Chapter 3

From Sarcopenia to Frailty: The Pathophysiological Basis and Potential Target Molecules of Intervention

Zhuowei Yu, Qingwei Ruan, Grazia D'Onofrio and Antonio Greco

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.69639

Abstract

Skeletal muscle is not only an endocrine organ but also one of core components of musculoskeletal system. Sarcopenia refers to a decline in the skeletal muscle mass and function. The former involves the size and number of changes in two types of myofibers, lower satellite cell density, and regeneration ability. The latter shows a loss of muscle strength. Frailty is a geriatric syndrome with multisystem impairment associated with increased vulnerability to stressors. Sarcopenia increases the risk of frailty and may be one of the major causes of physical frailty phenotype. Sarcopenia is also potentially associated with cognitive frailty phenotype. Aging might be the common underlying pathophysiology of sarcopenia and frailty. Therefore, there are some potential target molecules in aging-related signaling pathways that might be associated with sarcopenia and frailty. Nevertheless, sarcopenia can mediate metabolism and promote accelerate systemic aging, frailty, and age-related diseases by myokines in an endocrine manner. Lifestyle interventions (resistance exercise and dietary restriction) of gerontoscience are effective in the prevention of sarcopenia. Some pharmacological agents are registered in different phases of clinical trials for sarcopenia intervention. Phytochemicals, mTOR inhibitors, metformin and acarbose, NAD precursors, and sirtuin activators demonstrated that multiple target antiaging effects might also have preventive and therapeutic perspectives on sarcopenia and frailty.

Keywords: sarcopenia, physical frailty, cognitive frailty, aging

1. Introduction

Sarcopenia and frailty are two common geriatric conditions that may co-occur within a single individual with aging. Frailty is a heterogeneous clinical condition depended on different domains.

Definitions of frailty includes fried physical frailty phenotype (weight loss, exhaustion, physical inactivity, handgrip strength, and walk time) [1] and frailty index (use of walking aid, activities of daily living, incontinence, cognitive impairment, and multiple other components) [2]. Cognition performance decline is considered as a domain in Frailty index, but as "cognitive frailty" phenotype when physical frailty and potentially reversible cognitive impairment simultaneously occur [3]. Sarcopenia refers to decline in skeletal muscle mass and function, which includes primary sarcopenia, or age-related loss of muscle mass and function decline, and secondary sarcopenia resulting from nutrition, activity, and disease-related loss of muscle mass [4]. Sarcopenia is different from cachexia, which combines the loss of both muscle and fat. Obviously, physical frailty and sarcopenia share the core components, physical function impairment (weakness, slow walking speed, and balance problems), and sarcopenia is considered as the biological substrate and the pathway of physical frailty development [5, 6].

Although it is a controversy, sarcopenia and frailty are two separate conditions based on their definitions, and outpatients with sarcopenia were more likely to be more frail than frail outpatients to be sarcopenic [7]. Skeletal muscle is not only a component of muscloskeletal system but also an endocrine organ. Two components of sarcopenia also obviously contribute to frailty, a geriatric syndrome that has been defined as a multisystem impairment characterized by decreased reserve associated with increased vulnerability to stressors. First, the loss of muscle mass plays a critical role in unintentional weight loss of frailty in the elderly. Second, age-related loss of muscle strength, commonly referred as dynapenia, was associated with both sarcopenia and frailty [8]. Sarcopenia and frailty had the sensitivity and specificity for dynapenia of 33 and 89%, 17 and 98%, respectively. A longitudinal aging study with 731 community-dwelling older people demonstrated that dynapenia was related to the cognitive impairment [9]. Thus, dynapenia is also the important factor responsible for frailty. Moreover, muscle cross-talks with other tissues and organs by myokines in an endocrine manner to mediate metabolism and promote aging, diseases, and frailty. Here, we review the epidemiological evidence and pathophysiological basis of skeletal muscle aging, or primary sarcopenia, that result in frailty and potential target molecules of intervention. Particularly, we focus on the pathophysiological basis of sarcopenia, including age-related changes of nutrient and stress sensors, positive and negative regulators of muscle growth, and the maintenance of muscle mass and function. Moreover, we also summarize the underlying mechanisms of sarcopenia accelerating systemic aging, frailty, and age-related diseases. Finally, we looked for the potential target molecules of intervention of sarcopenia according to the pathophysiological basis and relevant signal pathways.

2. From Sarcopenia to frailty: the pathophysiological basis

2.1. From sarcopenia to physical and cognitive frailty: the epidemiological evidence

Frailty is heterogeneous and contains physical and cognitive multiple domains. In this context, the concept of "Cognitive frailty" becomes essential. It refers to simultaneous presence of physical frailty and potentially reversible cognitive impairment but without dementia [3]. Cognitive frailty includes reversible and potentially reversible subtypes [10] and may represent

http://dx.doi.org/10.5772/intechopen.69639

a precursor of neurodegenerative processes [10]. The link between physical function and cognitive decline provides important targets to develop effective preventive strategies in earlier cognitive impairment stages [3, 11, 12].

