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Sarcopenia and the Common Mental Disorders: a Potential Regulatory Role of Skeletal Muscle on Brain Function?

Julie A. Pasco[1,2] · **Lana J. Williams**[1] · **Felice N. Jacka**[1,3,4,5] · **Nicole Stupka**[1] · **Sharon L. Brennan-Olsen**[1,2] · **Kara L. Holloway**[1] · **Michael Berk**[1,3,6,7]

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Abstract While it is understood that body composition impacts on physical conditions, such as diabetes and cardiovascular disease, it is only now apparent that body composition might play a role in the genesis of common mental disorders, depression and anxiety. Sarcopenia occurs in ageing and comprises a progressive decline in muscle mass, strength and function, leading to frailty, decreased independence and poorer quality of life. This review presents an emerging body of evidence to support the hypothesis that shared pathophysiological pathways for sarcopenia and the common mental disorders constitute links between skeletal muscle and brain function. Contracting skeletal muscle secretes neurotrophic factors that are known to play a role in mood and anxiety, and have the dual role of nourishing neuronal growth and differentiation, while protecting the size and number of motor units in skeletal muscle. Furthermore, skeletal muscle activity has important immune and redox effects that impact behaviour and reduce muscle catabolism.

Keywords Sarcopenia · Sarcopenic obesity · Depression · Anxiety · Inflammation

Introduction

While it is known that body composition impacts on medical disorders, such as diabetes and cardiovascular disease, it is now apparent that body composition is associated with the genesis of the common mental disorders, depression and anxiety. It is clear that obesity is linked to the risk for depression in a bi-directional manner [1]. While there is some evidence linking obesity with anxiety disorders, this association

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✉ Julie A. Pasco
juliep@barwonhealth.org.au

Lana J. Williams
lanaw@barwonhealth.org.au

Felice N. Jacka
felicejacka@gmail.com

Nicole Stupka
nicole.stupka@deakin.edu.au

Sharon L. Brennan-Olsen
sharob@barwonhealth.org.au

Kara L. Holloway
khollo@barwonhealth.org.au

Michael Berk
mikebe@barwonhealth.org.au

[1] School of Medicine, Deakin University, Geelong 3220, Australia

[2] NorthWest Academic Centre, Department of Medicine, The University of Melbourne, St Albans 3021, Australia

[3] Department of Psychiatry, The University of Melbourne, Parkville 3010, Australia

[4] Murdoch Children's Research Institute, Melbourne 3000, Australia

[5] Black Dog Institute, Sydney, NSW, Australia

[6] Florey Institute of Neuroscience and Mental Health, Parkville 3052, Australia

[7] Orygen, The National Centre of Excellence in Youth Mental Health, Centre for Youth Mental Health, Parkville 3052, Australia

remains unclear because of the cross-sectional nature of most of the studies to-date and the heterogeneity of anxiety disorders [2]. However, the possible role of muscle, which is the component of body composition important for vitality and well-being, remains largely unexplored.

Sarcopenia, which means 'poverty of flesh', occurs in ageing and comprises a progressive deterioration in the mass, strength and function of muscle tissue [3]. Such deterioration can have serious health consequences, and sarcopenia is the prime driver of the decreased independence and quality of life associated with ageing [4]. Peak muscle mass and strength are attained in late adolescence/early adulthood followed by an age-related decline; decreases in both total and appendicular skeletal muscle mass can become particularly marked in the elderly [5•]. Achievement of optimal peak muscle mass and performance, and a slowing or reversal of age-related muscle deterioration [6, 7], should be a focus of health recommendations across the lifecourse, aimed at reducing the burden of disability and frailty in later life.

The purpose of this review is to address the hypothesis that sarcopenia is linked to the common mental disorders. The face validity for this tenet derives from the evidence of common pathophysiological pathways for sarcopenia, anxiety and depression, that involve neurotrophins, oxidative stress and inflammation, and modulated by lifestyle behaviours (Fig. 1). For example, contracting skeletal muscle is a major source of neurotrophic factors which appear to play a critical role in psychiatric illness. Furthermore, skeletal muscle activity has important immune and redox effects that both reduce muscle catabolism [8] and enhance mood [9].

