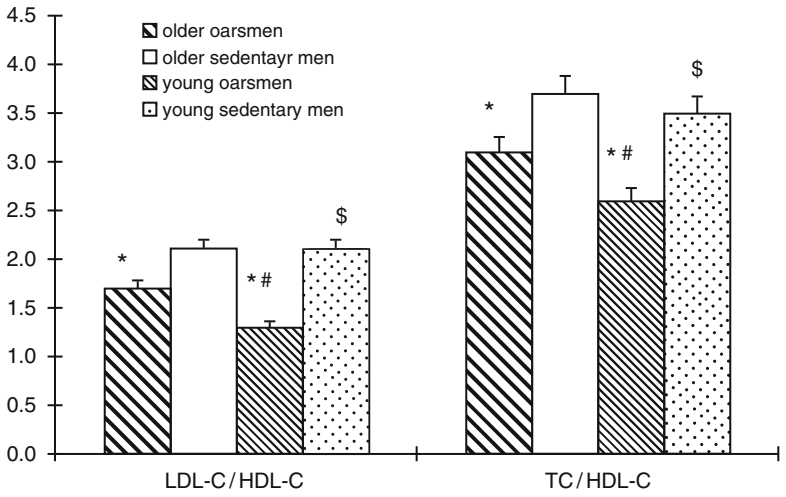

Fig. 25.2 Atherosclerosis indices (the ratio of low density lipoprotein, LDL-C, to high density lipoprotein-cholesterol, HDL-C, and that of total cholesterol, TC, to HDL-C). Values are means ± SD, *P < 0.05 difference between oarsmen and sedentary men in the same age groups, #P < 0.05 difference between older oarsmen and young oarsmen, $P < 0.05 difference between older oarsmen and young sedentary men (Figure from Yoshiga et al. (2002a))

25.3 Rowing as a Resistance Exercise

Resistance exercise is recommended for the prevention of osteoporosis and sarcopenia. Osteoporosis, or bone disease characterized by loss of bone mass and density, increases the risk of facture. An osteoporosis fracture is most likely to occur in wrist, spine, shoulder, and hip and can lead to long-term nursing home care, especially in elderly people. Sarcopenia is defined as age-related muscle wasting and weakness. Muscle mass significantly decreases after 45 years of age in both men and women (Janssen et al. 2000) and this decrease is inevitable even in healthy elderly people. Sarcopenia is associated with the risk of falls, functional impairment, and physical disability. Therefore, preventing osteoporosis and sarcopenia is important for maintaining QOL in elderly people. Fortunately, a previous study demonstrated that resistance exercise can increase the skeletal muscle mass and function of even very old people (Fiatarone et al. 1990).

Rowing exercise involves almost every muscle in the body and can require great power (Secher 1983) . During rowing exercise, the trunk motion accounts for 50 % of the total rowing power and the leg motion counts for 40 % (Tachibana et al. 2007). Muscles of the trunk and legs play an essential role in various movements, including walking, standing up, raising the legs, and stabilizing the body. It is critically important for elderly people to prevent trunk and leg muscle wasting. Thus, rowing is recognized as a useful resistance exercise for increasing muscle mass.