Epidemiological studies suggested that sarcopenia increases the risks of both physical frailty and cognitive impairment. Loss of muscle mass and strength is associated with increased dependence, frailty, and mortality. Low appendicular lean mass related to body mass index could detect patients at risk for frailty [13]. A cross-sectional study with small subjects, 273 Japanese community-dwelling older women aged >65 years showed that sarcopenia was related only with prefrailty and frailty, and cognitive decline was related to frailty [14]. However, several studies showed an association between sarcopenia parameters and cognitive impairment. Low handgrip strength was shown to correlate with a decrease in Mini Mental State Examination (MMSE) score [15]. Other studies also reported an association between handgrip strength and the risk of Alzheimer disease and the rate of cognitive decline [16–18]. In prospective studies, a decrease in physical performance in relation to future dementia was demonstrated [19, 20]. Subjects aged >65 years who scored low in a physical performance test had a three-times higher risk of developing dementia at a 6-year follow-up [21]. Recently, the new concept of "Motoric Cognitive Risk (MCR) syndrome" was defined as having mild cognitive impairment (MCI) and slow gait, supporting the common underlying mechanism in physical and cognitive impairment [22]. MCR offered further benefit on predicting dementia than MCI or slow gait alone. A recent study demonstrated an association between increased risk of cognitive impairment, mainly MCI, and poor lower extremity function [21].

2.2. Aging promotes sarcopenia and frailty

Factors relating to skeletal muscle mass and strength changes include the loss of motor units innervating muscle, age-related hormone changes, muscle hypoxia resulting from atherosclerosis and chronic proinflammatory status, decreased physical activity and protein intake, age-related insulin resistance, and mitochondrial dysfunction [23]. Aging leads to a preferential reduction of type II myofiber size. There is a significant loss of type II muscle fibers, lower satellite cell density, and lower satellite cell/fiber ratio in older individuals with sarcopenia [24]. The loss of motor units innervating muscle, especially type II myofibers [25], and the decreased blood flow to muscle [26] results in the loss of muscle mass. Meanwhile, many elderly population with insulin resistance who maintains the sensitivity of glucose metabolism, but not protein synthesis, show age-related anabolic resistance, meaning the reduced muscle protein synthesis [27, 28]. However, muscle of older individuals with type 2 diabetes [29] metabolic syndrome [30] demonstrated a significant low proportion of type I fibers that is positively associated with the severity of insulin resistance. Thus, the loss of muscle mass and the alterations of myofiber type proportion due to insulin resistance could potentially affect whole body glucose homeostasis [31]. Age-related hormone changes, for example, the decline of anabolic hormone testosterone leads to the loss of both muscle mass and strength [32]. The decline in both growth hormone and insulin-like growth factor 1 are related to the loss of muscle mass but not muscle strength [33]. Muscle hypoxia results from atherosclerosis and chronic proinflammatory status leads to the loss of both muscle mass and strength [25]. Other factors, decreased physical activity and protein intake, also involve in the loss of muscle mass.

Age-related decline of the levels of 25(OH) vitamin D due to a decreased production of 25(OH) vitamin D in skin or a decline in vitamin D absorption can result in the decline of muscle function [25]. Age-related insulin resistance causes an increase of fat infiltration into muscle and a decline in muscle strength [34]. Mitochondrial dysfunction in aging skeletal muscle causes oxidative damage and the decline of energy generation to maintain function properly [35].

The biological mechanisms underlying the association between sarcopenia and frailty are uncertain [36]. Any plausible explanations are that physical, motor, and cognitive functions are not causally related but are affected by common underlying pathophysiology [37]. Frailty, cognitive impairment, and sarcopenia share many common risk factors, such as immune or inflammatory response, oxidative stress, and hormonal dysregulation [38, 39]. In view of this, frailty, cognitive impairment, and sarcopenia may be highly interrelated [38, 40]. Inflammatory markers such as C-reactive protein and interleukin-6 concentrations are correlated negatively with muscle strength and physical performance [41, 42]. According to the definition of cognitive frailty, physical factors are the potential causes of cognitive impairment. In a study, high levels of these markers are associated with a 66% increase in cognitive impairment risk at 4-year follow-up in elders with metabolic syndrome [43]. Elevated oxidative stress [44], decreased sex steroid levels [45, 46], and insulin resistance [47, 48] are also involved in the association between physical and cognitive dysfunction.

2.3. The maintenance of muscle mass and function

The maintenance of normal muscle mass and function depends on the dynamic balance between positive and negative regulators of muscle growth. Muscle growth promoters include follustatin (FST), bone morphogenetic proteins (BMPs), brian-derived neurotrophic factor (BDNF), and irisin. Muscle growth suppressors contain myostatin, transforming growth factor beta (TGFβ), activins A and B, growth, and differentiation factor-11 and -15 [49, 50]. Age-related changes of these molecules, together with other factors, such as age-related diseases, chronic low-grade systemic inflammation, insulin resistance, endocrine aging, low physical activity, aging-related impairment of neuromuscular junction dysfunction, and contractile insufficiency because of skeletal muscle-specific troponin T leakage from sarcomere, result in imbalance between positive and negative regulators of muscle growth and sarcopenia development [49]. Muscle growth suppressors through the antibody-coupled, T-cell receptor/anaplastic lymphoma kinase 4,5 (ActR/Alk 4,5), or type I and II TGFβ receptor (TβRI and TβRII), phosphorylate mothers against decapentaplegic homolog 2/3 (SMAD 2/3), then combine SMAD 4 and inhibit the activation of an alternative pathway/mammalian target of rapamycin (Alt/mTOR) signal. TGFβ promotes SMAD3 binding to the promoters of both fibronectin type III domain containing 5 (FNDC5) and procaspase-activating compound 1α (PAC-1α), and suppresses the expression of irisin and PAC-1α [51].The elevated growth differentiation factor 11 (GDF11) increases the risk for age-related frailty and comorbidities [50]. Muscle growth promoters through their receptors phosphorylate SMAD 1/5/8 decrease the inhibition of Alt/mTOR signal and maintain muscle mass and strength. Insulin resistance due to aging, obesity, and diabetes results in the suppression of insulin/insulin-like growth factor-1/phosphatidyl Inositol 3-kinase/protein kinase B (IGF 1/PI3K/AKT)/mTOR, and muscle hypotrophy and dysfunction of metabolism;

