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Oxandrolone for Clinical Therapy: An Update

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ABSTRACT

Oxandrolone is an anabolic steroid derived from testosterone with no toxicity, prevalently used for burned lesions in children or with short stature and delayed puberty. Oxandrolone increases protein synthesis in muscle and other tissues for its metabolic effects. It seems suitable for patients with sarcopenia, cachexia, and other chronic diseases such as heart failure, liver disease, osteoporosis, and neurodegenerative diseases. In menopausal women, oxandrolone reduces the side effects due to low estrogen levels. The effect of oxandrolone in osteoporosis in men and women is related to its activation of androgen receptors (AR) directly and after aromatization on estrogen receptors (ER). In neurodegenerative diseases, the efficacy of oxandrolone is related to the capability to stimulate myelin regeneration in central and peripheral nerves. This review aims to consider the clinical effects of oxandrolone in men and women. Considering that this molecule was synthesized many years ago and given the low cost, no clinical research has been conducted by the pharmaceutical industry, and the clinical interest in this drug has fallen.

Keywords

Oxandrolone, Estrogen Receptors (ER), Androgen receptors, Liver disease, Heart failure, Neurodegenerative diseases.

Introduction

Oxandrolone is an androgenic steroid chemically derived from testosterone, exhibiting androgen and anabolic action. The anabolic action is characterized by increased protein synthesis and muscle growth in men and women [1,2]. The androgenic effects are characterized by the development and maintenance of primary and secondary sexual characteristics in males, while in women, the effects are mainly characterized by deepening voice, baldness, sexual activity, clitoris increase.

The tissue's response to androgen steroids is due to the activation of androgen receptors (AR) [3], a protein encoded on the X chromosome. The androgen passes through the cell membrane at the cellular level and binds to the AR in the cytosol. The AR complex is transferred to the nucleus and binds to DNA, activating the protein synthesis. Androgens activate a specific nuclear receptor, directly affecting target gene transcription. These genes encode muscle-specific transcription factors, enzymes, structural proteins, and microRNAs. In addition, the anabolic action of androgens is partly established through crosstalk with other signaling molecules such as Akt, myostatin, IGF-I, and Notch. Finally, androgens may exert non-genomic effects in muscle by increasing Ca(2+) uptake and modulating kinase activities. In conclusion, the anabolic effect of androgens on skeletal muscle is not only explained by the activation of the myocyte androgen receptor. Still, it is also the combined result of many genomic and non-genomic actions [4].

The key point is that skeletal muscle metabolism is essential to maintaining health conditions through mitochondrial homeostasis [5], muscle strength, and functional capacity [6]. The effectiveness of a high protein diet supplementation on muscle mass (1 g/kg body weight) is influenced by inflammation. Systemic inflammation reduces muscle mass, increasing muscle loss, while muscle gain is associated with reduced systemic inflammation [7].

Hypermetabolism at the skeletal muscle level is a classic, highly complex, and multifactorial challenge to overcome in patients with severe burns and chronic diseases. The chronic increase of circulating stress mediators, such as catecholamines, cytokines,

and glucocorticoids, induces a multiorgan hypercatabolic response resulting in lipolysis, glycogenolysis, and proteolysis, insulin resistance and lipotoxic state, worsening hypermetabolic response [8]. If hypermetabolism is not blocked or reversed, the patient may succumb to sepsis and/or multiorgan failure [9]. The burn lesions are the most effective expression of burn-induced muscle catabolism, inducing a significant burden on the recovery process, as a 10%–30% loss impairs immune responses and delays wound healing, thereby increasing the risk of infection. A 40% loss becomes fatal [11].

Oxandrolone increases appetite [11] and muscle protein synthesis, essential in maintaining health conditions; lack of physical activity is the cause of most chronic diseases [12]. The therapy with oxandrolone is indicated in patients with hypermetabolism, systemic metabolic, and inflammatory derangements where the skeletal muscle metabolism is notably altered. Oxandrolone is the only anabolic androgenic steroid (AAS) FDA-approved in the US for the treatment of patients with weight loss after severe trauma, major surgery or infections, malnutrition due to alcoholic cirrhosis, and Duchenne's or Becker's muscular dystrophy [13]. Skeletal muscle dysfunction may be attributed to hypermetabolism, which is consequential to burns et al., major surgery, or infections such as HIV, malnutrition, alcoholic cirrhosis, and muscular dystrophies such as Duchenne's (Fenichel or Becker's diseases. Oxandrolone has been pharmacologic approved interventions for wasting [14].

Pharmacology

Oxandrolone is a nonaromatizable androgen anabolic steroid synthesized in 1962 [15] with the chemical name 17β-hydroxy-17α-methyl-2-oxa-5α-androstane-3-one. It belongs to the 17α-alchilated groups of androgens that induces protein synthesis and increases muscle mass [16] in healthy young [5] and elderly men [8], inducing positive metabolic changes.

