Chapter 10

Anabolic/Androgenic Steroids in Skeletal Muscle and Cardiovascular Diseases

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/53080

1. Introduction

Testosterone exerts significant effect on muscle cells, and abnormalities of plasma concentrations can cause both skeletal muscle and cardiovascular diseases. Low levels are known to be associated with hypogonadism and have recently been linked to sarcopenia and metabolic syndrome; high levels are associated with hypertrophy. However, most evidence of the link between testosterone and metabolic actions is observational. Studies targeted to establish the mechanisms for such effects at the cell level and their correlation with *in vivo* models will broaden our understanding of the role played by these male steroid hormones in the pathophysiology of muscular and metabolic diseases.

1.1. Physiology of the androgens

Anabolic/androgenic steroid hormones are part of the male reproductive endocrine axis. Androgens are the male sex hormones responsible for development of the male reproductive system. Testosterone is the main androgen circulating in the blood and it is secreted from the testes, while other androgens, such as androstenedione and dehydroepiandrosterone (DHEA) come mainly from the adrenal gland. In some tissues the androgen actions require that testosterone can be converted to dihydrotestosterone by action of 5α-reductase, and in other tissues, including adipose tissue, testosterone can also be converted into estradiol by aromatization of the androgen ring.

Endocrine actions of testosterone are under control of the hypothalamus-pituitary-gonad axis. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the secretion of luteinizing hormone (LH) from the anterior pituitary (adenohypophysis). In

the Leydig cells of the testes, the binding of LH to its receptor activates the uptake of circulating cholesterol, the steroid precursor for biosynthesis of all androgens. In the last step of testosterone biosynthesis, androstenedione is converted to testosterone, which is the main secreted component (95% of circulating androgens). In some cases testosterone acts directly on the cells of the target organ, but in others the active hormone is formed within the cells of the target organ by reduction of testosterone at position 5 of the steroid ring to yield the more active dihydrotestosterone. Androgens are responsible for primary and secondary sexual characteristics in men and also for the development of skeletal muscle mass and strength, erythropoiesis, and bone density, amongst other functions.

The divergent effects that androgens have between the sexes can be explained by differences in concentration, metabolism, and receptor expression. Male sex hormones are also known to fluctuate along the day and throughout life. Testosterone levels are usually low in males before puberty. However, after puberty, the testosterone level increases and reaches its peak around the age of 20–25 in men. As aging occurs, testosterone levels decline.

From total circulating levels of testosterone, only the free fraction of testosterone, the part dissolved in the plasma, is biologically active. In blood, free circulating testosterone is around a 2%, while the rest of the hormone is bound in different proportions to sex hormone binding globulin (SHBG) and albumin. However, the bio-available bound testosterone can be released on demand, as the albumin binding is weak. Thus, a higher apparent concentration of free testosterone is available to act in specific tissues.

The androgens have a variety of peripheral actions. They are anabolic throughout the body. That is, they stimulate protein synthesis. It is for this reason that the male body composition is generally larger and more muscular than the female. Androgen axis alterations are due mainly to deficiency or excess of testosterone, and the final effect will depend on whether the imbalance occurs before or after puberty. Before puberty, it can lead to delayed activation or never reached puberty (hypogonadism). If in excess, the hormone will have the opposite effect promoting early puberty accompanied by growth problems characterized by bone epiphysis alterations. Testosterone deficiency during embryonic development will condition a feminization of the external genitalia in men. After puberty, given the role of the male sex hormone on spermatogenesis, testosterone deficiency can induce infertility. Exogenously induced elevated testosterone concentrations cause hypertrophy in several tissues, with the effects on skeletal and cardiac muscle being critical.

In men, plasma testosterone concentrations range from 300 to 1000 ng/dL, whereas in women circulating levels of testosterone are about 10% of those observed in men [2, 3]. The body composition of men is regulated by testosterone concentrations [4, 5]. Pharmacological suppression of endogenous testosterone levels in healthy young subjects increased fat mass and decreased fat free mass and protein synthesis in muscle, suggesting a direct effect of androgens on body metabolism of lipids and proteins [6]. Healthy young subjects suppressed of endogenous testosterone levels and supplemented with different testosterone doses (from 25 mg to 600 mg testosterone enanthate/week) for 20 weeks increased the volume of the quadriceps muscle in a dose dependent manner, as determined by nuclear magnetic resonance. At the his-

http://dx.doi.org/10.5772/53080

tological level, this increase was explained by an increase in the area of type I and II muscle fibers [7]. In bone tissue, testosterone deficiency is associated with decreased bone density with increasing tissue turnover markers. Thus, hormone replacement therapy in patients with hypogonadism has been established as effective to increase bone density [5]. Although testosterone and its derivatives are well known for their androgenic properties and anabolic effects, so far the effects of androgens on muscle remain incompletely understood.

1.2. Androgen mechanisms of action

Androgens exert most of their effects through direct binding to specific intracellular receptors acting as transcriptional activators [8]. Intracellular androgen receptors have been described in skeletal and cardiac muscle cells in addition to other tissues [9, 10]. The intracellular receptor mediates the "classic" genomic response to testosterone and is characterized as a 110-kDa protein with domains for androgen binding, nuclear localization, DNA binding, and transactivation. The conserved domain structure has 3 major functional regions, an NH-terminal transactivation domain, a centrally located DNA binding domain (DBD), and a COOH-terminal hormone-binding domain (HBD). The COOH-terminus contains an additional activation domain and a hinge region connecting the HBD and the DBD. Upon ligand binding, the nuclear receptors translocate to the nucleus, where they dimerize and bind to regulatory DNA sequences on target genes to either activate or repress transcription [11]. These effects are slow, with a latency period before onset, but they are also long lasting, remaining active for several hours after hormone stimulation. Several co-regulatory proteins that bind and regulate the activity of receptors have been identified. These include both co-activators that positively regulate transcriptional effects of intracellular receptors after ligand binding and co-repressors that negatively regulate receptor activity. In addition to this transcriptional or genomic mode of action, increasing evidence suggests that androgens can exert rapid, non-genomic effects. The time course of these responses is not compatible with the classic genomic mechanism for the action of steroids, since they have a rapid onset without an apparent latency period. Common to these early effects is a fast increase in intracellular Ca^{2+} and activation of Ca^{2+}-dependent pathways and second messenger cascades [12, 13]. Second messenger induction by non-genomic steroid action is insensitive to inhibitors of either transcription or translation. Little is known about these non-genomic effects in cardiac and skeletal muscle cells other than the generation of different patterns of Ca^{2+} signals and also the activation of complementary Ca^{2+}-dependent pathways involved in these responses. An interesting hypothesis is that these second messenger cascades may ultimately serve to modulate the transcriptional activity of the intracellular androgen receptor and its associated global response [14-16].

