Oral Drugs Related with Muscle Wasting and Sarcopenia. A Review

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Abstract
Sarcopenia is a geriatric syndrome characterized by progressive and generalized loss of skeletal muscle mass and function. Reported prevalence of this geriatric syndrome differs depending on the definition, the population and the method used to identify sarcopenia. The causes of sarcopenia are multifactorial, and can include genetic influence, immobility or disuse, endocrine factors, inflammation and nutritional deficiencies. These disorders involve an imbalance between anabolic and catabolic pathways that rules muscle mass. Many drugs taken regularly for common conditions may interact with some mechanisms that can alter the balance between protein synthesis and degradation. This may lead to a harmful or a beneficial effect on muscle mass and strength. Widely prescribed drugs could play an important role during the time of onset and development of sarcopenia. In this paper, we reviewed the current understanding of how can drugs contribute positively or negatively on sarcopenia and muscle wasting. We decided to focus this review on oral common drugs, which are usually prescribed in older adults, leaving aside other drugs as hormone therapy.

Introduction

The International Working Group on Sarcopenia defined sarcopenia as ‘age-associated loss of skeletal muscle mass and function’ [1]. This is similar to the European Working Group on Sarcopenia in Older People (EWGSOP), which provided a working definition of sarcopenia in 2010 as ‘a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death’ [2]. The EWGSOP recommends using the presence of both low muscle mass and low muscle function (strength or performance) for the diagnosis of sarcopenia [2]. EWGSOP suggests a conceptual staging for this complex syndrome. Pre-sarcopenia is characterized by low muscle mass without impact on muscle strength or performance; sarcopenia is characterized by low muscle mass, plus low muscle strength or low physical performance; and severe sarcopenia is identified when all 3 criteria of the definition are met (low muscle mass, low muscle strength and low physical performance) [2]. According to this definition, while sarcopenia is mainly observed in older people, it can also develop in younger adults. For this reason, some authors have introduced the term dynapenia to describe the age-associated loss of muscle strength, which is not caused by neurologic or...
muscular diseases [3]. Prevalence of sarcopenia differs depending on the definition used, the population and the method used to identify sarcopenia. According to EWGSOP, the prevalence in 60–70 years is reported as 5–13%, while the prevalence ranges from 11 to 50% in people >80 years [2, 4].

Pathophysiology and Muscle Wasting

Sarcopenia is a geriatric syndrome with multiples causes, which can include genetic influence, immobility or disuse, endocrine factors, inflammation and nutritional deficiencies (fig. 1) [1, 2]. These disorders involve an imbalance between anabolic and catabolic pathways that rules muscle mass. The major anabolic pathway involves activation of the Akt mammalian target of rapamycin (mTOR), which leads to increased muscle protein synthesis [5]. Insulin-like growth factor 1 (IGF-1), branched-chain aminoacids, exercise, testosterone and B2-adrenergics agents upregulate this pathway and are known to promote muscle growth [6]. During the aging process, there is a decline of anabolic hormones such as testosterone, growth hormone and IGF-1, leading to decreased protein synthesis [7]. Insulin resistance, which occurs with aging and obesity, plays an important role in decreasing available glucose and protein for muscle anabolism [7].

Muscle atrophy occurs when the rate of muscle protein degradation exceeds the rate of muscle protein synthesis. The major catabolic pathways include the activation of the ubiquitin proteasome pathway and calpain and caspasess under transcriptional control of the transcription factors forhead box O and nuclear factor (NF)-κB [8]. Inflammation mediated by cytokines and inactivity are two of the most important situations which stimulates this transcription factors, especially NF-κB signaling [8]. Obesity and some diseases result in an increase in proinflammatory cytokines such as interleukin (IL)-6, IL-1 and/or tumor necrosis factor alpha, which lead to protein catabolism through the activation of NF-κB [9]. Aging is associated with an increase in some cytokines, but it is not clear if it is due to age alone or due to underlying comorbidities that accompany old age [10]. Another important pathway leading to muscle atrophy is the myostatin pathway, which acts by downregulating the Akt-mTOR pathway [6]. Other pathways, summarized by Ali and Garcia [8], that contribute to the onset of sarcopenia include an increase in muscle apoptosis and autophagy activity and a decrease in mitochondrial function and satellite cells, essentials for muscle repair.

Objectives

Many drugs taken regularly for common conditions may interact with some of these mechanisms. This may lead to a harmful or a beneficial effect on muscle mass and strength. In this paper, we reviewed the current understanding of how can drugs contribute positively or negatively on sarcopenia and muscle wasting (fig. 3). We decided to focus this review on oral common drugs, which are usually prescribed in older adults, leaving aside other drug as hormone therapy.

Renin–Angiotensin System

Renin converts angiotensinogen to angiotensin I, and this is converted to angiotensin II through the action of angiotensin-converting enzyme (ACE). ACE also catalyzes the inactivation of bradykinin. The formation of angiotensin II mainly results in vasoconstriction, catecholamine release and aldosterone secretion, mediated by receptors AT1. It has been suggested that beneficial effects
of ACE inhibitors and angiotensin receptors blockers (ARBs) is due to this improved oxygen delivery [11] and by direct positive actions on the skeletal muscle [12, 13].