Unlike other orally administered C17alpha-alkylated AASs, the novel chemical configuration of oxandrolone confers a resistance to liver metabolism and marked anabolic activity. In addition, oxandrolone does not exhibit effects (jaundice, cholestatic hepatitis, peliosis hepatis, hyperplasia, and neoplasms) attributed to the C17alpha-alkylated AASs. Oxandrolone is generally well tolerated, and the most commonly documented adverse effects are transient elevations in transaminase levels and reductions in high-density lipoprotein cholesterol levels.

Oxandrolone acts by inhibiting multiple burn-induced inflammatory mediators as cytokine antagonists in catabolic patients [17] and inhibiting the cortisol effect for human sepsis rheumatoid arthritis [18] and for the cachexia associated with human immunodeficiency virus and opportunistic infections [19].

Oxandrolone has an excellent safety profile, is orally administered (approved dosing concentration: 5–20 mg/d), has fewer potential side effects than other androgens, and is well tolerated in women [13,20]. Various studies have shown that oxandrolone has potent anabolic effects in conditions associated with cachexia and wasting [20,21]. At supraphysiological doses, the major toxicity of anabolic steroids is expressed by psychiatric and psychological disturbances. There is no convincing evidence that malignancies are induced in athletes who abuse them. Gross disturbance of sexual and reproductive function occurs in both sexes. Hypogonadal states can be shared and prolonged. Their abuse by athletes should be carefully evaluated, and prolonged use by the young should be discouraged [22]. Table 1 reports the myotrophic and anabolic activity of the most popular anabolic androgenic steroids. Oxandrolone is a potent anabolic steroid [15] with a myotrophic activity ten times superior to testosterone with a similar anabolic activity. In a randomized clinical trial, oxandrolone, 20 mg/d, substantially increased the lean tissue accrual and strength gains compared with physiologic testosterone replacement alone, in eugonadal men with HIV-associated weight loss [23].

Table 1: Effect of myotrophiv and anabolic activity of the most popular anabolic androgenic steroids. *Dissociation of the androgenic and other hormonal activities from the protein anabolic effect of steroids. Handbook of experimental Pharmacology. 1976; 43: 361-401.*

Steroids	Myotrophic activity	Anabolic activity	value
methandienone	**0,6**	**0,20**	**3**
Metenolone acetate	**0,86**	**0,12**	**7**
Nandrolone decanoato	**3,2-4,9**	**0,41-0,31**	**12,1-10,6**
Norbolethone	**3,44**	**0,15-0,17**	**20**
Noretandrolone	**0,77-1,0**	**0,06-0,38**	**2-16**
Oxandrolone	**3,22**	**0,24**	**13**
Oxymetholone	**1,34**	**0,42-0,61**	**2,2-3,2**
Oximesterone	**3,2**	**0,45**	**7,1**
Stanazolol	**2,0-2,7**	**0,33-0,52**	**6-10**
Testosterone	**0,36**	**0,28-0,50**	**0,7-1,3**

Oxandrolone Therapy in Severely Burned Children

Various studies have investigated the effect of oxandrolone in post-burned children, evidencing a more rapid physical recovery and healing, increasing protein synthesis [24-32] and increased growth rate [26,33], increasing lean body mass, bone mineral rate (BMC) [27,29,34] and are summarized in Table 2.

A follow-up study was undertaken to evaluate the effect of oxandrolone for 2 years on long-term BMC and bone mineral density (BMD). Patients between 0 and 18 years of age with ≥30% of total body surface area burned were consented to an IRB-approved protocol and randomized to receive either placebo (n = 84) or 0.1 mg/kg oxandrolone orally twice daily for 24 months (n = 35). Patients were followed prospectively from the time of admission until 5 years postburn in a single center; BMD was found to significantly increase with long-term oxandrolone administration, indicating a significantly reduced risk for future fracture. Patients had significantly greater height velocity than controls throughout the first 2 years. The administration of long-term oxandrolone was more efficacious than the administration for 12 months. The therapy was well tolerated without side effects [29].

Porro et al. [27] found that patients 0 to 18 years old with burns covering >30% of the total body surface area were randomized to receive a placebo (n = 152) or oxandrolone, 0.1 mg/kg twice daily for 12 months. The administration of oxandrolone improves the long-term recovery of severely burned children in terms of height, BMC, cardiac work, and muscle strength, as well as increases BMC. These results persisted for 5 years [27]. A recent systematic review [35] and other studies confirmed these results [33,36].

