European Journal of Internal Medicine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Narrative Review

Aging of the endocrine system and its potential impact on sarcopenia

Giovanni Vitale [a,b,*], Matteo Cesari [c,d], Daniela Mari [a,e]

[a] Department of Clinical Sciences and Community Health (DISCCO), University of Milan, Milan, Italy
[b] Laboratory of Endocrine and Metabolic Research, Istituto Auxologico Italiano IRCCS, Cusano Milanino (MI), Italy
[c] Gérontopôle, Centre Hospitalier Universitaire de Toulouse, Toulouse, France
[d] INSERM UMR1027, Université de Toulouse III Paul Sabatier, Toulouse, France
[e] Geriatric Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy

ARTICLE INFO

Article history:
Received 14 July 2016
Received in revised form 18 July 2016
Accepted 19 July 2016
Available online xxxx

Keywords:
Sarcopenia
Hormones
Aging
IGF-I
Vitamin D
Testosterone

ABSTRACT

Sarcopenia, occurring as a primary consequence of aging, is a progressive generalized decline of skeletal muscle mass, strength and function. The pathophysiology of sarcopenia is complex and multifactorial. One major cause of muscle mass and strength loss with aging appears to be the alteration in hormonal networks involved in the inflammatory processes, muscle regeneration and protein synthesis.
This review describes the recent findings concerning the role of the aging on the endocrine system in the development of sarcopenia. We also report the benefits and safety of hormone replacement therapy in elderly subjects and discuss future perspectives in the therapy and prevention of skeletal muscle aging.

1. Introduction

Aging is a natural process characterized by a progressive loss in physiological function leading to increased risk of diseases and mortality rate. Physical function declines with age, increasing the risk for several adverse health outcomes, such as falls, fractures, disability, loss of independence, reduced quality of life, hospitalization, institutionalization and death. This condition, characterized by the loss of skeletal muscle mass and function, is called *Sarcopenia* [1]. Sarcopenia is associated with several changes in body composition [2]. After the age of 35 years, a physiological decline of muscle mass occurs at an annual rate of 1–2% with a 1.5% per year reduction in strength, which accelerates around 3% after the age of 60 years. The loss in lean tissue is greater in men than in women [2–4]. This modification in body composition is frequently masked by unchanging body weight secondary to an increase in fat mass, that infiltrates also the skeletal muscle. Indeed, atrophy of muscle type II fibers, loss of motor units and a replacement by adipose and connective tissue within muscle are typical findings of sarcopenia. In addition, during skeletal muscle aging, a deficiency in muscle regeneration after injury has been observed [5].

The pathophysiology of sarcopenia is complex and multifactorial. One major cause of strength and muscle mass decline with aging process appears to be the alteration in several hormonal networks, involved in the inflammatory processes, muscle regeneration and protein synthesis (Fig. 1). Indeed, the endocrine system is not spared from the detrimental effect of aging [6].

The aim of this review was to describe the role of the aging on the classical endocrine system in the development of sarcopenia. A comprehensive search of PubMed was performed using the following search string: sarcopenia AND (hormones OR testosterone OR estrogens OR DHEA OR cortisol OR vitamin D OR GH OR IGF-1 OR ghrelin OR diabetes OR oxytocin). The references of the retrieved papers were used to find more literature.

2. Testosterone

Serum testosterone levels decline at a rate of about 1% per year from the age of 30–40 years in healthy men [7]. In women, circulating testosterone decreases rapidly from 20 to 45 years of age [8]. This decline in testosterone appears to be associated, particularly in men, with a decline in muscle mass and strength [9]. Indeed, testosterone is the main physiological anabolic hormone able to increase protein synthesis in skeletal muscle and to promote muscle regeneration via satellite cell activation [10].

In several epidemiological studies, low testosterone levels were associated with reduced muscle mass and/or strength and/or increased risk of falls [11–13]. However, other longitudinal studies about the association between circulating testosterone levels and change in muscle

* Corresponding author at: Istituto Auxologico Italiano, via Zucchi 18, Cusano Milanino (MI) 20095, Italy. Fax: +39 02 61911 3033.
E-mail address: giovanni.vitale@unimi.it (G. Vitale).