http://dx.doi.org/10.5772/intechopen.69639

the less activated Alk fails to block the nuclear translocation of Foxo 3 to enhance the expression of autophagy-related genes and the consequent protein degradation [31, 52].

2.4. Sarcopenia accelerates systemic aging, frailty, and age-related diseases

Skeletal muscle influence systemic aging and lifespan by nutrient and stress sensors and myokines [53]. DNA damage and mutations are particularly prominent in aging skeletal muscle. Overexpression of phosphoenolpyruvate carboxykinase (PEPCK-C) and mitochondrial uncoupling proteins delays reproductive aging and decreases the incidence of several age-related diseases. Nutrient and stress sensors in sarcopenia include decreased sirturin 1 resulting from low nicotinamide adenine dinucleotide (NAD)+ synthesis and high NAD+ consumption and low adenosine monophosphate-dependent protein kinase (AMPK) activity, which results in the decline of the activity of peroxisome proliferator-activated receptor gamma coactivator-1a (PGC-1a) [54, 55]. The overexpression of AMPK and PGC-1a in muscle not only delays the age-related muscle deterioration but also slows the functional decline of other tissues, delay age-related metabolic defects, including systemic low-grade chronic inflammation, insulin resistance, increase in the stress resistance of the organism and extend lifespan. The other two nutrient sensors, insulin/insulin-like growth factor (IIS) and mTOR signaled nutrient abundance (high fat, amino acids, and sugar diet) and anabolic activity, are major accelerators of aging. mTOR inhibition by rapamycin or mTORC1 activity inhibition by genetical modification, and the downregulation of mTORC1/ribosomal protein S6 kinase beta-1 (S6K1) increases lifespan in mammals [55]. The decrease in regenerative capacity and skeletal muscle loss with age coincides with suppression of IIS pathways which is an attempt to promote longevity of the organism and survival within the tissue [56]. Age-related sarcopenia is associated with an increase in abdominal obesity, which refers to sarcopenic obesity [57]. Sarcopenic obesity leads to the infiltration of fat into the muscle and the accumulation of triglycerides within the cell, which impairs the function of the insulin receptor substrate causing insulin resistance, a lower lipid buffering capacity, and anabolic resistance in muscle [23, 58]. Sarcopenic obesity also results in cognitive impairment because of insulin resistance. In a cohort of 1570 older British men, compared with participants in the normal cognitive aging group, those elder men with severe cognitive impairment were more likely to be sarcopenic, with waist circumference >102 cm, BMI >30 kg/m^2 and to be in the upper quintile of total fat mass, central fat mass, peripheral fat mass, and visceral fat level after age-adjusted multinomial logistic regressions [59]. In experiment animal mouse, obesity in combination with sarcopenia exacerbates blood-brain barrier disruption, neuroinflammation, and oxidative stress of hippocampus, which likely contribute to the remarkable cognitive decline [60]. Calorie restriction and exercise increase the concentrations of metabolic effectors NAD+ and AMP but reduce the concentrations of the hormonal effectors IIS and growth hormone. Meanwhile, these interventions also decrease the levels of glucose, amino acids, and lipids, recover downstream activity, such as DNA repair, mitochondrial biogenesis, and function, promote homeostasis, decrease frailty and comorbidities.

Beyond the profound influence on systemic aging and body metabolism, muscle secrete myokines, which act on muscles and other tissues, such as adipose, bones and brain in an autocrine, paracrine, and endocrine fashion [61]. The metabolites released from muscle and the interactions

between muscle and nerve also participate in the systemic effects of muscle on the organism's physiology. Exercise can activate PGC-1α/FNDC5 pathway, promote myokine irisin secretion, induce hippocampal BDNF release, and improve cognitive function [62].