Oxandrolone in Growth Retardation

The effect of oxandrolone on growth stimulation in children is known since 1973 [37]. The clinical effects of anabolic hormones in malnutrition and other catabolic states have been the subject of considerable research during the past several decades. Oxandrolone increases growth in children with cachexia and wasting [38] and improves high growth velocity [39]. Many studies have shown the effect of oxandrolone on delayed growth and puberty [9,40-46], also associated with growth hormone (GH) [41], and are reported in Table 3.

Table 2: Effect of oxandrolone in severely burned children.

Authors	n. patients	Daily dose (mg/kg)	Duration time	Clinical effects
Feathers, 2024 [24]	24 burns unit	n.s,	n.s	Oxandrolone use varies greatly across services within the UK. National guidelines would further facilitate trusts' and clinicians' use of Oxandrolone appropriately.
Giusti, 2022	14 burn patients	0.2 mg	14 days	Prevented the reduction of LBM compared to placebo and was safety.
Sousse, 2016 [30]	54	0.2	12 months	Clinical general improvement and of the pulmonary function
Herndon, 2016 [26]	612	0.2	48 months	attenuates burn-induced growth arrest and BMD
Reeves, 2016 [29]	84	01 x2	5 years	greater improvements in BMC, BMD, and height velocity.
Porro, 2012 [27]	70	0.2	12 months	Improvement of long-term recovery in height, BMC, and muscle mass.
Miller, 2008 [33]	review	0.2	12 months	Prospective, randomized, controlled studies supported efficacy and safety of oxandrolone.
Przcora, 2007	51	0.1	12 months	Improvement in lean body mass and cardiopulmonary capacity.
Murphy, 2004 [34]	20	0.1	6-12 months	Improvement in lean body mass, BMC, and BMD.
Thomas, 2004 [31]	35	0.2	12 months	Constitutive proteins such as albumin, prealbumin, and retinol-binding protein levels increased and the acute phase reduced.
Wolf, 2003 [32]	32	0.2	5 days	Muscle biopsies and gene expressions significantly improved net muscle protein synthesis.
Hart, 2001 [25]	14	0.1x2	One week	Improvement in muscle protein metabolism through enhanced protein synthesis efficiency.

BMD= bone mass density; BMC= bone mineral content;

Table 3: Effect of oxandrolone in delayed growth and puberty (CDGP).

Authors	n. patients	age	Daily dose mg/kg	Duration of treatment	Studies type	Clinical outcome
Gault, 2021 [40]	92 Turner syndrome		0.05	4 years	Randomized placebo-controlled trial	Oxandrolone still significantly increased final height by 4.1 cm.
Sas, 2014 [44]	Turne syndrome	8-10	0.06 mg/kg/day + GH 0.03-0.05 mg/kg/day	2 years	Summary of collaborative venture Dutch, UK, US.	The addition of Ox to GH treatment leads to an increase in adult height, on average 2.3-4.6 cm.
Salehpour, 2010 [43]	91 CDGP boys	12.6-14.6 years	2.5	2 years	Randomized, placebo-controlled trial	Significantly increased the height standard deviation score and bone age compared to placebo.
Schroor,1995 [45]	18	11-15	0.1	30-57 months		Increased height gain.
Wilson, 1995 [46]	40	11-14	0.1	1 year	Randomized, placebo-controlled trial	low-dose oxandrolone can increase both height and weight velocity in boys
Bassi, 1993 [9]	11	10.6-14.1	0.1	6-12 months	Observational	No significant effect on the pattern of pubertal growth, nor on the rate of sexual maturation or on final height.
Malhotra, 1993 [42]	10	12.4-15.5	2.5		Observational	Height velocity increased. No effect on the GH axis
Loche, 1991 [41]	16	13.7 12.8	Oxa 0.07 mg/kg GH (0.6 U/kg/ week sc 5-6 times/week)	6 months	Randomized Clinical trial	Low-dose oxandrolone is as effective as GH in accelerating growth in boys (1, 2) with CGD.

Oxandrolone is also associated with growth hormone (GH) in the treatment of growth retardation. In Turner syndrome, the combination of oxandrolone with GH for a period of 4 years in female children of 4-11 years had significant benefit without side effect [47] and in another group of 36 girls of 7-13 years [48].

Oxandrolone in Malnutrition, Cachexia and Muscle Wasting

In patients with chronic diseases, the loss of muscle mass (sarcopenia) and body weight should be treated to prevent cachexia. The Cachexia Consensus Conference, has defined cachexia as "a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass" [49].

Generally, in cachexia, or wasting, the progressive loss of skeletal muscle and adipose tissue is associated with fatigue and weakness, clinically relevant. It is commonly observed in chronic diseases, including cancer, AIDS, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and chronic renal failure [50,51,52]. Cachexia is associated with an increased mortality risk and morbidities, prolonged convalescence [53], and an increased risk of infection [52]. The loss of muscle mass is due to an increased muscle protein breakdown and an increase in systemic inflammatory mediators, such as the proinflammatory cytokines interleukin (IL)-6 and IL-8, and tumor necrosis factor-α [54].