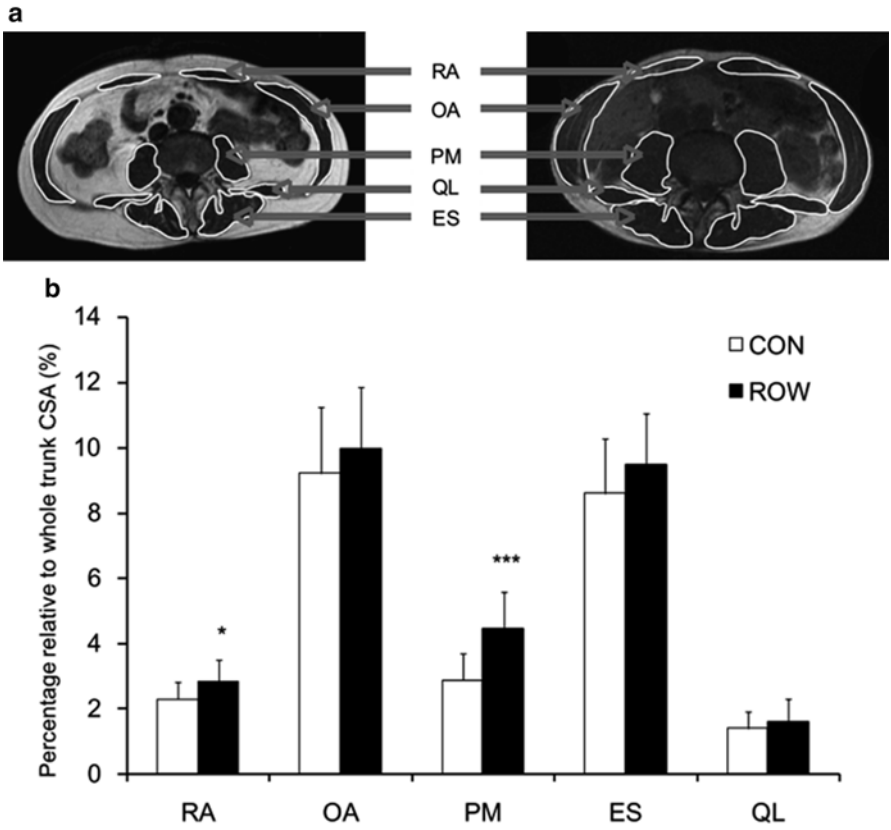

Fig. 25.3 (**a**) Magnetic resonance imaging of the trunk area of an untrained man (*left*) and an elderly male rower (*right*) obtained at the L3–4 level. (**b**) The percentages of muscle cross-sectional area to whole trunk area in untrained men (CON) and elderly male rowers (ROW). *RA* rectus abdominis, *OA* oblique abdominal, *PM* psoas major, *ES* erector spinae, *QL* quadratus lumborum. * $P<0.05$, *** $P<0.001$ vs. CON (Image and figure from Asaka et al. (2010))

Recently, we examined the body composition of elderly rowers assessed by dual-energy X-ray absorption (DXA) and magnetic resonance imaging (MRI) (Asaka et al. 2010; Sanada et al. 2009; Yoshiga et al. 2002b). In the DXA study, we demonstrated that arm, leg, and trunk lean soft tissue mass were significantly higher in elderly rowers than in elderly untrained controls and bone mineral density was also significantly higher in senior rowers than in senior sedentary controls (Sanada et al. 2009). In MRI studies, leg extension muscle cross-sectional area and muscle power in elderly male rowers was significantly larger than in elderly untrained men (Yoshiga et al. 2002b). Furthermore, elderly male rowers had 20 % larger trunk muscle cross-sectional area, especially in the rectus abdominis and psoas major muscles, and greater isometric trunk flexion force than elderly untrained men (Fig. 25.3) (Asaka et al. 2010).

We also evaluated cross-sectionally the effects of rowing on the morphological and physiological characteristics of elderly female rowers by comparing elderly female rowers with elderly untrained women and walkers. Elderly female rowers have higher CRF and lower % body fat than untrained and walking-trained women. Trunk muscle cross-sectional area in elderly female rowers was significantly larger, particularly the psoas major (by 45 %), than both untrained female rowers and walkers.

These results indicate that rowing, as a resistance exercise, is good for preventing osteoporosis and sarcopenia.

25.4 Effect of Rowing in Elderly People

More information is needed to evaluate the health benefit of rowing for elderly people. We evaluated the effects of 6 month rowing training on CRF, visceral fat, atherosclerosis index, and muscle size in elderly untrained men. Eighteen healthy untrained men aged between 65 and 78 participated in this study. The participants were divided into a control group and a rowing-training group. The rowing-training group trained three times a week for 6 months; each training session consisted of a 5 min warm-up, 2 sets of 10 min workouts, and a 5 min cool down on a rowing ergometer (Concept II, model C, Morrisville, Vt., USA). During the 10 min workouts, exercise intensity was 65–80 % of each person's maximum heart rate (HRmax). No participants complained of any pain, such as back or knee pain, during rowing training.

CRF in the rowing training group was significantly increased and the atherosclerosis index decreased after 6 months of rowing training. In the visceral fat area, there was a great variance in values between the individuals and no significant effect of the training was observed in visceral fat area between the control group and the rowing training group. However, half of the participants in the rowing training group decreased their visceral fat area by more than 25 %.

Trunk and leg muscle cross-sectional areas significantly increased in the rowing training group after 6 months of training. More specifically, in the trunk area, the rectus abdominis and psoas major dramatically increased as compared to other muscles in response to the rowing training. These results agreed with the previously-obtained results of our cross-sectional study targeting elderly rowing-trained men. The rectus abdominis and psoas major muscles are recruited eccentrically throughout all rowing phrases, resulting in a higher rate of muscular hypertrophy than in other muscles. Furthermore, both the rectus abdominis and the psoas major are important for balancing while standing and walking. Therefore, rowing exercise has important implications for daily activities in elderly people.

Our results confirm that rowing exercise involves elements of both resistance and aerobic exercise and that rowing is a beneficial exercise for promoting good health in elderly people.