2. Musculoskeletal conditions related to androgens

Emerging syndromes and new approaches to classic diseases are now being linked to androgens. The androgen-associated diseases that will be discussed in this section include hypo-

gonadism of the elderly (late onset hypogonadism [LOH]), sarcopenia, and the "metabolic syndrome." The interrelation between these diseases and decreased androgen levels is complex in the sense that these diseases are not only androgen dependent but that many other factors intervene in their development. Figure 1 shows the relationship between each of these diseases with the others, demonstrating that they are not "pure" androgen-dependent syndromes. With exception of LOH, which has implicit the concept of low androgen levels, neither sarcopenia nor metabolic syndrome are solely androgen-dependent diseases. It is important to bear this characteristic in mind when considering sarcopenia and metabolic syndrome, as there are numerous causes that may be behind the same clinical presentation. Further, the role of each of the hypothesized components may be very different from one patient to the other. The fourth disease that will be discussed here is Kennedy's disease, a hereditary X-linked neurodegenerative disease that affects mainly the androgen receptor function. In this sense, the pathophysiology of this disease is somewhat different from the 3 previously considered syndromes.

We will review the current definition of each syndrome, the epidemiology, the pathophysiology, and the effects that testosterone supplementation has demonstrated upon the evolution of the disease. After presenting these syndromes, we will highlight the differences observed among clinical studies in relation to age of populations analyzed, type of study, and expected outcome. This issue is important because it may affect the obtained results and therefore the subsequent conclusions.

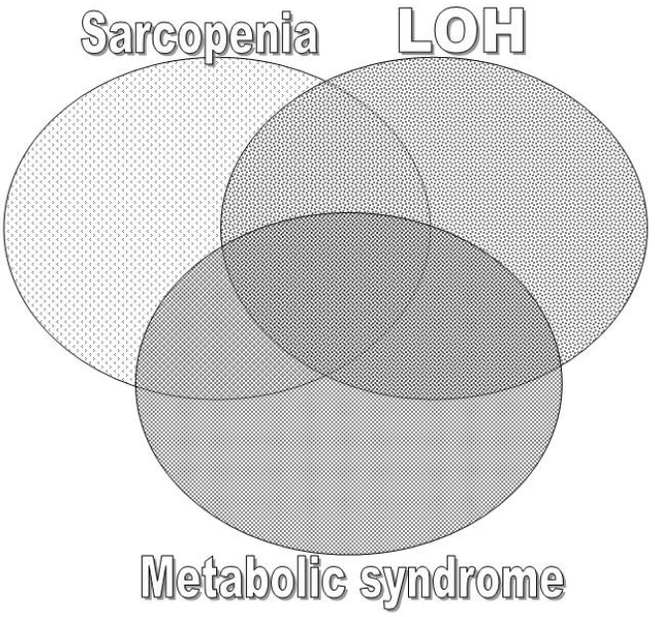

Figure 1. Clinical expression of 3 syndromes, their relationships, and androgen dependence. Each syndrome has components of "pure" disease. Thus, certain components particular to metabolic syndrome are expressed without muscle mass compromise (sarcopenia) or androgen levels decrease (LOH), although frequently, in association with the common dependence of these diseases upon advanced age, the clinical picture will associate the presence of more than 1 of these syndromes (i.e., metabolic syndrome plus sarcopenia). In another scenario, the expression of a disease, for example, sarcopenia may have decreased androgen levels among its pathophysiologic determinants.

http://dx.doi.org/10.5772/53080

2.1. Late onset hypogonadism (LOH)

Definition: Hypogonadism in the adult male can be considered as a syndrome, i.e., a constellation of signs and symptoms that collectively characterize a disease/disorder. Currently, there are guidelines to the diagnosis and treatment of this emerging disorder. According to these guidelines [17] the diagnosis of late onset hypogonadism (LOH) should be considered in patients who complain of specific symptoms, mainly in the areas of sexual function (decreased libido, impaired erectile function, shrinking testes), the musculoskeletal system (muscle weakness, increased adiposity, low bone mineral density), and psychological symptoms (depressed mood, decreased vitality, sleep disturbance). In these patients, a low morning serum total testosterone level, measured on 2 different occasions, will confirm the diagnosis of LOH [17, 18]. Wu et al. (2010) [19] conducted a study to establish criteria to more accurately diagnose LOH in the clinical setting. They look for the presence of characteristic symptoms that could help to reach an accurate diagnosis of LOH. After evaluating 3369 men in a cross-sectional study along with data obtained from questionnaires and a single testosterone measurement, the authors came to the conclusion that the combination of at least 3 sexual symptoms and decreased testosterone levels would make the diagnosis of LOH more accurate.

The normal reference levels for total testosterone in adult males vary from 300–1000 ng/dL. Morning levels (before 10 AM) below 250 ng/dL will make the diagnosis highly probable. A second total testosterone measurement is required to confirm the diagnosis. These tests should generally be followed by studies that help in determining the anatomical level of the endocrine failure, in order to confirm the cause of hypogonadism (primary, secondary, or mixed) [19, 20].

Epidemiology: According to the definition of Wu et al. (2010), the actual prevalence of LOH is 2.1% in a random population sample from Europe in men aged 40 to 79 years. The prevalence increased with increasing age of the participants, ranging from 0.1% in men aged 40 to 49 years to 5.1% in men 70 to 79 years of age [19]. Another study carried out in Boston, USA, used slightly different symptoms to define symptomatic hypogonadism. This study indicated an overall prevalence of symptomatic hypogonadism of 5.6%, showing an increased prevalence of 18.4% in men in their 70s [21]. A study performed in Hong Kong established a prevalence of 9.5%. As in the above-cited studies, an increase in the prevalence of hypogonadism was seen with increasing age of patients. Other conclusions that can be obtained from the epidemiological studies are that hypogonadism starts as early as the fourth decade, and that the presence of comorbid conditions (such as type 2 diabetes mellitus and cardiovascular diseases) also increases the prevalence of this syndrome [18].

Pathophysiology: Mean values of testosterone levels have declined in 75 year old men to approximately two-thirds of the values seen in young males [22]. Cross sectional and longitudinal studies have confirmed the observation that testosterone levels decline with age [18, 23-25], and that general health status plays a crucial role in arresting the fall of plasma testosterone. The time of blood sampling also affects the testosterone level, and the slope of the relationship between testosterone and aging [26, 27]. It was shown in healthy North-American men that tes-

tosterone decreased progressively at a rate that did not vary significantly with age from the third to the ninth decades. In this study, the magnitude of the decrease in total testosterone was 3.2 ng/dL per year, similar to other studies [23]. Other investigators reported a decrease of 0.8% per year in total testosterone levels (cross-sectionally) in a population of men ranging from 40–70 years [26]. Free and albumin-bound testosterone decreased at 2% per year, whereas SHBG tended to increase at 1.6% per year. These changes tend to include a shift toward inactive bound testosterone *vs* free bioavailable testosterone [24, 26].