Associations Between Sarcopenia and Common Mental Disorders

Using observational cross-sectional data from community-dwelling people aged 60 years and older in Ireland, the odds ratio (OR) for physical frailty was associated with a higher likelihood of anxiety and depressive symptoms, independent of age, sex and past mood and anxiety (OR 4.3, 95 % CI 1.5–11.9) [10••]. In this study, physical frailty was measured using the Fried biological syndrome model that incorporated slow walking speed, poor grip strength, physical inactivity, poor endurance and weight loss [11]. In a cross-sectional Korean study, also involving men and women aged 60 years and older, individuals with self-reported depression or those taking antidepressants had lower appendicular skeletal muscle mass than those free of depression or antidepressant use (4.2 % lower in men and 3.7 % lower in women) [12]. Multivariable logistic analyses revealed that the odds for depression in men were 51 % lower for each standard deviation increase in appendicular skeletal muscle mass; however, the association was not significant in the adjusted model for women. In another study, this time involving hospitalised patients, those identified with sarcopenia were more likely to suffer from depression, have a longer length of hospital stay, were at greater risk of non-elective readmission and had a higher mortality rate [13].

There are some published data from the USA on sarcopenia as a therapeutic target in depression. In a clinical trial involving a home-based telemedicine exercise intervention for middle-aged and older individuals, management of sarcopenia using resistance training was associated with a reduction in depressive symptoms [14]. Similarly, in an Australian secondary prevention study of individuals at risk of type 2 diabetes, a 10-week programme of resistance training at low-moderate and moderate-high intensities involving major muscle groups, resulted in improved muscle strength and reduced depressed mood, such that the percentage change in relative muscle strength correlated with the change in scores for the Cardiac Depression Scale (r=-0.46, p=0.008) [15].

Potential Mechanisms Linking Sarcopenia and Common Mental Disorders

Neurotrophins Neurotrophins promote neuronal survival, differentiation and synaptic potentiation. Brain-derived neurotrophic factor (BDNF) acts on neurons in both the central and peripheral nervous systems and drives neurogenesis in the hippocampus [16]. The hippocampus is a key region of the brain, implicated in psychiatric illness; it has been shown that hippocampal volume is reduced in adults with depression [17], while antidepressants increase neurogenesis [18]. Despite its name, BDNF is produced in a variety of tissues, including skeletal muscle. BDNF is expressed in myoblasts in culture and in myogenic progenitors, known as satellite cells, which are responsible for growth and repair of skeletal muscle [19]; however, the role of satellite cells in the regeneration of old muscle remains unclear [20]. Skeletal muscle-derived BDNF functions as a retrograde survival factor for regenerating motor neurons [19], with the capacity to reduce the denervation-induced atrophy of skeletal muscle seen in sarcopenia. Similarly, neurotrophin-3, a key brain neurotrophin, is expressed by muscle [21]. BDNF is one of the most explored biomarkers in depression [22], and increases in BDNF parallel improvements in mood [23]. Neurotrophin-3 is similarly implicated in depression, albeit with a much smaller evidence base [24].

Inflammation and Oxidative Stress Many studies report a role of chronic inflammation and oxidative stress in the pathophysiology of many common chronic diseases, especially in association with ageing [25, 26, 27•]. In an observational study of more than 2000 participants in the Health, Aging and Body Composition Study, tumour necrosis factor alpha

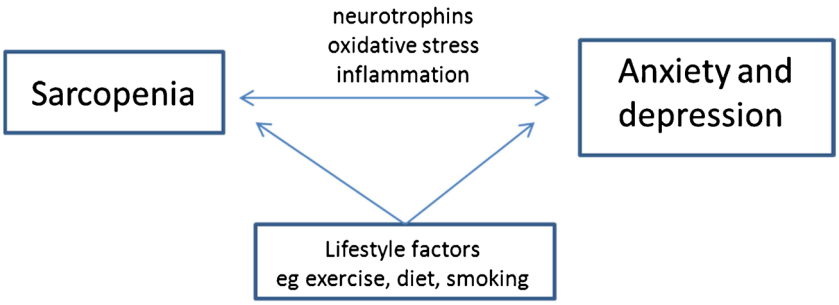

Fig. 1 Schematic pathways linking sarcopenia and the common mental disorders, anxiety and depression. The mediating roles of immune and redox effects are shown, together with suggested common lifestyle risk factors

(TNFα) was consistently associated with declining muscle mass and strength [28]. Obesity is an inflammatory state, as adipocytes synthesise and secrete pro-inflammatory cytokines [29]. Serum markers, such as C-reactive protein (CRP) and interleukin (IL)-6, increase with increasing fat mass—and are negatively associated with appendicular lean mass [30]. The occurrence of sarcopenia in the context of obesity, particularly abdominal obesity, which is also seen with ageing [31], constitutes the condition known as sarcopenic obesity [32, 33]. Sarcopenic obesity is similarly an inflammatory state, and this condition contributes to catabolic effects on muscle [34].

