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Decreasing Lean Body Mass with Age: Challenges and Opportunities for Novel Therapies

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Skeletal muscle, a principal component of body composition, along with fat and bone mass, is highly important for metabolic health since divergences from normal values are associated with several pathological conditions. Skeletal muscle mass and muscle strength exhibit a steady decline after the fourth decade of life and the rate of decline is accelerated with aging [1]. Loss of skeletal muscle mass is an independent risk factor for osteoporosis, falls and fractures, impaired function and mortality [2]. For this reason, there is a great interest to define the risk factors and the mechanisms that contribute to this.

Investigators with the Kangbuk Samsung Health Study evaluated the risks of rapid decreases in lean mass in reaction to age and sex among relatively young Korean adults, participants in a health screening program [3]. The authors point out that lean mass decreases significantly with aging, even among relatively young adults. This decrease was more noticeable among women who displayed a greater risk of a rapid decrease in lean mass, compared to men. Additionally, the percentage of fat mass lost increased as the participants aged.

There is a considerable number of studies regarding the loss of lean mass in the elderly and its relationship with metabolic diseases as well as mortality [4]. However, this is the first large-population study which examined this phenomenon in a population with a relatively wide age range and demonstrated that the same phenomenon exists even in younger adults. Kim et al. [3] attributed their findings to aging processes, sex-related genetic differences and racial differences, too. Hormonal and mitochondrial factors may play important roles, too.

The human skeletal muscle demonstrates age-associated mitochondrial changes, such as age-related decline in mitochondrial DNA and mRNA capacity, mitochondrial ATP production and oxygen consumption which lead to the formation of giant, bioenergetically inefficient mitochondria that release more reactive oxygen species [5]. Consequently, this mitochondrial dysfunction gives rise to activation of skeletal muscle apoptosis which causes the skeletal muscle atrophy that occurs with aging, a condition characterized by a reduction of skeletal mass, changes in protein synthesis, replacement of muscle fibers with fat and development of fibrosis [6].

It is noteworthy that the loss of muscle mass is often concealed by an unaltered or even increasing body mass index, due to increased adiposity. The co-presence of sarcopenia and obesity is defined as a syndrome which is relatively novel and it is called sarcopenic obesity (SO) [7]. These two conditions share common pathophysiological mechanisms such as insulin resistance (IR), increased levels of proinflammatory cytokines and inflammation, oxidative stress as well as specific hormonal changes. Specifically, IR, which develops with age, seems to be very closely associated with mitochondrial dysfunction, muscle fiber atrophy, changes in muscle fiber type and the development of skeletal muscle lipid deposition [7]. Moreover, insulin plays a key-role in maintaining muscle mass through stimulation of

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protein synthesis and thus IR prompts proteolysis in muscles [8]. As regards the role of inflammation and oxidative stress, which are also associated with aging, it has been suggested that sarcopenia is a proinflammatory state [9]. Oxidative stress promotes the expression of transcription factors like nuclear factor κB, which stimulates proteolytic pathways and augments the generation of proinflammatory cytokines and the cytokine-related aging process [9]. Tumor necrosis factor α affects protein synthesis by modifying translation initiation [10]. Furthermore, high levels of interleukin 6 and C-reactive protein seem to be associated with a more pronounced decline in muscle strength [11].

Skeletal muscle is considered to be a secretory organ. One of its secreted factors (myokines) with an important role in the control of skeletal muscle mass is myostatin. Myostatin belongs to the transforming growth factor β family, is a strong inhibitor of skeletal muscle differentiation and growth [12] and it seems to be related to muscle function parameters, such as strength and power. The peptide binds to a transmembrane receptor, the activin receptor IIB (ActRIIB) which regulates intracellular signaling pathways and activates proteins in the Smad family. These proteins decrease the levels of MyoD, a factor that cause enhanced myoblast proliferation [12,13]. Knockout mice repeatedly manifested significant skeletal muscle hypertrophy [14], whereas dramatic muscle atrophy was observed when myostatin was being administered systemically [15]. Humans with mutations related to myostatin deficiencies have increased muscle mass, too. A representative example is a newborn with increased muscle mass compared with other newborns [16]. This child was found to have a myostatin null mutation and also other family members were exceptionally strong. Also, myostatin seems to be involved in several functions of the human body. Towards this direction is a study in Colombian people which has been recently completed [17]. The investigators aimed to examine and validate three myokines (myonectin, myostatin, and fibroblast growth factor 21) as IR biomarkers.

A sufficient number of studies have demonstrated the association of myostatin with sarcopenia. Higher serum and mRNA levels were observed in old individuals compared to younger participants [18]. However, contradictory findings derive from other studies which did not report any age-related differences in circulating protein or skeletal muscle myostatin mRNA levels [19]. These data may suggest that myostatin may not be a primary provocation for sarcopenia.

It is also very interesting that myostatin levels in skeletal muscle may be altered in relation to adipose tissue, particularly in SO. It has been demonstrated that myostatin deficient mice have a lesser amount of subcutaneous adipose tissue and that myostatin RNA can be isolated in adipocytes [20].

Inhibiting myostatin activity may thus lead to effective therapeutic strategies for increasing muscle mass and strength or even for controlling excess body fat. Similar to animal studies, the myostatin expression and secretion levels were increased in skeletal muscle from extremely obese women in comparison with non-obese individuals and the circulating concentrations of myostatin were correlated with IR [21]. Furthermore, women who received the highest dose (3 mg/kg) of ACE-031, a soluble form of ActRIIB, not only had a significant increase in total body lean mass, but they also lost fat mass after 57 days of observation. In addition to these, the changes in the serum biomarkers for adipose tissue, adiponectin and leptin, reinforced the finding of improved fat metabolism [22]. Follistatin is an antagonist of myostatin signaling through binding to the ActRIIB receptor [13]. Transgenic mice overexpressing follistatin specifically in skeletal muscle have been shown to present exaggerated increase in muscle growth similar to that seen in myostatin-knockout mice [23]. In addition to follistatin, follistatin-like 3 is a protein with structural and functional properties, similar to those of follistatin, and it seems to be a very strong inhibitor and the major binding-inhibiting protein of myostatin [24]. Nevertheless, it remains unclear whether inhibition of the myostatin/ActRIIB pathway might have other beneficial or adverse effects on other organs or tissues and this is an active area of investigation [25].

In summary, myostatin inhibition and/ or the interplay of hormonal factors that act by binding to the ActRIIB seem to have the capability to increase the skeletal muscle mass and reduce the adipose mass although existing data regarding the potential effects of myostatin inhibition are limited. The quality of the tools that we have at our disposal is not satisfying and due to this, slow progress has been made in the field. Thus, further work in this direction is required. In any case, the findings of the study by Kim et al. [3], regarding the lean mass decrease even among young adults, articulate the need for developing effective therapeutic methods for the treatment of this condition.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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