3. From sarcopenia to frailty: the potential target molecules of intervention

The major causes of frailty include chronic diseases, such as congestive heart failure, diabetes, chronic obstructive pulmonary disease (COPD), anemia, polymyalgia rheumatic, and endocrine disorder; decreased nutrient intake because of anorexia resulting from social factors, decline in taste and smell, altered fundal compliance, enhanced release of cholecystokinin, increased leptin and cytokines, sarcopenia, and pain [63]. Treating the chronic diseases can reverse the loss of muscle mass and frailty, such as with angiotensin-converting enzyme inhibitors in some patients with congestive heart failure, both erythropoietin and darbepoietin-α in the individuals with anemia, and vitamin B12 supplementation in acrocytic anemia and related cognitive impairment. Lifestyle interventions play critical roles in the prevention of sarcopenia, frailty, and cognitive impairment. Physical exercise, particularly resistance exercise, can improve muscle mass and strength in the elderly [64, 65] and obese elderly [58]. Individuals with higher initial adiposity experience less improvement in both muscle strength and physical function [66]. Moreover, the addition of caloric restriction during resistance training improves mobility and does not compromise other functional adaptations to resistance training [66]. Resistance training also can increase circulating irisin [67] and improve cognitive performance [62]. In addition, physical exercise and caloric restriction can benefit age-related insulin resistance, reduced mitochondrial biogenesis, and failure of autophagy [68]. However, it is undesirable to use caloric restriction alone in sarcopenic elderly, which results in further loss of lean tissue mass. The oldest olds also with anabolic resistance and frailty find it difficult to perform resistance exercise to achieve benefit effects.

Dietary interventions including protein intake, antioxidants, and vitamin D fortification may benefit the conditions of sarcopenia and frailty. Protein supplies the amino acids, especially leucine, which may activate the signaling pathways required for muscle synthesis. Vitamin D deficiency is common in individuals with sarcopenia, frailty, and cognitive impairment. However, the effects of both protein supplementation and vitamin D intervention on muscle strength and physical performance have mixed results [69]. Although individuals with higher overall antioxidant status have better physical function, such as walking speed [70], antioxidant interventions might not attenuate, and even aggravate sarcopenia due to the health-promoting action of reactive oxygen spices [71].

There are no licensed treatments for sarcopenia and frailty. Pharmacological agents proposed and focused by investigators, with potential for treating sarcopenia include the myostatin signaling pathway and hormone replacement therapy (**Table 1**), currently are at various stages of development [72]. Myostatin, the family member of TGF-β, is a skeletal muscle-specific myokine. Myostain binding with activin type IIB receptor inhibits myoblast proliferation, muscle

Mechanism of action	Drug name	Drug developer	Indication sought	Study phase
I. Myostatin antagonists				
Activin receptor trap	ACE-031	Acceleron	Duchenne muscular dystrophy	Phase 3 (trial terminated early)
Myostatin antibody	REGN-1033	Regeneron/Sanofi	Sarcopenia	Phase 2
	LY-2495655	Eli Lilly	Hip arthroplasty Elderly Fallers Cancer cachexia	Phase 2
	PF-06252616	Pfizer	Inclusion body myositis	Phase 1
Activin receptor inhibitor	Bimagrumab (BMY338)	Novartis	Sarcopenia Hip fracture Cancer and COPD cachexia	Phases 2 and 3 Phase 2
II. Selective androgen receptor modulators	Enobasarm (ostarine)	GTx	Cancer cachexia	Phase 3 (did not meet primary endpoint)
III. Skeletal troponin activators	Tirasemtiv CK-2017357	Cytokinetics	Amyotrophic lateral sclerosis myasthenia gravis	Phases 2 and 3

Table 1. Pharmacological agents in development with potential for treating sarcopenia [72].

strength, and mass by negative regulation of mTOR signaling [73]. Myostatin inhibition by activin receptor trap or inhibitor and myostatin antibody might be useful agent for the treatment of human muscle degenerative diseases (**Table 1**) [72]. Testosterone supplementation is another major focus for drug discovery of sarcopenia. Testosterone could increase both muscle mass and strength in men but are linked to adverse cardiovascular events with short durations of therapy [74, 75]. In order to decrease the side effects of testosterone, the selective androgen receptor molecules, including steroids and nonsteroids, have been developed, and some are at phase 3 (**Table 1**). Tirasemtiv is a fast skeletal troponin activator that sensitizes the sarcomere to calcium and amplifies the function of muscle in neuromuscular diseases, such as Amyotrophic Lateral Sclerosis and myasthenia gravis (**Table 1**) [76, 77].

Age is the greatest risk factor for nearly every major cause of mortality in developed nations [78] and the profound effect of aging on sarcopenia, frailty, and cognitive impairment is often overlooked. A number of aging-associated molecular signals might be the potential target in the prevention and treatment of sarcopenia, frailty, and cognitive impairment. Genetic or pharmacological regulation of NAD+/Sirt1, sestrins/AMPK/PGC1α, IGF-1/Akt/mTOR, TGF-β, myostatin, activins, GDFs /SMAD2/3, BMPs/SMAD1/5/8 signal molecules, myokine irisin and FGF21, the antagonist of myokine myostatin propeptide follistatin or follistatin-like 3, and urocortins can not only improve muscle mass and/or function but also delay frailty and age-related diseases [31, 54, 68]. Besides dietary restriction and exercise, geroscience interventions with translational potential include mTOR inhibitors, metformin and acarbose, NAD precursors and sirtuin activators, modifiers of senescence and telomere dysfunction, hormonal and

circulating factors, and mitochondrial-targeted therapeutics [78]. Phytochemicals obviously are ideal geroscience interventions with translational potential. They not only have multiple target molecules in many aging-related signalling pathways, such as sestrins/AMPK/PGC1α, IGF-1/Akt/mTOR, against chronic inflammation and oxidative stress but also have systemic influence with low side effects, including skeletal muscle and other domains of frailty [79, 80].