The mechanisms behind this age-associated decline in male hormone levels are still unclear. Various alterations have been described in the elderly men that can lead to LOH. The main points where the physiology of androgens has been found to be affected by age are the testes, the hypothalamus, and the transport protein, SHBG. Primary testicular changes play an important role in age-associated testosterone decline. Leydig cells in the elderly have demonstrated a reduced secretory capacity in response to stimulation with recombinant LH [28]. This decrease has been related to a reduction in the number of Leydig cells. In addition to the decline in testicular reserve seen in the elderly, an altered neuroendocrine regulation, mainly at a hypothalamic level, has been suggested. Moderate increases of basal gonadotropin levels have been observed in response to the decline in testosterone levels, but not all studies agree with this observation [22]. The increases in GnRH as well as LH are thought to be abnormally low in response to the testosterone decline induced by the aforementioned Leydig cell alterations, implying a failure at some point in the neuroendocrine axis. It has been shown that the anterior pituitary has a preserved LH response to exogenous pulsate GnRH stimulation [28], suggesting, in line with other studies, the role played by the hypothalamus and the deficit of GnRH. Finally, increases in SHBG binding capacity have also been related to LOH. This change would result in an even greater decrease of free and bioavailable (albumin-bound) testosterone levels. The cause for this increase in SHBG binding capacity is still unknown.

In conclusion, testosterone decline in the elderly appears to have multiple causes, involving the testicular, hypothalamic, and transport levels. These alterations may be present in different proportions in different patients, making LOH a difficult syndrome both to understand and to treat.

Considerations for testosterone administration: The ability to diagnose hypogonadism with increasing accuracy does not mean that the decision of which patients to treat, how to treat them, and for how long, will be easy. Probably, because of the lack of long-term longitudinal studies that prove the safety of testosterone treatment, there is some degree of agreement not to reach supra-physiological levels with testosterone supplementation. This method of testosterone replacement therapy, in non-pharmacological doses, is presently accepted as a treatment for men diagnosed with LOH. Assuming that a correct diagnosis of hypogonadism has been made, following the above-mentioned guidelines, the choice of whom to treat should be clearer. Next, in the process of treating LOH, it is important to bear in mind the desired outcomes of androgen supplementation, i.e., whether to look only for normalization of plasma testosterone levels or also for prevention or amelioration of generally associated conditions such as osteoporosis and frailty, among others. Testosterone ad-

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ministration to elderly men has been shown to induce beneficial effects on bone, muscle, heart, blood vessels, and mood. The problem is that many of these studies have been unable to demonstrate significant changes in endpoints such as functionality, independence, risk of fractures, etc. Furthermore, in earlier studies about testosterone supplementation, not only "pure" hypo-androgenic men were enrolled to participate, but also men with low-normal testosterone levels, which may have altered the final results. The risks associated with testosterone supplementation are an important issue influencing the decision to treat or not to treat. The development of polycythemia is a common complication of androgen therapy. It has been observed that hematocrit invariably increases with testosterone administration, and that this complication is the most frequent reason for the discontinuation of therapy [24, 29]. Concerning the cardiovascular risks, a recent study conducted in elderly patients with mobility limitations was terminated early because of an increase in the number of adverse cardiovascular events in the testosterone treated group [30]. However, a meta-analysis of randomized controlled trials that included 19 studies showed that there were no statistical differences between placebo and treated groups in relation to cardiovascular events [29]. One of the hypothesis to explain the increased cardiovascular risk is that exogenous testosterone can shift plasma lipids to a pro-atherogenic state [24], and another meta-analysis [4] that examined 29 randomized controlled trials showed a significant decrease in total cholesterol values that was more pronounced in hypogonadal men along with a reduction in HDL-cholesterol (HDL-C) that was detectable only in study populations with higher pretreatment testosterone concentrations. This effect was dependent on the formulation of testosterone used.

Finally, one of the most recognized concerns about testosterone replacement therapy is the risk of developing prostate cancer. It has long been postulated that exogenous androgens can have a causative role in prostate cancer. On the other hand, androgen deprivation therapy has demonstrated a clear role for endogenous androgens in an already settled prostatic cancer. Therefore, the question remains open whether subclinical, "occult," prostatic lesions could develop into a neoplasia due to exogenous androgen administration. At the level of the prostate tissue, 6 months of testosterone replacement therapy in men with LOH showed no differences with placebo when considering prostate histology, tissue biomarkers, gene expression, and incidence or severity of prostate cancer [31]. Other studies that analyzed the association between testosterone treatment and prostate cancer did not find convincing evidence for this relationship [32, 33]. Nevertheless a meta-analysis [29] has shown a higher risk of detection of prostate events (incidence of prostate cancer, elevated prostatic-specific antigen, prostate biopsies) and increases in International Prostate Symptom Score (IPSS) in treated *vs* placebo groups.

In conclusion, benefits of testosterone replacement in LOH men have been established, but functional studies that demonstrate a significant improvement in large population samples are scarce and clinical studies of the risks of testosterone replacement therapy are still contradictory. Larger longitudinal, randomized placebo controlled studies are needed to draw definitive conclusions. At present, treatment is recommended for men diagnosed with LOH with appropriate monitoring of the prostate and the cardiovascular and hematological systems.

2.2. Sarcopenia

Definition: This term was proposed in 1989 by Irwin Rosenberg to describe a multifactorial syndrome that occurs with age and results in a loss of skeletal muscle mass and function [34]. The Greek word "sarx" means flesh, and "penia" means loss, suggesting with this name the principal organ and function targeted by this syndrome [35]. In 2010, a European Consensus definition and diagnosis of sarcopenia stated that sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength, with the risk of adverse outcomes including physical disability, poor quality of life, and death. This working group also recommended criteria for the diagnosis of sarcopenia and highlighted the need to confirm low skeletal muscle mass to make the diagnosis [36].