25.5 Indoor Rowing Ergometer for Elderly People

Rowing exercise on an indoor rowing ergometer is safe, easy, and effective training for the elderly because rowing is performed in a sitting position. The best known rowing ergometer is the Concept2 rowing machine (Morrisville, Vt., USA); it has a slide seat. The seat of a racing boat is also a slide seat; therefore, the Concept2 rowing machine is a very good training tool for athletes. On the other hand, it is reported that the biochemical load is lower on a slide seat rowing ergometer than on a stationary rowing ergometer (Holsgaard-Larsen and Jensen 2010). Therefore, the Yamatake Company (Aichi, Japan) is developing a new type of rowing ergometer named the "e-Rowing" ergometer and we assessed that machine. The e-Rowing machine was thus named because it is an "electronic", "ecological", and "enjoyable" rowing ergometer for people of all ages, although it is especially intended for elderly people. The e-Rowing ergometer can easily be used at home because it is small and after a bout of training is done it can be turned into a bench, for example, in a living room (Fig. 25.4).

The seat of the e-Rowing machine is fixed; kicking the stretcher (footstep) with its board moves the stretcher forward. After kicking the stretcher, the rower leans slightly backward and pulls the hand grip by flexing the arms (Video 25.1). A series of rowing movements generates energy, and the obtained electrical energy can be used for resistor as a thermal energy to control the exercise workload. Therefore, the e-Rowing has the self-completion type energy generation system and doesn't need any external power source. This mechanism makes it possible to minimize the size of the e-Rowing ergometer to a total length of 150 cm, almost 100 cm shorter than the popular Concept2 rowing ergometer. The e-Rowing ergometer has an additional function; it can connect to the internet. The data obtained during e-Rowing exercise can be transferred via Wi-Fi to a laboratory far from the exercise location for analysis; the analyzed data can be returned to the exerciser to aid sports and/or medical experts to create a personalized training menu or exercise prescription. Exercise scientists can also use the accumulated data for health-related research. We would like to build a "health network" of connected e-Rowing machines.

Fig. 25.4 A new type of indoor rowing ergometer, the e-Rowing ergometer (*left*). After training, the e-Rowing ergometer can be converted to a bench with cover (*right*)

Fig. 25.5 A 94-years-old man in a wheelchair using the e-Rowing ergometer in his home. He is wheelchair-bound because he fractured his hip 1 year before this photograph was taken

One of the most unique and beneficial characteristics of the e-Rowing ergometer is that wheelchair-bound people can use it. Fig. 25.5 is a picture of an elderly wheelchair-bound man using an e-Rowing machine. This 94-years-old man fractured his hip 1 year before this picture was taken, and now he is recovering by using the e-Rowing ergometer in his home. Any wheelchair can easily be connected to the e-Rowing ergometer (Video 25.2). If a potential user cannot move their legs, exercise can be performed using arms alone; likewise, if a person cannot move their arms, they can exercise using just their legs. The e-Rowing has been developing specifically for elderly people with weak upper body strength and/or weak leg muscles so that these people can improve their muscle function.

25.6 Recommendation of Rowing for Elderly People

We examined a 6 month rowing training program for elderly people that required almost 30 min of exercise, including warm-up and cool-down. This amount of exercise is difficult for weak elderly people to perform. According to an evaluation of

various epidemiological studies, The Ministry of Health, Labour and Welfare of Japan has set the reference values for the quantity of physical activity, exercise, and physical fitness for health in the "Exercise and Physical Activity Reference for Health Promotion 2006", which 2013 has been revised as "Physical Activity Reference for Health Promotion 2013". In that document, "MET"(Metabolic Equivalents of Task) is defined as the unit of intensity of physical activity and "METs · hour" is a unit to express the quantity of physical activity."23 METs · hour"per week of physical activity and exercise is recommended as optimal. In addition, "4 METs · hour" per week of exercise are recommended for people 18–64 years of age. For people over 65 years of age, the recommended quantity of physical activity is "10METs · hour" per week. Their slogan "let's start with plus 10" makes the suggestion that daily physical activities or exercises be increased gradually by adding 10 more minutes of activity every day.

A MET of rowing with moderate effort requires is 4.8-7.0 METs (Ainsworth et al. 2011). Therefore, 10 min of rowing five times per week at the upper moderate effort level of 7.0 METs will require 5.8 METs · hour and more than meets the recommended level of exercise; 10 min of rowing five times per week at the lower moderate level of 4.8 METs, will require 4 METs · hour and is also sufficient to meet the recommended level of exercise.

Therefore, we recommend 10 min of rowing exercise for elderly people to maintain their health, in accord with the recommendations given in the "Physical Activity Reference for Health Promotion 2013".