4. Conclusion and perspective

Sarcopenia is one of the important causes of physical frailty. Frailty contains different phenotypes, such as physical frailty and cognitive frailty or multiple domains in frailty index. Skeletal muscle influences body metabolism, systemic aging, accelerates physical frailty, cognitive impairment, and decrease healthy lifespan. Individuals with primary sarcopenia have an increase in the risk for frailty, cognitive impairment, and age-related diseases. Aging might be the common mechanism of sarcopenia, frailty, and cognitive impairment. Cognitive frailty is an important target of the prevention for both physical and cognitive disability [81]. Although some pharmacological agents are registered in different phases of clinical trials for sarcopenia intervention, no drug is really used for the clinical treatment of sarcopenia. Phytochemicals have effects on multiple targets of aging-related signaling pathways, and other targeted aging molecules, such as mTOR inhibitors, metformin and acarbose, NAD precursors, and sirtuin activators [78, 82], have preventive and therapeutic perspectives on sarcopenia, frailty, and age-related diseases.

Acknowledgements

This work was supported by grants from the Shanghai Hospital Development Center (No. SHDC12014221), Shanghai Municipal Commission of Health and Family Planning, Key developing disciplines (2015ZB0501).

Author details

Zhuowei Yu[1,2], Qingwei Ruan[1,2]*, Grazia D'Onofrio[3] and Antonio Greco[3]

*Address all correspondence to: 13661717346@163.com

1 Shanghai Institute of Geriatrics and Gerontology, Shanghai Key Laboratory of Clinical Geriatrics, Huadong Hospital, Shanghai, China

2 Research Center of Aging and Medicine, Shanghai Medical College, Fudan University, Shanghai, China

3 Department of Medical Sciences, Geriatric Unit & Laboratory of Gerontology and Geriatrics, IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo, Foggia, Italy

References

[1] Fried LP, Tangen CM, Walston J, et al. Frailty in older adults evidence for a phenotype. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2001;**56**:M146eM157

[2] Rockwood K, Stadnyk K, MacKnight C, et al. A brief clinical instrument to classify frailty in elderly people. Lancet. 1999;**353**:205-206

[3] Kelaiditi E, Cesari M, Canevelli M, et al. Cognitive frailty: Rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. The Journal of Nutrition Health and Aging. 2013;**17**:726-734

[4] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis report of the European working group on sarcopenia in older people. Age Ageing. 2010;**39**:412-423

[5] Bernabei R, Martone AM, Vetrano DL, Calvani R, Landi F, Marzetti E. Frailty, physical frailty, sarcopenia: A new conceptual model. Studies in Health Technology and Informatics. 2014;**203**:78-84

[6] Landi F, Calvani R, Cesari M, Tosato M, Martone AM, Bernabei R, Onder G, Marzetti E. Sarcopenia as the biological substrate of physical frailty. Clinics in Geriatric Medicine. 2015;**31**(3):367-374

[7] Reijnierse EM, Trappenburg MC, Blauw GJ, Verlaan S, de van der Schueren MA, Meskers CG, Maier AB. Common ground? The concordance of sarcopenia and frailty definitions. Journal of American Medical Directors Association. 2016;**17**(4):371.e7-12

[8] Iwamura M, Kanauchi M. A cross-sectional study of the association between dynapenia and higher-level functional capacity in daily living in community-dwelling older adults in Japan. BMC Geriatrics. 2017;**17**:1

[9] Huang CY, Hwang AC, Liu LK, Lee WJ, Chen LY, Peng LN, Lin MH, Chen LK. Association of dynapenia, sarcopenia, and cognitive impairment among community-dwelling older Taiwanese. Rejuvenation Research. 2016;**19**(1):71-78

[10] Ruan Q, Yu Z, Chen M, et al. Cognitive frailty, a novel target for the prevention of elderly dependency. Ageing Research Reviews. 2015;**20**:1-10

[11] Desai AK, Grossberg GT, Chibnall JT. Healthy brain aging: A road map. Clinics in Geriatric Medicine. 2010;**26**:1-16

[12] Ruan Q, D'Onofrio G, Sancarlo D, Greco A, Yu Z. Potential fluid-biomarkers of pathologic brain changes in Alzheimer's disease, implication in the screening of cognitive frailty. Molecular Medicine Report. 2016;**14**(4):3184-3198

[13] Spira D, Buchmann N, Nikolov J, Demuth I, Steinhagen-Thiessen E, Eckardt R, Norman K. Association of low lean mass with frailty and physical performance: A comparison

between two operational definitions of sarcopenia-data from the Berlin Aging Study II (BASE-II). The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2015;**70**(6):779-784

[14] Nishiguchi S, Yamada M, Fukutani N, Adachi D, Tashiro Y, Hotta T, Morino S, Shirooka H, Nozaki Y, Hirata H, Yamaguchi M, Arai H, Tsuboyama T, Aoyama T. Differential association of frailty with cognitive decline and sarcopenia in community-dwelling older adults. Journal of American Medical Directors Association. 2015;**16**(2):120-124

[15] Auyeung TW, Lee JS, Kwok T, Woo J. Physical frailty predicts future cognitive decline-a four-year prospective study in 2737 cognitively normal older adults. The Journal of Nutrition Health and Aging. 2011;**15**:690-769