Epidemiology: Janssen et al. [37] conducted a study to establish reference parameters for total and regional skeletal muscle mass in men and women between 18 and 88 years old. They studied 468 healthy men and women using magnetic resonance imaging, and confirmed previous reports indicating that there are gender differences for regional and whole body muscle mass. Skeletal muscle mass relative to body weight was 38% in men and 31% in women. In relation to muscle distribution, the differences were greater for skeletal muscle mass in the upper body (40% less muscle in women) than in the lower body (33% less muscle). In this population, the loss of muscle mass with age began in the fifth decade (45 years), a finding that agrees with other observations such as fiber cross sectional area and isometric and isokinetic strength, which are reported to change substantially only after 45 years of age. Due to the recent evolution of sarcopenia as a recognizable syndrome, there is still not much agreement in relation to its prevalence in aging populations [38, 39]. Baumgartner et al. [34], based on a definition of sarcopenia as appendicular skeletal muscle mass <2 standard deviations below the sex-specific young-normal mean for estimates of skeletal muscle mass, found a prevalence of sarcopenia of 24.1% in Hispanic women and 23.1% in non-Hispanic white women aged <70 years. The prevalence in men <70 years old was lower, with 16.9% in Hispanic men and 13.5% in non-Hispanic white men. Another study [39], conducted to confirm the sarcopenia rates reported by Baumgartner et al. [34], used body muscle mass measurements and reported a prevalence of sarcopenia of 22.6% in women and 26.8% in men ≥65 years. A more recent study [38] conducted in Spain evaluated healthy elderly participants aged >70 years. The observed prevalence of sarcopenia was 33% in women and 10% in men, differing from those described in the USA and other geographical areas. Ethnicity as well as other characteristics, such as health status and age, could explain these observed differences.

The prevalence of sarcopenia generally increases with age. Baumgartner et al. [34] observed an increase in the prevalence of sarcopenia after 80 years that reached >50% of individuals. Iannuzzi-Sucich et al. [39] also described an increase in the prevalence of sarcopenia in a subgroup of the studied population (80 years or older), reaching 31% in women and 52.9% in men. In reference to the relationship between testosterone levels and physical performance in older men, the Framingham Offspring study [40] described a significant association between serum free testosterone levels, walking speed, and short performance physical battery (SPPB) results. Men with low baseline free testosterone had 57% higher odds of report-

ing incident mobility limitation and 68% higher odds of worsening mobility limitations. Total testosterone and SHBG were not significantly associated with mobility limitation, subjective health, or physical performance measures.

The prevalence of sarcopenia varies from one study to another and these differences can be explained by different definitions of sarcopenia, differences in the studied populations and their reference (control) populations, sample sizes, and methods used to measure skeletal muscle mass. The unification of criteria to diagnose sarcopenia as well as the methods used to assess it will certainly aid in a better knowledge of the prevalence of this syndrome.

Pathophysiology: Another unresolved issue of sarcopenia is the pathophysiology of this syndrome. Because aging affects multiple organs, sarcopenia has been proposed to be the result of a multifactorial process affecting muscle, motor units, inflammatory cytokines, anabolic hormones, and nutritional intake in the elderly [41, 42].

Muscle mass is determined by a balance between protein synthesis and breakdown. It has been established that with advancing age, there is a decrease in whole body protein turnover [43]. In contrast to what happens in cachexia, where both skeletal muscle mass and fat mass are decreased, in the elderly the loss of muscle mass is accompanied by gains in fat mass [44]. Examination of the synthesis rate of particular proteins in skeletal muscle has shown that there is a particular synthesis rate, at least for each cell compartment in the skeletal muscle. The synthesis rate of mitochondrial and myosin heavy chain (MHC) proteins declines with age, whereas the synthesis rate of the sarcoplasmic protein pool was unchanged [43]. Ferrington et al. (1998) [45] have shown changes in other key skeletal muscle compartments, such as the sarcoplasmic reticulum, in aged rats. The turnover rate of SERCA pumps and ryanodine receptors decreased, whereas calsequestrin showed no changes. Studies about other key contractile elements in aging muscle, such as the α-actin protein, are recently available [46], and it was shown that in the vastus lateralis muscles of middle-aged *vs* elderly individuals, an isoform switch occurred with a decrease in skeletal muscle α-actin and an increase in the cardiac isoform of α-actin. This change is in accordance with the idea of a fast-to-slow transformation process during aging in the skeletal muscle. In other atrophy models, such as prolonged bed rest, the loss of thin contractile filaments (actin) was larger than that of thick contractile filaments (myosin) [47].

In addition to changes in skeletal muscle mass, there are changes in the motor units innervating the muscles. In humans, there is a decrease in the number of functional motor units with age. These changes have been confirmed in aged rats, where a reduction in the number of muscle fibers innervated per motor axon [41] was evident. These changes will lead to a decreased skeletal muscle fiber/motor neuron interaction that can further explain the decline in coordinated muscle action.

Other elements involved in the development of sarcopenia may be the loss of anabolic factors including neural growth factors, growth hormone, androgens and estrogens, and physical activity. An increase in oxidative stress and inflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α), and a decrease in food intake with aging have also been implicated [41, 48]. Cross-sectional and longitudinal studies have demonstrated

that testosterone levels decrease with normal aging. Serum testosterone levels below the lower limit of normal, has a prevalence of 5% in healthy young men, up to 20% in the sixth decade, and increasing to 40–90% in men over 80 years [49]. Epidemiologic studies have demonstrated a relationship between levels of bioavailable testosterone and fat-free mass as well as muscle strength [49, 50]. These data correlated with physical performance tests. In the Framingham Offspring Study, men with low baseline of free testosterone concentrations showed a higher risk of incident or worsening mobility limitations [40]. In a study conducted in healthy young men to further elucidate the role of testosterone in the maintenance of skeletal muscle mass reported by Mauras et al. [6], a transient pharmacological hypogonadism was induced, decreasing fat-free mass, muscle strength, and fractional muscle protein synthesis in the volunteers. Despite this evidence, there are other studies, mainly that by Travison et al. [51], that have failed to show a clear association between testosterone concentration and physical function. This might be explained by certain aspects of the design of the study, including the selection of a younger population, a basal high physical activity level, mainly normal testosterone concentrations, and minimally demanding physical tests [50].

In short, testosterone has shown a tight association with skeletal muscle mass and a reasonable relationship with muscle strength, but no clear association with physical performance [50, 52]. The pathophysiology of sarcopenia appears, in conclusion, to be explained in part by intrinsic skeletal muscle changes associated with aging, but extrinsic causes also exist, and there are factors that aid in the development of sarcopenia or influence the degree of the attrition in skeletal muscle mass seen in the elderly.