25.7 Conclusion

"Rowing exercise, in contrast to most forms of exercise training that are commonly used for health maintenance, combines endurance and strength training." This observation was made by Dr. John O. Holloszy, who is one of the leading exercise physiologists and biochemists in the world, in the recommendation letter of"Health-Related Sports Science of Rowing" (Higuchi 2011). Because rowing combines aerobic and resistance exercise, it has positive effects on cardiorespiratory fitness and contributes to the prevention of both lifestyle-related diseases and sarcopenia in elderly people. Moreover, one of the most beneficial characteristics of rowing is that it is unlikely to inflict serious damage to the knees; rowing is, therefore, a safe exercise for people of all ages and abilities including the elderly as well as people with obesity and/or knee problems. Thus, rowing is a favorable tool to use to achieve an active life and active aging in the elderly population.

Acknowledgements These studies were supported by a grant-in-aid for scientific research (no. 20192289, M. Higuchi) from the Japan Society for the Promotion of Science; a research grant for health sciences from the Ministry of Health, Labour and Welfare; a medical health care research grant from the Consolidated Research Institute for Advanced Science and Medical Care at Waseda University; a grant-in-aid for the Global COE (Sport Science for the Promotion of Active Life)

from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan; and a research grant from the Organization for University Research Initiatives at Waseda University entitled “Paradigm shifts in a super-aged society”.

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Chapter 26
Influence of Aging on Postural Control in Terms of Sensory Movements

Kotomi Shiota

Abstract This chapter examines the influence of aging on posture control function from the viewpoint of sensory movements. Decreased ability to balance in elderly individuals has multiple contributing factors, including intrinsic physiological and musculoskeletal factors and extrinsic environmental factors. Inputs (information) to the visual, vestibular, and somatic systems that are needed to maintain balance decrease with age, as do the movement outputs and the muscle, joint, and bone strengths, which limit the overall functioning of elderly individuals. In fact, many elderly individuals experience body swaying even when they stand still. When perturbations to one of the sensory systems increases, affecting the dynamic balance, the body sway increases and the balance of elderly individuals becomes more unstable. Postural control in elderly individuals differs from that in young individuals. In addition, the visual control involved in postural control differs between young and elderly individuals. Various aging-related functional changes contribute to an individual's loss of balance, and studying this domain is more complicated in elderly than in younger individuals. Further studies are required to elucidate the related mechanisms.

Keywords Postural control • Sensory movement • Aging

26.1 Introduction

An individual's ability to balance requires a center of gravity as a base of support that stabilizes the posture. Not only does an individual's center of gravity allow them to maintain a standing position, but it also enables other everyday dynamic functions such as walking upright. A decrease in the ability to balance is strongly related to falls, which can necessitate the need for nursing care (Tinetti et al. 1993; Ruthazer and Lipsitz 1993; Shumway-Cook et al. 1997).

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5_26

Falls in elderly individuals have multiple contributing factors, including intrinsic physiological and musculoskeletal factors and extrinsic environmental factors. Graafmans et al. (1996) showed that in people who developed a need for nursing care due to a fall, the relative level of significance of an individual's ability to balance is 2.9 compared to 2.6 as seen in healthy individuals. The ability to balance is an important factor in predicting the future functional level of elderly individuals.

Effective postural control requires more than the ability to generate and apply force to control the body's position in space (Chandler and Duncan 1993; Howard 1982). The central nervous system must organize information from sensory receptors and proprioceptors throughout the body to determine the body's position in space. Peripheral input from the visual, somatosensory, and vestibular systems allows an individual to detect their body's position and movement in space with respect to gravity and the individual's surroundings.

The ability to balance includes sensory integration systems such as the visual, vestibular, and somatosensory systems. Postural movement strategies include motor coordination and kinematic systems (Shumway-Cook and Woollacott 2000; Horak 1997). These systems contribute to posture maintenance. The abovementioned functions of postural control decrease with age; accordingly, posture strategies of elderly individuals differ from those of younger individuals. Therefore, this section focuses on the influence of age on the sensory movement system.

26.2 Changes in the Posture and Center of Gravity with Aging

Body sway is the total joint torque that occurs with inertial force and muscular activity because of changes in the trunk, hip joint, and head, and foot pressure. Many researchers (Prieto et al. 1996; Agrawal et al. 2012) have shown that body sway gradually increases at ≥60 years of age. An increase in body sway is accompanied by a decrease in balance, which is an important factor that leads to falls in elderly individuals (Shumway-Cook et al. 1997). Our study results demonstrate the effects of an increase in body sway (Fig. 26.1). We compared the body sway between young and elderly individuals, and found that it increased significantly when elderly individuals kept their eyes closed versus when they kept their eyes open (Fig. 26.2).