[16] Alfaro-Acha A, Al Snih S, Raji MA, Kuo YF, Markides KS, Ottenbacher KJ. Handgrip strength and cognitive decline in older Mexican Americans.. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2006;**61**:859-865

[17] Taekema DG, Gussekloo J, Maier AB, Westendorp RG, de Craen AJ. Handgrip strength as a predictor of functional, psychological and social health. A prospective population-based study among the oldest old. Age Ageing. 2010;**39**:331-337

[18] Boyle PA, Buchman AS, Wilson RS, Leurgans SE, Bennett DA. Association of muscle strength with the risk of Alzheimer disease and the rate of cognitive decline in community-dwelling older persons. Archives of Neurology. 2009;**66**(11):1339-1344

[19] Wang L, Larson EB, Bowen JD, van Belle G. Performance-based physical function and future dementia in older people. Archives of Internal Medicine. 2006;**166**:1115-1120

[20] Camicioli R, Howieson D, Oken B, Sexton G, Kaye J. Motor slowing precedes cognitive impairment in the oldest old. Neurology. 1998;**50**:1496-1498

[21] Moon JH, Moon JH, Kim KM, Choi SH, Lim S, Park KS, Kim KW, Jang HC. Sarcopenia as a predictor of future cognitive impairment in older adults. The Journal of Nutrition Health and Aging. 2016;**20**(5):496-502

[22] Verghese J, Annweiler C, Ayers E, et al. Motoric cognitive risk syndrome: Multicountry prevalence and dementia risk. Neurology. 2014;**83**:718-726

[23] Kalyani RR, Corriere M, Ferrucci L. Age-related and disease-related muscle loss: The effect of diabetes, obesity and other diseases. Lancet Diabetes Endocrinology. 2014;**2**(10):819-829

[24] Purves-Smith FM, Sgarioto N, Hepple RT. Fiber typing in aging muscle. Exercise and Sport Sciences Reviews. 2014;**42**:45-52

[25] Morley JE. Frailty and sarcopenia: The new geriatric giants. Rev Invest Clin. 2016; **68**(2):59-67

[26] Leenders M, Verdijk LB, van der Hoeven L, et al. Patients with type 2 diabetes show a greater decline in muscle mass, muscle strength, and functional capacity with aging. Journal of American Medical Directors Association. 2013;**14**:585-592

[27] Rasmussen BB, Fujita S, Wolfe RR, Mittendorfer B, Roy M, Rowe VL & Volpi E. Insulin resistance of muscle protein metabolism inaging. FASEB Journal. 2006;**20**:768-769

[28] Fujita S, Glynn EL, Timmerman KL, Rasmussen BB & Volpi E. Supraphysiological hyperinsulinaemia is necessary to stimulate skeletal muscle protein anabolism in older adults: Evidence of atrue age-related insulin resistance of muscle protein metabolism. Diabetologia. 2009;**52**:1889-1898

[29] Oberbach A, Bossenz Y, Lehmann S, Niebauer J, Adams V, Paschke R, Schon MR, Bluher M & Punkt K. Altered fiber distribution and fiber-specific glycolytic and oxidative enzyme activity in skeletal muscle of patients with type 2 diabetes. Diabetes Care. 2006;**29**:895-900

[30] Stuart CA, McCurry MP, Marino A, South MA, Howell ME, Layne AS, Ramsey MW & Stone MH. Slow-twitch fiber proportion in skeletal muscle correlates with insulin responsiveness. Journal of Clinical Endocrinology and Metabolism. 2013;**98**:2027-2036

[31] Cleasby ME, Jamieson PM, Atherton PJ. Insulin resistance and sarcopenia: Mechanistic links between common co-morbidities. Journal of Endocrinology. 2016;**229**:R67-R81

[32] Baumgartner RN, Waters DL, Gallagher D, et al. Predictors of skeletal muscle mass in elderly men and women. Mechanisms of Ageing and Development. 1999;**107**:123-136

[33] Morley JE. Scientific overview of hormone treatment used for rejuvenation. Fertility and Sterility. 2013;**99**:1807-1813

[34] Rolland Y, Lauwers-Cances V, Cristini C, et al. Difficulties with physical function associated with obesity, sarcopenia, and sarcopenic-obesity in community-dwelling elderly women: The EPI-DOS study. The American Journal of Clinical Nutrition. 2009;**89**:1895-1900

[35] Hipple RT. Mitochondrial involvement and impact in aging skeletal muscle. Frontiers in Aging Neuroscience. 2014;**6**:211

[36] Clegg A, Young J, Iliffe S, Rikkert, MO, Rockwood K. Frailty in elderly people. Lancet. 2013;**381**(9868):752-762

[37] Hausdorff JM, Buchman AS. What links gait speed and MCI with dementia? A fresh look at the association between motor and cognitive function. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2013;**68**: 409-411

[38] Fulop T, Larbi A, Witkowski JM, et al. Aging, frailty and age-related diseases. Biogerontology. 2010;**11**(5):547-563

[39] Small GW. The pathogenesis of Alzheimer's disease. Journal of Clinical Psychiatry. 1998;**59**(Suppl 9):7-14