Treatment options and impact of testosterone administration: Considering that protein breakdown and muscle atrophy is the hallmark of sarcopenia, many interventions have aimed to block the increased muscle catabolism seen in this syndrome. Among them, treatment with anabolic hormones, vitamin D, nutrition, and exercise have been studied. Controversial results have been obtained with all of the above-mentioned interventions, but 2 of them, testosterone and exercise, have been more successful. As was the case in relation to testosterone and the pathophysiology of sarcopenia, clinicians must discriminate between the endpoints of the studies that supplement older men with testosterone. In fact, the action of testosterone can be different when looking at muscle mass, strength, power, and whole-body functional probes. The anabolic effect of testosterone in aging men tends to be similar of that observed in young men but in a lesser extent. In general, studies have reported increases in lean body mass and decreases in fat mass, with varying responses concerning strength. Some studies have reported changes in grip strength but no increases in lower body strength [53, 54]. Others do report significant improvements in leg strength [49, 55]. Considering that sarcopenia is a syndrome that affects quality of life and risk of falls, changes in leg strength must be a desirable effect of the selected treatment. The factors that might lead to results showing little improvement in physical function after testosterone treatment in elderly men remains to be investigated. Critical points that should be revisited are basal testosterone levels of the selected population and testosterone concentrations reached during androgen treatment. The rigor of the selected physical probes ideally will present a real challenge in order to avoid an early ceiling effect on the sensitivity of the test.

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Physical activity is always associated with a general well being outcome that stimulates cardiovascular, respiratory, and skeletal muscle systems. Endurance and resistance exercise has been shown to improve the rate of decline in muscle mass and strength that occurs with age, although resistance exercise have proven to be more effective increasing muscle mass and strength in older men [54]. There is controversy in the literature regarding the extent of the muscle response induced by exercise in the elderly. Some authors indicate that resistance exercise in older people produces smaller strength increases in absolute terms, but similar in relative terms, to younger people [55]. On the other hand, similar increases in percent muscle strength were found in healthy older individuals and in young people in a prospective investigation that also assessed changes at the satellite cell level following a heavy resistance strength training period [56].

It seems that a key feature of skeletal muscle, its plasticity, is retained even in very old individuals. Muscle cross sectional area, muscle strength, and physical performance have been shown to improve in very old nursing home residents [57] and in community residents [58] engaged in progressive resistance exercise training. The intensity of the resistance exercise required to obtain positive changes is also still under debate. The majority of studies suggest that a high intensity resistance exercise (70–90% of 1 repetition maximum) is needed in order to obtain the desired improvements in muscle mass and strength [59]. As little as 1 resistance training session per week has demonstrated positive strength changes [60]. This recent issue may be an interesting point to explore in order to attract interest of more individuals to participate in strength training programs that will aid in the prevention and treatment of sarcopenia.

In conclusion, understanding sarcopenia as a multifactorial syndrome also involves the potential discovery of a great number of therapeutic targets. So far, testosterone, but more clearly, exercise, have been the more successful therapeutic options. More studies with the newest therapies and/or improved exercise and hormone replacement therapies should be performed in order to gain advances against this quality of life (QOL)-threatening syndrome.

2.3. Metabolic syndrome

Definition: Metabolic syndrome is the collection of a number of metabolic abnormalities that lead to increased risk of cardiovascular disease and diabetes mellitus (DM) [61]. The definition of metabolic syndrome varies among international consensus groups. Four groups have proposed diagnostic criteria, the World Health Organization (WHO), the Study Group for Insulin Resistance (EGIR), the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), and the International Diabetes Federation (IDF). In general, all of these groups maintain similar criteria, but differ in their measurements and cut off points. The IDF and NCEP ATP III are currently the most used. The latter requires the presence of at least 3 of the following 5 criteria for diagnosis: central obesity, elevated triglycerides, low HDL cholesterol (HDL-C), hypertension, and impaired fasting glucose (greater than 110 mg/dL), without categories among the factors. Subsequently, the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) suggested considering 100 mg/dL as the cut off for glucose, while the International Diabetes Federation (IDF)

established as a basic requirement the presence of central obesity confirmed by abdominal circumference measurement [62, 63]. Despite the great diversity of clinical criteria for diagnosing metabolic syndrome, the central issue is to recognize that its presence means an increased cardiovascular risk for the diagnosed patient, and to take action to counteract its consequences.

Epidemiology: Depending on the criteria used, age, gender, and race, the prevalence of metabolic syndrome varies markedly. However, the prevalence increases with age independently of the other criteria used, and it is higher in males when using the criteria of the WHO and EGIR. With the WHO criteria, the prevalence for men and women under 55 years is 14% and 4%, respectively, and 31% and 20% in the older age [62, 63]. In United States, using NCEP ATP III criteria, the overall prevalence is 24%, and increases directly with age and body mass index. In young Americans ages 12 to 19 years the prevalence is 4.2%, and it exceeds 40% by 65 to 69 years. A meta-analysis encompassing 172,573 patients concluded that there is a risk of cardiovascular death that is significantly higher in people with metabolic syndrome and that this is not only explained by its components separately [64].

Pathophysiology: Body fat is an important component of metabolic syndrome because adipose tissue is insulin-resistant in obesity, which increases free fatty acid (FFA) levels in the plasma. This has a direct effect on insulin target organs including liver and muscle, through specific actions that block the intracellular signaling of the insulin receptor. Moreover, in patients with metabolic syndrome, the adipose tissue was predominantly abdominal and associated with increased visceral fat as compared with peripheral distribution. Adipocytes in visceral fat are more metabolically active, releasing more FFA and inflammatory cytokines that drain directly to the liver via the portal circulation. This phenomenon, known as lipotoxicity, will be responsible for insulin resistance in these organs and the pancreas and unregulated high blood glucose. Lipo-toxicity also affects the cardiovascular system. In addition, FFA are able to increase oxidative stress, encourage a pro-inflammatory environment, and reduce systemic vascular reactivity, which are all factors negatively affecting cardiac cells. In association with these negative changes in adipose tissue, low testosterone levels worsen the clinical setting in the metabolic syndrome. Decreased androgen levels are associated with obesity, mainly with visceral fat accumulation. Epidemiological studies have demonstrated statistically significant correlations between plasma levels of testosterone and adipose tissue distribution, insulin sensitivity, lipoprotein metabolism, and the hemostatic system, among others. All of these cardiovascular risk factors impact endothelial function. It should be noted that these effects of testosterone vary according to sex and age. In normal men, plasma testosterone levels are correlated directly with HDL-C and inversely with triglycerides, LDL-cholesterol (LDL-C), fibrinogen, and plasminogen activator inhibitor type 1 (PAI-1). In addition, testosterone levels have correlated inversely with body mass index (BMI), waist circumference, visceral fat accumulation, insulin, and FFA. It is postulated that in men, low testosterone becomes a new element of the metabolic syndrome [61, 65].