Poor posture occurs in elderly individuals because of transformations in the spinal column (Takai et al. 2001; Fujita 1995; Lewis and Bottomley 1990), which contributes to increased body sway. The line along the center of gravity of individuals in the standing position observed in the sagittal plane ideally passes through these points: the mastoid process, anterior shoulder joint, hip joint, center of the knee joint, and ankle. When an appropriate standing posture is maintained, there is minimum muscular activity of the antigravity muscles, such as the erector spinae muscle group, biceps femoris muscle, and gastrocnemius muscle. However, the problem is that it influences activity of the postural line.

Postural misalignment is caused by a decreased range of motion and loss of spinal flexibility. In many elderly individuals, these changes can lead to characteristic flex-

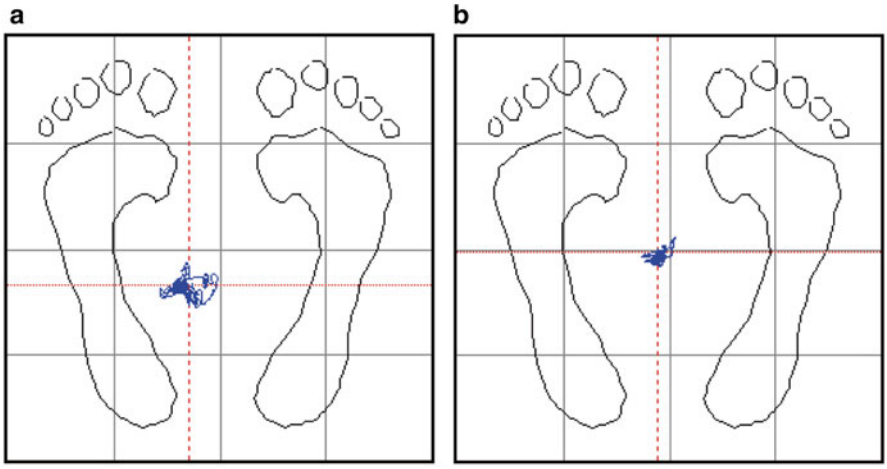

Fig. 26.1 Static balance test with open eyes. (**a**) Elderly individual (68 years old). (**b**) Young individual (20 years old)

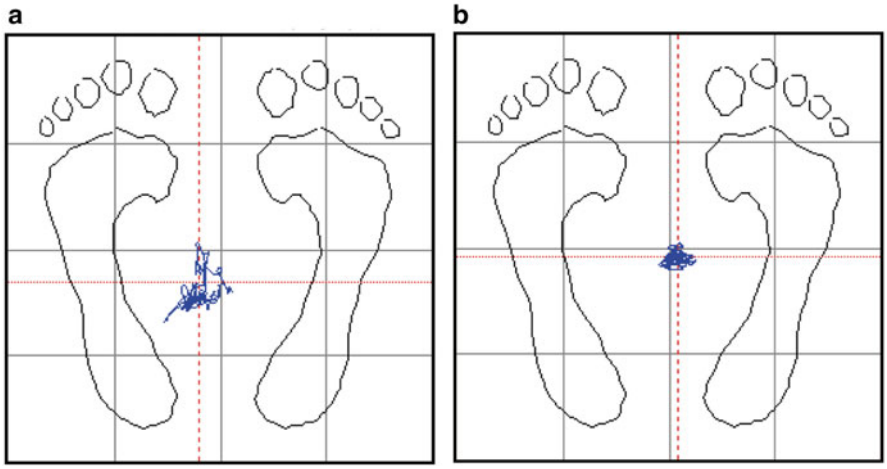

Fig. 26.2 Static balance test with closed eyes. Body sway is higher in elderly individuals. In addition, the body sway in elderly individuals increases when their eyes are closed compared to when their eyes are open. Furthermore, the center-of-gravity line in elderly individuals is shifted backward compared to that in younger individuals. (**a**) Elderly individual (68 years old). (**b**) Young individual (20 years old)

ing. This includes head forward, kyphosis, lordosis, hip flexion, and knee flexion. As a result, the center of the body mass moves toward the heel (Figs. 26.1a and 26.2a) and the postural strategy changes in elderly individuals. The muscular strength of their lower limbs is insufficient to maintain their posture, which leads to an increase in the incidence of backward falls.

Stalenhoef et al. (2002) reported that a body sway of 3.9 is often reported as a factor associated with subsequent falls. However, falls actually happen in active situations when individuals are working and when changes in direction occur. Increased body sway in the standing position is known to make an individual unstable or to increase their risk of falling, but thorough study is needed to determine whether the evaluation of an individual's static standing position can be used to predict their fall risk.