[40] Ruan Q, D'Onofrio G, Sancarlo D, Greco A, Lozupone M, Seripa D, Panza F, Yu Z. Emerging biomarkers and screening for cognitive frailty. Aging Clinical and Experimental Research. 2017. DOI: 10.1007/s40520-017-0741-8 [Epub ahead of print]

[41] Cesari M, Penninx BW, Pahor M, et al. Inflammatory markers and physical performance in older persons: The InCHIANTI study. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2004;**59**:242-248

[42] Schaap LA, Pluijm SM, Deeg DJ, Visser M. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. American Journal of Medicine. 2006;**119**:526:e529-526. e517

[43] Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. Journal of the American Medical Association. 2004;**292**:2237-2242

[44] Berr C, Balansard B, Arnaud J, Roussel A-M, Alpérovitch A. Cognitive decline is associated with systemic oxidative stress: The EVA study. Etude du Vieillissement Arteriel. Journal of American Geriatrics Society. 2000;**48**:1285-1291

[45] Hogervorst E, Bandelow S, Combrinck M, Smith AD. Low free testosterone is an independent risk factor for Alzheimer's disease. Experimental Gerontology. 2004;**39**:1633-1639

[46] Szulc P, Duboeuf F, Marchand F, Delmas PD. Hormonal and lifestyle determinants of appendicular skeletal muscle mass in men: The MINOS study. The American Journal of Clinical Nutrition. 2004;**80**:496-503

[47] Srikanthan P, Karlamangla AS. Relative muscle mass is inversely associated with insulin resistance and pre-diabetes. Findings from the third National Health and Nutrition Examination Survey. The Journal of Clinical Endocrinology & Metabolism. 2011;**96**:2898-2903

[48] Craft S. Insulin resistance and Alzheimer's disease pathogenesis: Potential mechanisms and implications for treatment. Current Alzheimer Research. 2007;**4**:147-152

[49] Kalinkovich A, Livshits G. Sarcopenia—The search for emerging biomarkers. Ageing Research Reviews. 2015;**22**:58-71

[50] Egerman MA, Cadena SM, Gilbert JA, et al. GDF11 increases with age and inhibits skeletal muscle regeneration. Cell Metabolism. 2015;**22**(1):164-174

[51] Tiano JP, Springer DA, Rane SG. SMAD3 negatively regulates serum irisin and skeletal muscle FNDC5 and peroxisome proliferator-activated receptor Y co-activator 1-α during exercise. The Journal of Biological Chemistry. 2015;**290**(12):7671-7684

[52] Sakuma K, Aoi W, Yamaguchi A. Current understanding of sarcopenia: Possible candidates modulating muscle mass. Pflugers Archiv—European Journal of Physiology. 2015;**467**:213-229

[53] Demontis F, Piccirillo R, Goldberg AL, et al. The influence of skeletal muscle on systemic aging and lifespan. Aging Cell. 2013;**12**(6):943-949

[54] Bonkowski MS, Sinclair DA. Slowing ageing by design: The rise of NAD+ and sirtuin-activating compounds. Nature Reviews Molecular Cell Biology. 2016;**17**(11):679-690

[55] López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013;**153**(6):1194-1217

[56] Sharples AP, Hughes DC, Deane CS, Saini A, Selman C, Stewart CE. Longevity and skeletal muscle mass: The role of IGF signalling, the sirtuins, dietary restriction and protein intake. Aging Cell. 2015;**14**(4):511-523

[57] Jura M, Kozak LP. Obesity and related consequences to ageing. AGE. 2016;**38**:23

[58] Tardif N, Salles J, Guillet C, Tordjman J, Reggio S, Landrier JF, Giraudet C, Patrac V, Bertrand-Michel J, Migne C, Collin ML, Chardigny JM, Boirie Y, Walrand S. Muscle ectopic fat deposition contributes to anabolic resistance in obese sarcopenic old rats through eIF2α activation. Aging Cell. 2014;**13**(6):1001-1011

[59] Papachristou E, Ramsay SE, Lennon LT, Papacosta O, Iliffe S, Whincup PH, Wannamethee SG. The relationships between body composition characteristics and cognitive functioning in a population-based sample of older British men. BMC Geriatrics. 2015;**15**:172

[60] Tucsek Z, Toth P, Sosnowska D, Gautam T, Mitschelen M, Koller A, Szalai G, Sonntag WE, Ungvari Z, Csiszar A. Obesity in aging exacerbates blood-brain barrier disruption, neuroinflammation, and oxidative stress in the mouse hippocampus: Effects on expression of genes involved in beta-amyloid generation and Alzheimer's disease. The Journals of Gerontology, Series A, Biological Sciences and Medical Sciences. 2014;**69**(10):1212-1226

[61] Ilich JZ, Kelly OJ, Inglis JE, et al. Interrelationship among muscle, fat, and bone: Connecting the dots on cellular, hormonal, and whole body levels. Ageing Research Reviews. 2014;**15**:51-60

[62] Wrann CD, White JP, Salogiannnis J, et al. Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. Cell Metabolism. 2013;**18**(5):649-659

[63] Sinclair AJ, Morley JE and Vellas B. Pathy's Principles and Practice of Geriatric Medicine. 5th ed. UK: John Wiley & Sons, Ltd; 2012. pp. 1387-1393