Testosterone regulates the deposition of triglycerides in the abdominal fat tissue by lipoprotein lipase enzymes and a hormone sensitive lipase. Testosterone has an anticoagulant and profibrinolytic action, and by decreasing fibrinogen and PAI-1, it also has a pro-ag-

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gregatory effect through decreased platelet cyclooxygenase activity. During eugonadism, testosterone stimulates hormone-sensitive lipase and lipolysis. Thus, in testosterone deficiency, lipolysis is inhibited, favoring the accumulation of adipose tissue [6], which is reversed by testosterone administration. In addition, it has been reported that in hypogonadal patients, the deposition of visceral adipose tissue leads in turn to a further decrease in testosterone concentrations via conversion to estradiol by the aromatase. This leads to further abdominal fat deposition and a higher testosterone deficiency [4, 66]. In parallel, hyperinsulinemia is associated with decreased SHBG production, which decreases plasma total testosterone [67]. To date, the question of whether hypogonadism influences insulin resistance by increased abdominal obesity or whether obesity favors the reduction of plasma testosterone concentrations is still debated. However, insulin resistance leads to increased risk factors including increased triglycerides, lower HDL, and predominance of LDL-C. To these lipoprotein factors are added intolerance to carbohydrates, high blood pressure, and pro-coagulant and antifibrinolytic states [68]. Clinical studies show that men exhibit higher susceptibility to atherosclerosis than pre-menopausal women. The available data indicate that the evolution of atherosclerosis is more rapid in males, independent of dyslipidemia or evidence of endothelial damage, than in females [69]. The actual evidence indicates that low androgen concentrations are strongly associated with increases in cardiovascular risks including atherogenic lipid profile, insulin resistance, obesity, and metabolic syndrome [70, 71].

Impact of testosterone administration: Clinical studies generally show that the effects of exogenous testosterone on cardiovascular risk factors differ considerably depending on the dose, route of administration, and duration of treatment, as well as by age and condition of the patient. The findings most frequently observed are a decrease in HDL-C, a slight decrease in LDL-C, with sustained stability of the relationship between them, and moderation of insulin resistance leading to a decrease in triglyceride levels and visceral fat mass. Other less marked effects of androgen therapy are reduced levels of atherothrombotic lipoprotein Lp(a) and fibrinogen. According to current evidence, androgen therapy may exert beneficial or deleterious effects on various factors involved in the pathogenesis of atherosclerosis, and therefore further studies are required in order to determine optimal testosterone supplementation.

2.4. Considerations regarding clinical studies dealing with testosterone supplementation in sarcopenia and metabolic syndrome

Figure 2 emphasizes some of the determinants that should be considered when analyzing clinical studies working with androgen replacement therapy in sarcopenia and metabolic syndrome. It is important to bear in mind the level of testosterone that is sought with the proposed treatment and from this starting point, other important considerations must be made, including age of the individuals, in order to place the conclusions in an adequate context according to the population seeking treatment.

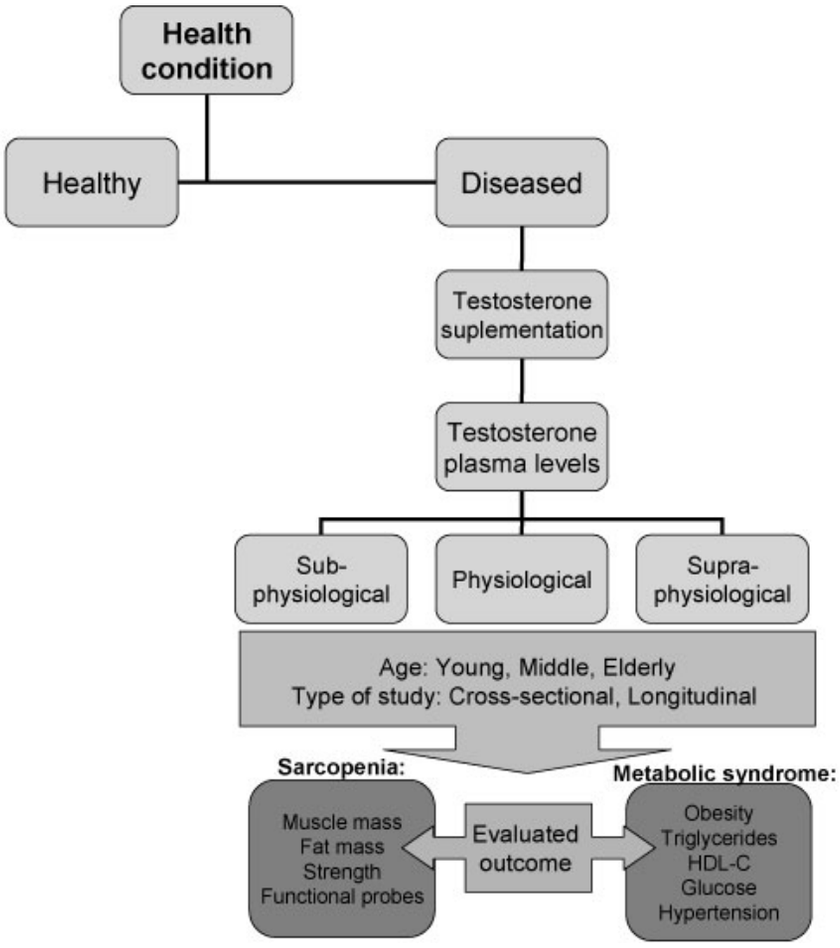

Figure 2. Highlight of some key considerations in studies of testosterone supplementation for sarcopenia and metabolic syndrome. The process starts with the diagnosis of the disease. From this point, therapy will be initiated and varying testosterone levels can be reached, normal, sub-, or supra-physiologic. Once in this condition, the type of study and the age of the studied sample will influence the results. Most importantly, the expected outcome should be clearly stressed in order to avoid any ambiguity.

2.5. Spinal and bulbar muscular atrophy (Kennedy's disease)

Definition: Spinal and bulbar muscular atrophy (SBMA), or Kennedy's disease, is an infrequent hereditary X-linked neurodegenerative disease that affects approximately 1/40,000 men, typically from age 30 years [72, 73]. It is characterized by slow degeneration and loss of motor neurons in the medulla and spinal cord [74, 75]. Patients exhibit progressive weakness, atrophy of facial, bulbar, and limb muscles, sensory disturbances, and hyper-creatine kinase (hyperCKemia), together with signs of androgen insensitivity [76]. Heterozygous and homozygous females are asymptomatic [77, 78], and the latter may have a subclinical phenotype [73]. The clinical signs are manifested initially as postural and perioral tremor, and progress to proximal or distal weakness of the limbs, dysarthria, dysphagia, hanging jaw, fasciculations, and muscle cramps [76, 79]. Muscle biopsies show changes associated with denervation, such as increased fiber size variability, atrophic fibers, and clumping of sarcolem-

mal nuclei and necrotic fibers [80, 81]. Nerve biopsy may show reduction of large myelinated fibers [82]. The disease usually progresses irreversibly and most patients die of pneumonia associated with dysphagia and disorders of the pharyngeal and laryngeal musculature, and some may require mechanical ventilation during the course of the disease [74, 83].