26.3 Efficacy of Static Versus Dynamic Balance Test and Body Function Evaluation

We considered whether either a static or a dynamic balance test could reflect body function characteristics in 21 individuals (Shiota et al. 2008). No significant correlations were observed between the power and time to peak torque of knee extensors by using a Biodex® (Biodex, USA) while balance was being assessed by using a Romberg balance test with a GRAVICORDER® (Anima, Japan). Correlations were observed between active balance as measured by the ATT-up (Adaption test toes-up) test with the EquiTest System® (NeuroCom, USA), and the knee extensor power, knee extensor time to peak torque, ankle plantar flexion power as measured by using a Biodex®, and ankle dorsiflexion power assessed by using a μ-Tas® (MT-1, Anima, Japan). A significant relationship was detected between muscle power and active balance. Individuals with high muscle power and short time to peak torque possessed a high capacity for balancing stably and learning improved postural control.

Muscle strength is an important factor in maintaining balance. Various factors affect balance ability, and elderly individuals with high balance ability also had high muscular strength in our study (Shiota et al. 2008). Additionally, elderly individuals with low balance ability had low muscular strength. In other words, both muscle strength and postural adjustments contribute to the dynamic balance. Postural adjustments in the standing position require sustained activity of the antigravity muscles, which is regulated by using information from the visual, somatic, and vestibular systems (Nashner 1982). The muscular strength of the lower limbs is related to an individual's ability to maintain balance for climbing stairs and walking.

The lack of a significant relationship between muscle power and static balance may be due to a decreased range of motion and loss of spinal flexibility in elderly individuals. Elderly individuals tend to use a hip strategy to maintain postural control that may be affected by arthritis, deformed joints, muscular weakness, and other conditions (Horak et al. 1989; Manchester et al. 1989). In addition, balance requires that the range of the support base measured in-plane should be able to maintain the center-of-gravity line. As a result, an individual's static balance quality may not predict their susceptibility to falls, which occur more often in active situations such as walking, turning around, and climbing stairs.

Body sway is a recently developed index of standing posture, and various methods have been developed to measure it. Yasuda et al. (2012) introduced a method

called the "Foulage test" which measures body sway by asking subjects to stand on a force plate. Shumway-Cook and Woollacott (2000) defined body sway as a stability limiter when individuals were asked to perform a task in the standing position posture. For example, there are methods to measure the reach-limit level of body sway (LOS: Limit of Stability) when individuals perform activities in the standing position. However, further study is necessary to determine whether this evaluation can be used as an index of instability to predict falls.

26.4 Aging-Related Sensory System and Postural Control Changes

Postural control is usually achieved through information obtained from the peripheral visual, somatosensory, and vestibular systems. All of these systems are affected by age (Horak 1997; Tideiksaar 1996; Weken et al. 1996; Judge et al. 1995; Woollacott et al. 1986).

In elderly individuals, the degree of body sway increases in the closed-eye condition compared to the open-eye condition. In addition, input from the somatosensory system decreases at a younger age than does input from the visual system. Therefore, as Peterka and Black (1991) and Shumway-Cook and Woollacott (2000) reported, elderly individuals rely increasingly on vision to maintain postural control.

Many studies of the effect of vision on maintaining a stable stance have examined the amplitude of sway with eyes open versus sway with eyes closed and found a significant sway increase in normal individuals with their eyes closed. Visual input provides information about one's position as well as head motion with respect to surrounding objects (Lord et al. 2000; Lee and Lishman 1975; Owen 1985). Therefore, vision is uniquely important; among the senses that contribute to stance, it is usually the primary source of information regarding the body's position in space. As changes occur in the refractivity of the cornea and the crystalline lens with an increase in age, the receptive ability of the visual cells decreases. Therefore, it is necessary to consider that both decreased visual function and decreased visual information influence a person's balance in their environment.

The vestibular system consists of three semicircular canals, a utricle, and a saccule. The vestibular system captures the motion of the head and physical movement and participates in the posture adjustment process. Decreased counts in the number of inner or auditory hair cells and decreased numbers of nerve fibers contribute to vestibular system decline (Bergstrom 1973). Feelings of drifting and dizziness tend to occur because of these physiological changes.

The somatic sensations are divided into superficial and deep sensations; both are important to maintain balance. The superficial sense includes the tactile and pressure senses. In the standing position, the touch and pressure senses gather information such as the tread of the foot base (Doumas et al. 2008). The deep sensation includes the positional and vibrational senses. The joint positional sense recognizes movement and position of the joint, while vibration perception feels vibration.