Studies in rats show that a reduction of low-grade inflammation by ibuprofen slows loss of muscle and limits the development of sarcopenia [35]. Nuclear factor–kappaB (NF-κB) is thought to upregulate IL-6 and TNFα [36]. Furthermore, reactive oxygen species (ROS) serve as second messengers for TNFα in skeletal muscle, activating NF-κB both directly and indirectly [37]. Increased TNFα expression in serum and muscle promotes apoptosis in the mitochondria, causing loss of muscle fibres [38]; indeed, TNFα is recognised as one of the primary signals inducing apoptosis in muscle—and brain. The glutathione system dampens ROS in response to inactivity-mediated skeletal muscle atrophy [39].

Low levels inflammation and oxidative stress also play a role in depression [40•], and administration of exogenous cytokines such as IL-1, interferon alpha (IFNα) and TNFα evokes a depressed mood state [41]. Over a decade ago, elevated levels of complement component (C)4, IL-6 and CRP, but not C3, were found to be associated with depression [42]. Oxidative stress induced by administration of L-buthionine-(*S*, *R*)-sulfoximine (BSO) [43] and xanthine plus xanthine oxidase (X+XO) [44] promotes NF-κB-dependent inflammation [45] and causes anxiety-like behaviour in rats.

Antidepressant treatment normalises markers of oxidative stress and inflammation [46] and a positive correlation is seen between oxidative stress index values and depression severity [47], suggesting an immunomodulatory role for antidepressant medication. Similarly, etanercept, a TNFα inhibitor used to treat psoriasis, decreases anxiety and depression in a rodent model [48], and improves fatigue and reduces depression in psoriasis patients with high baseline CRP [49]. More recently, elevated translocator protein density, which is a central marker of neuroinflammation, is found in the brain during episodes of major depression [50].

In an Australian study that examined the association between serum levels of high-sensitivity (hs) CRP and risk of de novo major depressive disorder (MDD) over a decade among randomly selected women with no prior history of depression, MDD risk increased by 44 % for each standard deviation increase in log-transformed hsCRP (adjusted HR 1.44, 95 %CI 1.04–1.99) [51]. Serum hsCRP was thus identified as an independent predictor of de novo MDD risk. Complementing these data, exposure to statins and aspirin, which have anti-inflammatory properties, have been shown to reduce the risk for depression in both clinical [52, 53] and community [54] settings, implicating both inflammation and the glutathione antioxidant system in the pathophysiology of mood disorders. Clinical trials also show that treatment with *N*-acetyl cysteine (NAC), a precursor of cysteine and glutathione that has anti-inflammatory effects, improves depressive symptoms in unipolar and bipolar depression [55–57]. Taken in aggregate, this series of reports supports a role of inflammation and oxidative stress in the pathophysiology of both sarcopenia and the common mental disorders.

Sarcopenia, Mood and Anxiety: What Common Role Does Lifestyle Play?

Exercise In separate studies in Australia, ambulatory activity was reported to be associated with the maintenance of leg strength and muscle quality in older women [58], and habitual physical activity was found to be associated with a reduced likelihood of new depressive and anxiety disorders in older men and women [59]; both of these associations were driven by leisure-time activities. While resistance training is a recognised strategy for slowing or preventing the age-related loss of skeletal muscle mass and function [60], exercise and physical activity are recognised as effective strategies for treating depression and anxiety [61, 62, 63•] and reducing the risk for new onset of these disorders [59, 64•]. Contracting skeletal muscle produces BDNF [65], and exercise has been shown to enhance circulating BDNF in a range

of diverse settings such as during moderate exercise in patients with multiple sclerosis [66], endurance training in healthy young men [67] and in sprint athletes [68]. Insulin-like growth factor-1 (IGF-1) is one of the factors involved in the expression of BDNF; it is increased after exercise and has neurological effects [69] as well as modulating skeletal muscle growth and atrophy [70]. Exercise also increases a number of myokines such as IL-6 [71] that impact on lipid and glucose metabolism. Recovery after the exercise-induced IL-6 spike dampens the inflammatory response and oxidative burst activity [72]; the anti-inflammatory effects of BDNF [73] may play a role in this recovery. Chronic exercise is therefore known to down-regulate systemic inflammation and is the most evidence-based management strategy for insulin resistance [74]. Given the role of inflammation in depression [75], it similarly suggests that exercise-induced downregulation of IL-6 and the anti-inflammatory effects of BDNF may be relevant pathways.