**ACE Inhibitors**

Some studies have evaluated the impact of ACE inhibitors on muscle strength and performance. Onder et al. [14] showed a 3 years lower average decline in muscle strength and walking speed when ACE inhibitors were taken in an observational study among 641 aging disabled women. Other studies found similar results with better walking speed on persons taking ACE inhibitors [15, 16]. In a double-blind randomized controlled trial, 130 older adults were assigned to receive either perindopril or placebo for 20 weeks. The mean 6-minute walking distance was significantly improved in the perindopril group relative to the placebo group [17]. Improving muscle strength and walking speed may have a protective effect on the risk of sarcopenia.

**Angiotensin Receptors Blockers**

ARBs block AT1 receptor thus leading to a decrease in angiotensin II levels. This mechanism assumes that the same beneficial effects are expected in skeletal muscle

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**Fig. 2.** Pathways associated to loss of muscle mass.

**Fig. 3.** Oral drugs associated to muscle function.
than those seen with ACE inhibitors. Some authors showed an association between a decrease in the inflammatory cytokine IL-6 and ARB therapy [18, 19]. Burks et al. [20] indicate that the blockade of the AT1 receptor has beneficial effects on skeletal muscle remodeling in response to injury and conferring protection against disuse atrophy in sarcopenia by modulating the transforming growth factor-β (a known inhibitor of skeletal muscle regenerator) and Akt-mTOR pathways. In a study with older mice, it is suggested that treatment with losartan improves measures of physical function, decreases the inflammatory cytokine IL-6 and increases protective and antioxidant enzymes [21]. The Johns Hopkins University is conducting a clinical trial to see whether losartan can prevent the decrease in strength associated with aging, which will provide the evidence needed to clarify the association between sarcopenia and ARBs [22].

**Oral Antidiabetic Agents**

Diabetes mellitus is a syndrome with a prevalence that can reach 25% among those who are >65 years [23]. The association between diabetes and loss of muscle mass and strength is known [24–26] but is not entirely known how antidiabetic agents influence this association. It is nearly impossible to differentiate the effect of oral antidiabetic drugs from that of diabetes mellitus, but recently Cetrone et al. [27] published a review about how oral antidiabetics can affect muscular atrophy. The subfamilies most associated with muscle disorders are discussed in the following sections.

**Biguanides**

The mechanism of action of metformin is unknown, but it seems to act by increasing insulin sensitivity. However, the effects of metformin on muscle are still uncertain and therefore a matter of debate. Perez et al. [28] showed a relationship between metformin treatment with reduced proinflammatory cytokines regardless of glucose. However, metformin causes the inhibition of mTOR complex through activation of the AMP-activated protein kinase, causing a decrease in anabolic effects mediated by mTOR [29]. According to a recent paper, metformin use does not alter the expression of mTOR arguing this theory [30]. There is currently a clinical trial examining the use of metformin in preventing the development of sarcopenia in older people with prediabetes, which will bring light to the current scenario [31].

**Thiazolidinediones**

This family of oral antidiabetic, called glitazone, is an PPAR receptor agonist with a high ability to increase insulin sensitivity and possibly their anabolic effects [32]. Studies in mice have shown a decrease in proteolysis and muscle atrophy with the use of rosiglitazone [33, 34].

**Potassium Channels Blockers**

Sulfonylureas are a broad family of drugs that act by blocking the potassium channels and by producing a secretagogue effect on insulin [35]. Some in vitro studies have shown an induction of cell apoptosis with therapeutic doses of sulfonylureas [36, 37], which can lead to atrophy [38, 39]. Glinides have a mechanism of action similar to sulfonylureas with a shorter half-life [40], which also can cause atrophy in experimental animals [39]. However, the muscle effects of these drugs in humans are unknown.

**Incretins**

These oral agents inhibit the enzyme dipeptidil peptidase IV, which is responsible for degradation of endogenous incretin. They have hypertrophic and anti-apoptotic effects, as well as an improvement in insulin resistance sensitivity and muscle oxygen intake [41–44]. Despite being a relatively new drug, these beneficial actions on the muscle have made them very promising drugs against muscular atrophy and sarcopenia.

**Statins**

Statins are cholesterol lowering drugs widely used to reduce cardiovascular risk, even in the elderly. Although the drugs well tolerated, muscular side effects are fairly common [45] and may affect up to 29% of patients becoming the main reason for drug withdrawal [46]. This muscle toxicity is a syndrome that can arise from myalgia, muscle weakness and elevations of creatine kinase to rhabdomyolysis. It is dose dependent and usually resolves decreasing the dose or discontinuing treatment [47].