Accordingly, input from the somatic sensations provides information about one's physical position and movement, which contributes to muscle function and regulates posture. An age-related decrease in somatic sensations affects the joint positional sense and the vibratory perception ability of the foot, even in elderly individuals without neurological disease. Researchers have demonstrated that onset latency times for the tibialis anterior and quadriceps postural muscles become progressively longer in older adults as these people become more unstable (Woollacott et al. 1986).

It is reported that the nervous system gives precedence to visual information for adjusting the posture of normal individuals according to the somatosensory system in response to the latency of the plantar sensory rather than to the postural control response (Shumway-Cook and Woollacott 2000). However, the visual, somatosensory, and vestibular senses all decrease and the postural strategy changes with age.

26.4.1 Age-Induced (or Age-Related) Changes in Perturbation Response Control

In the EquiTest System® (NeuroCom, USA), a force plate and floor move at random, creating perturbations to the visual and somatosensory systems which are used to evaluate response latency and stability. Many studies using the perturbations approach have shown that the posture response of elderly individuals is decreased (Teasdale and Simoneau 2001).

In addition, many researchers (Woollacott et al. 1986; Horak et al. 1989) have studied the association between sensory perturbations and posture control and falling. Even if only one task is given while perturbations are interfering with the visual or somatosensory system in elderly individuals, the ability to balance decreases. Furthermore, the incidence of falls increases when perturbations interrupt the visual and somatosensory systems. Falls in elderly individuals are related to the sensory systems. If one sensory function cannot respond instantly, stability suffers much more in elderly individuals than in young individuals. Individual sensory functions decrease with aging, but decreases in balance abilities only occur when the visual or somatosensory systems are impacted (Teasdale et al. 1991).

The sensory decreased when elderly individuals were subjected to frequent perturbation stimulation. In our study (Shiota et al. 2008), young individuals adapted immediately to stimulation, whereas elderly individuals displayed delayed adaptation. The activity level of subjects observed during the fifth trial was less than that of the subjects in the first trial. This finding indicates that there may have been a learning effect in subjects with strong muscles. It is known that the adaptive ability decreases with age. Not only does the ability to respond to feedback decrease, but an individual's ability to control their response to perturbation decreases as well, especially in elderly individuals.

26.5 Visual Function and Postural Control

Finally, this section discusses the visual and postural control findings of our study. The visual system continuously sends information to the nervous system about an individual's physical position and movement as related to their environment. Visual system function is important for the maintenance of the ability to stably balance. If an individual cannot obtain clear visual information (such as when they are in a dark room), their balance becomes unstable. When moving from a light room to a dark room (or vice versa), the visual system requires time to adjust before it can recognize objects.

In our pilot study, we researched postural control during the adaptation process that occurs when one moves between light and dark rooms. We compared the total length of body sway (LNG) with a GRAVICORDER® (Anima, Japan) in 19 young people in an illuminated area (LNG: 108.3 ± 26.7 cm) and in darkness (LNG: 205.1 ± 57.1 cm) under three conditions. First, we measured body sway in the illuminated area; then each subject donned an eye mask and stayed in the dark for 5 min. The subjects then removed the eye masks and we measured body sway again in the illuminated area. Body sway was first measured during the adaptation process and then 3 and 7 min later.

We found that body sway gradually improved from just after (LNG: 132.7 ± 32.4 cm), to 3 min after (LNG: 110.5 ± 32.4 cm), to 7 min after (LNG: 91.5 ± 19.6 cm) removing the eye mask. Data collected at the last time point were equal to those collected in the beginning. This finding suggests that the change in visual information that occurs during the process of adapting from darkness to illumination affects postural control. In individuals whose walking ability has decreased, particularly in elderly individuals, the incidence of falls during trips to the restroom at night is high. Accordingly, we believe that the visual adaptation process affects postural control. This issue should be studied further.

The visual system distinguishes an object of interest and determines whether it is moving. With regard to the association between posture control and field of vision, one study reported that the parametric view has greater influence on the postural control system than foveal vision (Amblard and Carblanc 1980). However, it is important that the field of vision (the effective visual field) over which meaningful information can be obtained be wide. Because having a wide visual field helps an individual to sense an obstacle or danger, it is very important in postural control. Spatial attention and the ability to stop moving the eyes when needed are also very important in postural control.