Nutrition Adequate nutrition is essential for maintaining skeletal muscle and mental well-being. Prospective data describe a protective effect of dietary protein for sarcopenia [76] and positive associations of protein intakes with whole body muscle mass, appendicular muscle mass and upper arm muscle area [77]. Furthermore, muscle mass losses are considerably reduced for individuals with high protein intakes [78], and there are some data showing that consuming the recommended intake of red meat may be protective against depression [79]. Circulating levels of IGF-1 are positively related to protein intakes [80].

There is some evidence to suggest that antioxidants might protect skeletal muscle against oxidative stress. Higher dietary intakes of antioxidants, particularly vitamin C, were associated with better knee extension strength in a study of Italians aged 65 years and older [81]. Data from the Fourth Korean National Health and Nutrition Examination Survey showed that frequent consumption of fruit was associated with a lower likelihood of sarcopenia in elderly men and women, while a similar negative association was observed for frequent vegetable consumption, albeit in men only [82]. There are other data that support a role for poor diet as a risk factor for common mental disorders. Individuals with diets characterised by higher intakes of unhealthy 'Western-type' foods are more likely to have either MDD or dysthymia, while those with better quality diets, rich in vegetables, lean meats, fish and wholegrains, are less likely to have either mood or anxiety disorders [83–85]. These findings accord with the description of a diet high in fat and refined carbohydrate being regarded as an inflammatory dietary pattern that increases inflammation [86] and might increase the risk for physical and mental disorders initiated and exacerbated by chronic inflammation.

Low levels of circulating vitamin D can cause myopathy, which is linked to muscle weakness; serum levels of 25-hydroxyvitamin D below 50 nmol/L are associated with increased body sway, while levels below 30 nmol/L compromise muscle strength [87]. There is some evidence that low vitamin D levels also increase the risk for depression [88]. Hypovitaminosis D as a shared risk factor between muscle weakness and mood disorders might be explained, at least in part, by vitamin D's immunomodulatory effects [89].

Smoking Sarcopenia, anxiety and depression are among the many diseases attributed to, or exacerbated by, smoking cigarettes/tobacco [90–94]. A recent meta-analysis suggested that smoking was a risk factor for sarcopenia; however, interpretation of the results from multiple studies was hampered by the heterogeneity in methods used for identifying sarcopenia [95]. In a cohort study of children and adolescents in Norway, smoking in adolescence increased the risk for early adulthood anxiety [93]. Using prospective Australian data, smoking was identified as a risk marker for the onset of de novo MDD and, compared with non-smokers, the risk for MDD more than doubled for heavy smokers (>20 cigarettes/day) [94]. It is noteworthy that muscle dysfunction is common for patients with chronic obstructive pulmonary disease [96], and this is a population also vulnerable to depression [99]. Cigarette smoke generates free radicals, causing lipid peroxidation, oxidation of proteins and other tissue damage in smokers [97]. There is some evidence that cigarette smoke activates NF-κB and increases TNFα release and production [98]. The milieu of increased inflammation and oxidative stress increases muscle catabolism [99, 100] and also increases the risk profiles for anxiety and depression [9, 101].

Conclusions

Establishing a link between sarcopenia and common mental disorders may have major translational, clinical and public health implications, as sarcopenia is a condition open to modification. Currently, there is no coherent public health strategy for preventing common mood disorders, at least in part due to lack of knowledge of potentially reversible risk factors that might include modifiable health behaviours. While physical exercise is recognised as a valuable therapeutic modality for both depression and anxiety, the role of sarcopenia in vulnerability for psychiatric illness is largely unexplored.

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Compliance with Ethics Guidelines

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Human and Animal Rights and Informed Consent All studies by the authors involving animal and/or human subjects were performed after approval by the appropriate institutional review boards. When required, written informed consent was obtained from all participants.

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- • Of importance
- •• Of major importance

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