Traditionally, the mechanism of action of statins’ muscle toxicity has been associated with decreased Coenzyme Q10, an essential component in the mitochondrial respiratory chain [48]. It seems however that this is not the only mechanism of toxicity, and some authors propose other ways which would also be involved in geranylgeranyl pyrophosphate, cell apoptosis and dysfunction in glucose oxidation [49, 50]. Some studies have linked this muscular toxicity with muscle weakness [51, 52]. In a
3-year study monitoring 774 older adults, Scott et al. [53] associated greater decrease in muscle strength and increased risk of falls in patients who were treated with statins versus those who were non-treated.

**Vitamin D**

Vitamin D plays a role in numerous physiological processes and it is known that it has a much wider range of advantages than maintaining adequate serum calcium levels [54]. These properties can be dependent or independent of its binding on the nuclear receptor vitamin D receptor (VDR). Many studies have suggested that vitamin D is related to muscle strength and frailty [55–57].

Low vitamin D levels are common, especially in the elderly, where prevalence may reach 50% [58, 59]. This age-related reduction also appears to occur in VDR [60]. There is evidence to suggest that prolonged deficiency is associated with severe muscle weakness [61] and loss of muscle mass and strength [62]. In a 3-year follow-up study, lower levels of vitamin D were found to be predictive of decreased grip strength and muscle mass [63]. Some studies associate this weakness and loss of muscle mass with changes in muscle morphology, demonstrating a preferential atrophy of type II muscle fibers [64, 65]. In old rats, 9 months of vitamin D depletion induced skeletal muscle atrophy [66].

In addition, it seems there is an increased risk of a decline in physical performance with low vitamin D levels [67, 68]. In the InCHIANTI study, a prospective population-based study, 1,155 participants aged ≥65 years were included and low vitamin D levels were associated with poor physical performance, measured by a battery of tests, including walking speed, the ability to stand from a chair and the ability to maintain balance in progressively more challenging positions [69]. Muscle strength and physical performance are linked to risk of falls, and there is a large evidence of low levels of vitamin D associated with risk of falls in the elderly [70–72]. Vitamin D supplementation in an aging population may be important for the preservation of physical function and the reduction in risk of falls [73]. In a clinical trial on burn patients, vitamin D and calcium supplementation increased quadriceps strength [74]. In the same sense, vitamin D supplementation significantly increased muscle strength [75], and a recent randomized controlled trial demonstrated that supplementation with vitamin D over 4 months in older women with low vitamin D levels resulted in a 10% increase in muscle fiber size [76]. A meta-analysis showed that whereas vitamin D supplementation increases proximal muscle strength of the lower extremities in adults with vitamin D deficiency, it does not have a significant effect on muscle strength in adults with baseline vitamin D levels >25 nmol/l [77]. Same results have been shown in women after stroke, where vitamin D supplementation reverses muscular atrophy and increases strength [78].

Summarizing, vitamin D supplementation has demonstrated to have beneficial effects, increasing muscle strength and performance, and The Society on Sarcopenia, Cachexia and Wasting Diseases recommends checking vitamin D levels and replacing, if low, in all sarcopenic patients [79].

**Allopurinol**

Allopurinol is a drug widely used to treat gout. Its mechanism of action involves the reduction of plasma levels of uric acid from inhibiting xanthine oxidase (XO). Some authors have demonstrated a relationship between XO action and increased oxidative stress, declining muscle mass and strength in aged animals [80, 81]. Springer et al. [82, 83] showed that the inhibition of XO reduced levels of oxidative stress, maintaining muscle mass and reducing cachexia in cachectic animals. In another study with immobilized animals, Kondo et al. [84] showed an increase of 2 or 3 times the XO activity in the soleus muscle.

Therefore, it is reasonable to think that an inhibitor of XO, such as allopurinol, may be able to prevent muscle atrophy or even sarcopenia. In this direction, treatment with allopurinol in rats with extremities suspended for 14 days prevented the atrophy of the soleus [85]. More recently in humans, Beveridge et al. [86], after analysis of 3,593 patients for 10 years in a rehabilitation unit and evaluating the Barthel Index at admission and discharge, demonstrated a greater improvement in allopurinol-treated patients compared to the untreated, suggesting an association between the drug and improved functionality.

**Formoterol**

This drug, a highly potent β2-adrenoceptor-selective agonist which is used to treat bronchospasm associated with asthma, has been associated to an increased protein synthesis, decreased apoptosis and increased muscle regeneration [87, 88]. This fact introduced the use of β2-
adrenergic agonists as a possible drug for the treatment of cachexia [89]. In a study using rats affected by cancer cachexia, formoterol treatment reduces muscle wasting and does not negatively alter heart function [90].

**Conclusion**

In this review, we described that some widely prescribed oral drugs may have an effect on muscle. Although these results are not sufficiently strong to support any recommendation, there is growing evidence that shows that there is an association between drugs and muscle, and they may act as a trigger to develop sarcopenia and frailty. More research is needed to clarify most of the aspects mentioned in this review.

**Disclosure Statement**

The authors of the present article declare that they have no conflicts of interest.

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