Etiology: The disease is caused by the expansion of a polymorphic tandem repeat sequence of the triplet CAG in exon 1 of the androgen receptor gene (AR) located on the X-chromosome (locus Xq11–12). The normal number of repeats is 9 to 36 [84, 85] and in the case of SBMA the number of repeats identified is 40 to 62 [85, 86]. The CAG encodes the amino acid glutamine (Q), so that the AR is expressed with a polyglutamine (poliQ) sequence in the amino terminal transactivation segment [87]. SBMA is considered 1 of the 9 hereditary polyglutamine neurodegenerative diseases [75]. It has been shown that the greater number of repeats in the polyglutamine sequence, the receptor activity is decreased. Thus, in SBMA the AR has limited or null activity. This AR mutant resides in the cytoplasm as apoAR associated with heat shock proteins (Hsps) and accessory proteins until it binds its ligand (testosterone and dihydrotestosterone). The hormone binding induces the exposure of the bipartite nuclear localization signal [88, 89] and translocation to the nucleus, where it is partially degraded by nuclear proteasome [90]. The AR mutation is not able to bind coactivators and corepressors, and its classical androgenic action is not performed [69]. The patient shows signs of androgen insensitivity such as asymmetric gynecomastia, reduced fertility, testicular atrophy, oligospermia, azoospermia, erectile dysfunction, and reduced libido or diabetes [72]. The poli-Q expanded AR deregulates transcription by interfering with several transcriptional coregulators. The number of the repeats is negatively correlated with age disease onset and directly with the severity and progression of the disease [72, 76].

Pathophysiology: The precise mechanism of the disease is still unknown, but there is growing evidence that the poli-Q-expanded AR is not adequately degraded, resulting in the accumulation of fragments of the poli-Q amino terminal fragment [73, 91]. These are accumulated in the nucleus of motor neurons, dorsal root ganglia, or visceral cells, and exert toxic effects that cause dysfunction and loss of neurons [79, 88, 92]. Aggregation requires the presence of androgens, migration of the mutated AR to the nucleus, and inhibition of gene expression of essential factors for the viability of affected neurons [88]. Once it joins the ligand, either testosterone or dihydrotestosterone (DHT), the poli-Q expanded AR migrates to the nucleus and due to misfolding [84], does not perform its genomic functions in the androgen response elements (ARE), but instead forms nuclear aggregates [92]. The nuclear aggregates (neuronal intranuclear inclusions) contain fragments of mutated AR, ubiquitin proteasome system (UPS) (ubiquitin and 19S and 20S proteasome core components), and heat shock proteins (Hsp40, Hsp70 and Hsp90) [93]. Segments with poli-Q expansions form antiparallel beta strands, and by hydrogen bonds the strands form a beta sheet structure, resulting in aggregation of these misfolded proteins as intranuclear inclusions, either as oligomers or larger aggregates [94]. The mutated ARs in the nucleus undergo partial proteolysis due to misfolding, resulting in the production of truncated forms of the poli-Q-expanded AR oligomers. The accumulation of mutant AR aggregates is regarded as protective [95, 96], while diffuse accumulation in the nucleus is considered toxic [92]. These aggregates

are observed at light microscopy as inclusions in the nucleus and cytoplasm of affected motor and sensory neurons and those with no apparent signs of damage [92]. It has been found that the number of aggregates was not correlated with toxicity [88]. In addition, this same type of aggregate is seen in other tissues including scrotal skin and abdominal viscera [73]. There is clear evidence that mutated AR aggregation leads to transcriptional dysregulation in affected neurons [97]. Intermediate gene products have been described that reduce the expression of TFG-β receptor type II (TβRII), dynactin 1, and VEGF. Transgenic mice expressing a mutated AR with 97 glutamine repeats (AR-97Q) exhibited muscle atrophy and neurodegeneration similar to that of SBMA in studies, and this was associated with reduced transcription of TβRII [97]. Moreover, in a similar model of transgenic mice, AR-97Q was associated with early decrease in the expression of the p150 (*Glued*) subunit of dynactin (dynactin 1), and this was related to inadequate retrograde axonal transport resulting in the distal accumulation of neurofilaments, axonopathy with subsequent degeneration of motor neurons, and the onset of characteristic signs of SBMA, which was partially reversed by castration [98]. Overexpression of C terminus of heat shock cognate protein 70-interacting protein (CHIP) in double-transgenic mice significantly reduced the SBMA phenotype by promoting the degradation of the mutated receptor by way of ubiquitin proteasome system (UPS) and significantly reduced the appearance of nuclear aggregates of mutant AR [93], indicating that proper breakdown of mutated protein reduces the negative effects of poli-Q-expanded AR. Interestingly, over-expression of skeletal muscle tissue-specific normal AR induced a phenotype similar to SBMA in transgenic animals, mimicking the effects of poli-Q-expanded AR [75], which suggest that muscle dysfunction may at least partly be behind the pathology of motor neurons and is due to overexpression of the AR in the presence of androgens inducing decreased expression of VEGF, which is critical in maintaining the neuromuscular junction and the viability of motor neurons [75].

Treatment options: Clinical deprivation of androgens by various strategies has been tested, including the use of the competitive AR blocker flutamide, which was ineffective in animal models. The efficacy to prevent the peripheral conversion of testosterone to dihydrotestosterone (DHT) by blocking the enzyme 5-α-reductase using dutasteride has also been tested, and proved to be ineffective to prevent the progression of the disease [99]. The most promising strategy has been the use of leuprorelin, which is a LHRH analogue that reduces androgen secretion to undetectable levels in plasma and has proven effective in preventing toxic accumulation of mutated AR and neurodegeneration in human patients [100, 101]. Other experimental strategies are based on preventing the deregulation of transcription induced by the mutated AR, since it has been shown to inhibit the histone acetyltransferase (HAT) activity of nuclear proteins like Sp1 and cAMP response element-binding protein-binding protein (CBP) [102], which has been shown to induce a phenotype of SBMA and which has been prevented by histone-deacetylase inhibitors, such as sodium butyrate, in animal studies [100]. The strategy of increasing the degradation of mutated AR via the UPS or by induction of autophagy to reduce the presence of nuclear and cytoplasmic poli-Q AR has also been explored [88, 93], but to date the most effective mechanism to prevent progression of the disease is to reduce circulating androgen concentrations, thereby preventing migration of the mutated AR to the nucleus and its subsequent toxic effects.

http://dx.doi.org/10.5772/53080

3. Molecular basis of influence of high levels of testosterone on skeletal and cardiac muscle

High blood levels of androgens, above the physiological range, are produced by exogenous administration of testosterone or its synthetic derivatives. These hormones have been used by athletes to improve performance by increasing muscle mass and strength. Hypertrophy is the more recognized among the numerous documented hormonal effects of long-term use of androgens.