Therefore, we evaluated eye function with an eye mark camera (EMR-8B, NAC Image Technology, Japan) while investigating dynamic postural control by using the EquiTest in elderly (mean age, 67.8 ± 6.1 years) and young individuals (mean age, 19.1 ± 0.5 years) (n = 14 each). As has been noted earlier, age-related changes in visual function influence postural control (Fig. 26.3). The elderly individuals changed their visual lines more quickly to collect information about body position and spatial relationships. Furthermore, their onset of moving was delayed compared

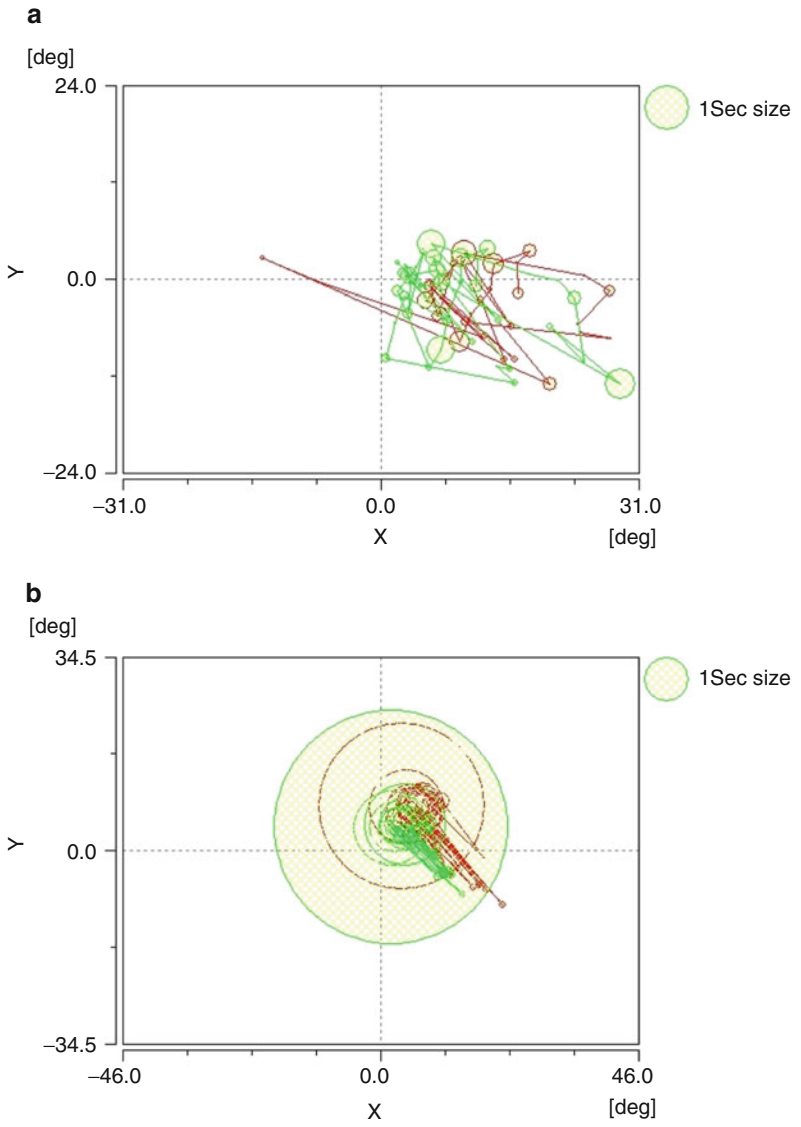

Fig. 26.3 Typical fixation-point pattern shifts in elderly individuals (Shiota and Ikeda 2009). The young individuals focused on one point, whereas the elderly individuals demonstrated a fast saccade while maintaining postural control. (**a**) Elderly individual (74 years old). (**b**) Young individual (19 years old)

with that of young people, meaning that it took elderly individuals longer to collect appropriate information required for postural control. That is, their visual information tended to provide temporally incorrect information to the central nervous system.

In addition, the convergence function that is necessary for the binocular cues of depth or distance perception decreased with age. Peripheral inputs from the visual, somatosensory, and vestibular systems are generally used to detect the body's position and movement in space with respect to gravity and the surrounding environment. However, it will be necessary to further clarify the correlation between visual function and physical function in future studies.

26.6 Summary

This chapter reports the age-related changes in postural control properties. Not only do the functions of the visual, vestibular, and somatosensory systems decrease, but the muscle, bone, and joint strength required for postural control declines with age. Aging decreases the sensory and movement functions needed to control the nervous system, including balance. This paper focuses on the sensory movement function that is important to balance, but it is necessary that the recognition and cognitive functions lead to safe and appropriate movements. In elderly individuals, cumulative decreases in individual sensory functions cause big problems. However, such decreases in body function induced by aging cannot be used to conclude the difference between individuals. An age-centric study of postural control that includes knowledge from various areas is expected in the future.

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K. Kanosue et al. (eds.), *Physical Activity, Exercise, Sedentary Behavior and Health*, DOI 10.1007/978-4-431-55333-5