[64] Peterson M, Sen A, Gordon P. Influence of resistance exercise on lean body mass in aging adults: A meta-analysis. Medicine & Science in Sports & Exercise. 2012;**43**:249-258

[65] Liu CJ, Latham NK. Progressive resistance strength training for improving physical function in older adults. The Cochrane Database of Systematic Reviews. 2009;(3):CD002759

[66] Nicklas BJ, Chmelo E, Delbono O, Carr JJ, Lyles MF, Marsh AP. Effects of resistance training with and without caloric restriction on physical function and mobility in overweight and obese older adults: A randomized controlled trial. The American Journal of Clinical Nutrition. 2015;**101**(5):991-999

[67] Jedrychowski MP, Wrann CD, Paulo JA, Gerber KK, Szpyt J, Robinson MM, Nair KS, Gygi SP, Spiegelman BM. Detection and quantitation of circulating human irisin by tandem mass spectrometry. Cell Metabolism. 2015;**22**(4):734-740

[68] Sanchis-Gomar F, Pareja-Galeano H, Mayero S, Perez-Quilis C, Lucia A. New molecular targets and lifestyle interventions to delay aging sarcopenia. Front Aging Neuroscience. 2014;**6**:156

[69] Dodds R, Sayer AA. Sarcopenia and frailty: New challenges for clinical practice. Clinical Medicine (London). 2016;**16**(5):455-458

[70] Kaiser M, Bandinelli S, Lunenfeld B. Frailty and the role of nutrition in older people. A review of the current literature. Acta Biomedicine. 2010;**81**(Suppl 1):37-45

[71] Sanchis-Gomar F, and Derbre F. Mitochondrial fission and fusion in human diseases. The New England Journal of Medicine. 2014;**370**:1073-1074

[72] Beaudart C, McCloskey E, Bruyère O, Cesari M, Rolland Y, Rizzoli R, Araujo de Carvalho I, Amuthavalli Thiyagarajan J, Bautmans I, Bertière MC, Brandi ML, Al-Daghri NM, Burlet N, Cavalier E, Cerreta F, Cherubini A, Fielding R, Gielen E, Landi F, Petermans J, Reginster JY, Visser M, Kanis J, Cooper C. Sarcopenia in daily practice: Assessment and management. BMC Geriatrics. 2016;**16**(1):170

[73] Garatachea N, Pinos T, Camara Y, Rodriguez-Romo G, Emanuele E, Ricevuti G, et al. Association of the K153R polymorphism in the myostatin gene and extreme longevity. Age (Dordr). 2013;**35**:2445-2454

[74] Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: A systematic review and meta-analysis of placebo-controlled randomized trials. BMC Medicine. 2013;**11**:108

[75] Wallis CJ, Lo K, Lee Y, Krakowsky Y, Garbens A, Satkunasivam R, Herschorn S, Kodama RT, Cheung P, Narod SA, Nam RK. Survival and cardiovascular events in men treated with testosterone replacement therapy: An intention-to-treat observational cohort study. Lancet Diabetes Endocrinology. 2016;**4**(6):498-506

[76] Sanders DB, Rosenfeld J, Dimachkie MM, Meng L, Malik FI; Tirasemtiv in Myasthenia Gravis Study Group. A double-blinded, randomized, placebo-controlled trial to evaluate efficacy, safety, and tolerability of single doses of tirasemtiv in patients with acetylcholine receptor-binding antibody-positive myasthenia gravis. Neurotherapeutics. 2015;**12**(2):455-460

[77] Russell AJ, Hartman JJ, Hinken AC, Muci AR, Kawas R, Driscoll L, Godinez G, Lee KH, Marquez D, Browne WF 4th, Chen MM, Clarke D, Collibee SE, Garard M, Hansen R, Jia Z, Lu PP, Rodriguez H, Saikali KG, Schaletzky J, Vijayakumar V, Albertus DL, Claflin DR, Morgans DJ, Morgan BP, Malik FI. Activation of fast skeletal muscle troponin as a potential therapeutic approach for treating neuromuscular diseases. Nature Medicine. 2012;**18**(3):452-455

[78] Kaeberlein M, Rabinovitch PS, Martin GM. Healthy aging: The ultimate preventative medicine. Science. 2015;**350**(6265):1191-1193

[79] D'Onofrio G, Sancarlo D, Ruan Q, Yu Z, Panza F, Daniele A, Greco A, Seripa D. Phytochemicals in the treatment of Alzheimer's disease: A systematic review. Current Drug Targets. 2016. [Epub ahead of print]

[80] Corrêa RC, Peralta RM, Haminiuk CW, Maciel GM, Bracht A, Ferreira IC. New phytochemicals as potential human anti-aging compounds: Reality, promise, and challenges. Critical Reviews in Food Science and Nutrition. 2016. [Epub ahead of print]

[81] Panza F, Seripa D, Solfrizzi V, Tortelli R, Greco A, Pilotto A, Logroscino G. Targeting cognitive frailty: Clinical and neurobiological roadmap for a single complex phenotype. Journal of Alzheimer's Disease. 2015;**47**(4):793-813

[82] Verdin E. NAD^+ in aging, metabolism, and neurodegeneration. Science. 2015;**350** (6265):1208-1213

IntechOpen