http://dx.doi.org/10.1016/j.ejim.2016.07.017
0953-6205/

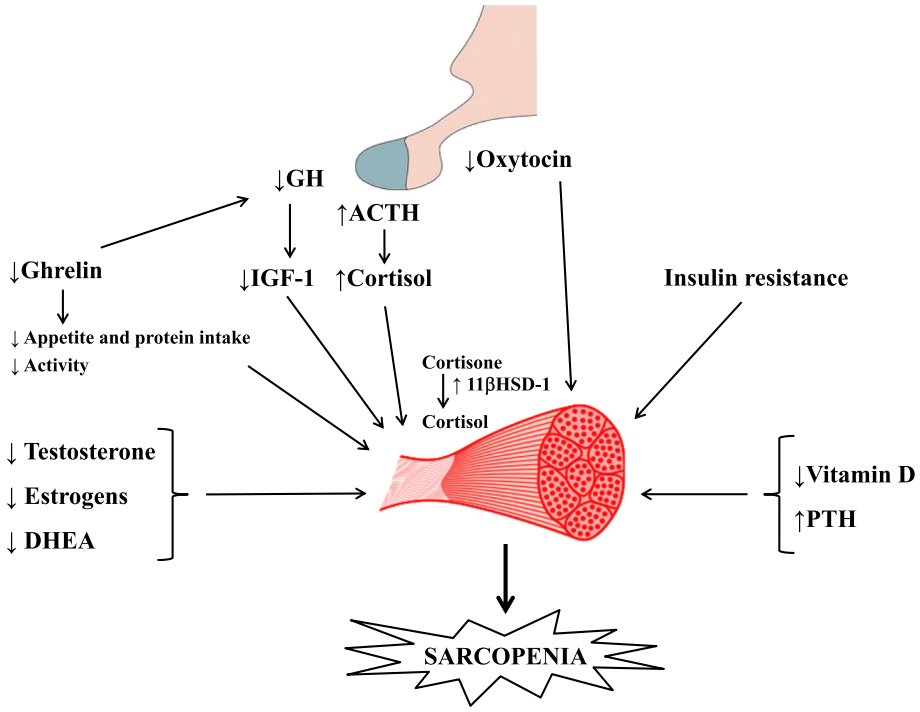

Fig. 1. Schematic diagram showing the age-related hormonal and metabolic alterations with detrimental effects on skeletal muscle and potentially involved in the development of sarcopenia. 11βHSD-1: 11β-hydroxysteroid dehydrogenase type 1. ACTH: adrenocorticotrophin hormone. DHEA: Dehydroepiandrosterone. GH: growth hormone. IGF-1: insulin-like growth factor type 1. PTH: parathyroid hormone.

mass, strength or physical performance have provided conflicting evidence in the elderly. While low circulating values of testosterone were associated with loss of muscle mass [14,15], muscle strength [15] and reduced physical performance [16], in other studies the association between androgen levels and age-related changes in skeletal muscle mass and function was less consistent [17–19].

In young and middle-aged men with classical hypogonadism testosterone replacement therapy has been shown to induce a number of beneficial effects, such as an increase in weight and muscle mass and decrease in fat mass, with a low frequency of adverse events [20]. However, the clinical benefits of testosterone therapy in elderly men with age-associated decline in testosterone levels are unclear. This could be related to the wide heterogeneity between studies on this theme concerning criteria adopted for the enrollment, type of drug used as replacement, formulation, dosage and duration of the therapy [21]. In 2006 a meta-analysis, including 11 randomized trials, reported that testosterone replacement therapy induced a moderate improvement in muscle strength in men aged 65 years and older [22]. A more recent meta-analysis showed that androgen replacement therapy was able to increase muscle mass in elderly men and that is influenced by the duration of the treatment and the method of administration of the drug [23]. In 2010 a trial of androgen replacement in community-dwelling men, 65 years of age or older, with limited mobility and several comorbidities was terminated early because of increased cardiovascular adverse events. The testosterone group showed improvement in muscle strength and physical function compared with placebo [24]. This study emphasized that this therapy is not free of side effects. Indeed, during androgen therapy older men appeared to be more susceptible to side effects, mainly related to the cardiovascular, hematological and urogenital systems [21]. Since the risk/benefit ratio of androgen replacement therapy is unclear, it is suggested to avoid therapy in frail elderly until better outcome data are available [25].

In a multicenter set of trials, called "The Testosterone Trials", 790 men (65 years of age or older with a serum testosterone concentration <275 ng/dl and symptoms indicative of hypogonadism) were treated with testosterone gel or placebo gel for 12 months. The percentage of men who had an increase of at least 50 m in the 6-minute walking distance was not significantly different between two arms in the Physical Function Trial, but the difference resulted to be significant when men in all three trials were included (20.5% after testosterone vs. 12.6% after placebo, $P = 0.003$). Treatment was well tolerated and the rates of adverse events were similar in the two groups [26].

A novel class of androgen receptor ligands, called selective androgen receptor modulators, that selectively target the androgen receptors in different tissues, have been recently developed. They act as strong receptor agonists in skeletal muscle, but as weak agonists or antagonists in prostate and sebaceous glands [27]. In few preliminary studies, these compounds have shown to increase muscle mass in the absence of the unpleasant side effects seen with the traditional anabolic agents [28,29]. Further studies are awaited to establish the efficacy and safety of these agents in the treatment of sarcopenia in the elderly.

3. Estrogens

Menopause is associated with a marked reduction in estrogen levels. These hormonal changes have a detrimental effect on muscle mass and partially explain the accelerated decline in muscle mass and strength, frequently observed in postmenopausal women [30]. Indeed, estrogens have beneficial effects on muscle strength and mitigate inflammatory responses and post-injury disruption in skeletal muscle through satellite cell activation and proliferation [31].

In women, hormone replacement therapy appears to delay age-related muscle loss and accumulation of fat in skeletal muscle [32]. A meta-analysis showed that postmenopausal women treated with hormone replacement had a small but significant beneficial effect on muscle strength (about 5% greater than in untreated control) [33].

4. Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a natural steroid and precursor hormone produced by the adrenal glands and transformed to androgens or estrogens in several tissues. The skeletal muscle is able to convert

Please cite this article as: Vitale G, et al, Aging of the endocrine system and its potential impact on sarcopenia, Eur J Intern Med (2016), http://dx.doi.org/10.1016/j.ejim.2016.07.017