Muscle mass is regulated by the normal balance between synthesis and degradation of muscle proteins. There is consensus that the use of testosterone leads to hypertrophy by increasing net protein synthesis over protein degradation, however the pathways responsible for this effect, and this dependence of intracellular androgen receptor, have not been fully described to date. Moreover, testosterone activates skeletal muscle satellite cell and mesenchymal stem cell differentiation, which also accounts for the clinical effect of this hormone on body composition [103, 104]. Side effects related to use of anabolic steroids are focused especially on the cardiovascular system [105]. It is known that there are increases in blood pressure and peripheral arterial resistance [105-108], and there are also effects on the heart muscle, primarily left ventricular hypertrophy with restricted diastolic function [109-111]. Severe cardiac complications (heart failure, atrial fibrillation, myocardial infarction or sudden cardiac death) in strength athletes with acute anabolic/androgenic steroid abuse have also been reported [112, 113].

The anabolic actions of androgens enhance muscle strength and increase muscle size clinically [6, 7, 114]. *In vivo*, androgens increase skeletal muscle mass and induce cardiac hypertrophy [10, 109]. The effect of androgens may occur through either the classically described intracellular androgen receptor pathway (genomic pathway) or via a fast, non-genomic pathway. In contrast to the genomic pathway (minutes to hours), the non-genomic pathway has measurable effects in seconds to minutes. It is elicited by hormones, the effects of which cannot be abrogated by transcriptional inhibitors, and may occur without requiring the hormone to bind the intracellular receptors or the receptor to bind DNA [115].

As noted, hypertrophy processes involve changes in gene expression controlled by intracellular androgen receptor-mediated pathways, and recent studies have demonstrated an alternative rapid intracellular androgen receptor-independent mode of testosterone action. The establishment of the testosterone-androgen receptor complex acts as a transcriptional factor for the expression of different genes and proteins necessary for protein synthesis, energy production, and cell growth, which are also crucial for hypertrophic growth. Now, aside from the classical action mechanism of testosterone, non-classical effects have also been implicated in the growth of the muscle cell. Hypertrophy in both skeletal and cardiac muscle is an adaptive response of the cell to increase force and contractile activity. Although initially beneficial, the prolonged activation of muscle cells by hypertrophic stimuli may produce detrimental effects. Unlike that in cardiac muscle, hypertrophy of skeletal muscle cell is a reversible process.

Several pro-hypertrophic stimuli activate common pathways in the muscle cell [116]. Among pathways activated by these stimuli, key regulators are phosphatidylinositol-3 kinase (PI3K)/Akt and mitogen-activated protein/extracellular signal-regulated kinase kinase (MEK/ERK1/2) pathways [117-119]. It has also been proposed that testosterone actions involve membrane receptors that stimulated early intracellular signaling pathways through interaction with G proteins in primary cultures of skeletal muscle cells [12] as well as cardiac myocytes [120]. Common to these early effects are the fast intracellular Ca^{2+} increase, activation of Ca^{2+}-dependent pathways, and second-messenger cascades. Ca^{2+} is one of the most diverse and important intracellular second messengers as well as a key element in the excitation-contraction coupling of muscle cells. Ca^{2+} has been related to hypertrophy because of its ability to promote the activation of the protein phosphatase calcineurin through the establishment of a Ca^{2+}/calmodulin complex [121]. Calcineurin promotes translocation of the nuclear factor of activated T cells (NFAT) from cytoplasm to nucleus. NFAT family proteins are responsible for the expression of the early fetal genes, which are expressed during fetal development. These are silenced in adult stages but are re-expressed during cardiac hypertrophy, and thus are considered as hypertrophic markers [119, 121, 122].

Interlinked signaling pathways are related to hypertrophy of the muscle cells. Moreover, it has been described that testosterone induces intracellular Ca^{2+} increase through a non-genomic action mechanism in skeletal muscle cells [12, 13] and cardiomyocytes [120]. Studies in cultured muscle cells show that through a nongenomic mechanism, testosterone is implicated in the activation of a membrane receptor coupled to a Gαq protein, thus resulting in the production of IP_3 and release of Ca^{2+} from endoplasmic reticulum [12, 120]. These Ca^{2+} oscillations induce the activation of ERK 1/2, which in turn phosphorylates mammalian target of rapamycin (mTOR), promoting hypertrophic cardiac growth [15].

The PI3K/Akt pathway has been related to cell survival and proliferation in almost all cell types. However, the up-regulation of the pathway by several stimuli induces cardiac hypertrophy. One of the most common downstream targets of Akt is the protein kinase glycogen synthase kinase 3-β (GSK3-β) [123]. Activated GSK3-β phosphorylates several members of the NFAT family, which promotes their translocation from nucleus to cytoplasm. Akt phosphorylates and inhibits GSK3-β, which increases the residence of NFAT in the nucleus. Moreover, Akt has the ability to phosphorylate mTOR, another downstream target of the PI3K/Akt pathway. In muscle cells, protein synthesis is highly regulated by mTOR, which stimulates protein translation and ribosome biosynthesis [124]. The mTOR lies upstream of critical translation regulators such as the 40S ribosomal protein S6 kinase 1 (S6K1) and the eukaryotic initiation factor 4E-binding protein 1 (4E-BP1). Activation of the mTOR pathway is a critical step to induce cardiac hypertrophy by testosterone *in vitro* [15].

Thus, considering the current information available regarding androgen actions on muscle cells, it has been proposed that muscle hypertrophy induced by testosterone requires both androgen receptor activity and signal transduction pathways to control protein synthesis.

http://dx.doi.org/10.5772/53080

4. Perspectives of androgen-mediated physiological and pathological responses

The role of androgens in modulating both musculoskeletal and cardiovascular function is of the highest importance, especially considering that androgen deficiency is strongly associated with several medical conditions, including sarcopenia, metabolic syndrome, obesity, diabetes, hypertension and atherosclerosis. Testosterone deficiency, as observed in LOH, further deprives muscle of important anabolic effects of androgens in human males. The action mechanism of androgens involves both androgen receptor and signal transduction pathways, so, essential for the diagnosis, clinical and pharmacological intervention studies, a detailed knowledge of these pathways is required. As cardiovascular side effects of testosterone reduce its actual therapeutic use, research in this field is badly needed to have a detailed knowledge of the effects of androgen alterations in order to elaborate safe therapeutic replacement protocols that appear to have a broad potential for high incidence pathological conditions.

Acknowledgment

This work was supported by FONDECYT (grant 1120259 to M.E. and grant 1110467 to E.J.) and by ACT 1111 (E.J.). C.B. is a CONICYT doctoral fellow (AT 24091020).

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