Patients with trauma, bacterial infections, thermal injury, or sepsis syndrome often have rates of protein turnover 30-50% higher than similar individuals without injury [55,56].

The role of androgen therapy in these conditions should be considered essential to reduce complications and hospitalization time. The use of oxandrolone in the treatment of catabolic disorders, malnutrition, underweight patients, chronic debilitating disease, wasting, and neuromuscular disease is strong evidence of its clinical efficacy [13].

Sheffield-Moore et al. [2] found that Muscle protein synthesis and breakdown were determined by a u-compartment model using stable isotopic data obtained from femoral arterio-venous sampling and muscle biopsy. before and after 5 days of oral OX (15 mg/day). Muscle protein synthesis and breakdown were also significantly increased after short-term therapy.

Orr et al. [13] in a review showed that oxandrolone is safely used to promote anabolism in the clinical setting for chronic wasting conditions as well as in the prevention and treatment of frailty associated with loss of muscle tissue in aging (sarcopenia). Oxandrolone is reported to be generally well tolerated, and the most commonly documented adverse effects are transient elevations in transaminase levels and reductions in high-density lipoprotein cholesterol levels. However, the clinical benefit are acceptance of a therapeutic option in sarcopenia and other chronic wasting conditions.

In *Chronic obstructive pulmonary disease (COPD)* patients, weight loss is a common complication associated with negative outcomes. A low BMI, age, and low PaO_2 are significant independent predictors of increased mortality and body weight has an independent effect on survival in COPD [57]. A prospective clinical trial conducted on 82 patients showed that Oxandrolone administration at the dose of 10 mg/day, was effective to facilitate weight restoration in patients with COPD and the weight gain was primarily in lean body mass [21]. Due to these anabolic effects, emerges that anabolic steroids should be considered in the treatment option in COPD patients suffering from muscle wasting [58].

In chronic heart failure (CHF) patient sarcopenia (loss of muscle mass and function, a precursor stage of cachexia) and cachexia are strong predictors of frailty and mortality. Although the main intervention is nutritional support in combination with resistance exercise training, the support of anabolic drugs, including androgens, selective androgen receptor modulators (SARM), growth hormone (GH), and IGF-1, compounds can be essential [59]. Androgen sustains muscle mass and heart efficiency. Androgen deprivation therapy, as observed in patients with prostate cancer, caused a higher risk of heart failure than nonusers [60]. Androgen supplementation may improve left ventricular architecture, function, physical capacity, and quality of life [61] and reduce the mortality rate. Testosterone has significant positive effects on muscle mass and function, and low endogenous testosterone has been described as an independent risk factor for CHF in a study with 618 men.

Lower plasma levels of testosterone are associated with myocardial damage, lower exercise capacity, and higher mortality risk in men with HF [62] and increasing all-cause mortality in women [63]. However, the use of testosterone is controversial because of possible side effects [64]. So, oxandrolone as an androgen can be considered a helpful therapy in CHF with sarcopenia.

Effect on the Liver

Various clinical studies conducted on humans demonstrated that androgen steroids have a beneficial effect on liver function and regeneration. Particularly, androgens favor the delivery of fat deposits in the liver in alcoholists, as in hepatic steatosis [65], in patients with high triglyceride levels [66,67]. In animals, the administration of testosterone prevented liver injury caused by toxic chemical substances such as carbon tetrachloride [68], thioacetamide [41], and ethionine [69].

Oxandrolone is effective in reducing alcoholic hepatitis. In a study involving 273 male patients affected by severe alcoholic hepatitis, with caloric intake (greater than 2,500 kcal/day) to promote anabolism), oxandrolone treatment reduced 6-mo mortality (4% active treatment vs. 28% placebo. With nutrition therapy, oxandrolone should be added to the regimen [70].

In 43 patients with laboratory features of alcoholic hepatitis were randomly assigned to receive one of four regimens: 1) standard

therapy, consisting of abstinence, a balanced, nutritionally adequate diet, and multivitamins; 2) oxandrolone (20 mg orally four times a day) plus standard therapy; 3) nutritional supplementation, consisting of 2 L daily of 3.5% crystalline amino acids (in 5% dextrose), given by peripheral vein; or 4) a combination of oxandrolone and nutritional supplements. The addition of oxandrolone to nutritional supplementation was well tolerated and led to more rapid improvement in the clinical outcome [71].

In a long term study conducted on 2141 patients affected by alcoholic hepatitis [72]. The administration of mg 80 per day of oxandrolone improved liver function and reduce the mortality rate. Furthermore, the improvement was observed after a few months after suspension of the therapy [73]. In 23 patients a liver biopsy was performed and showed a marked improvement of liver tissue in patients who received oxandrolone. Another studies evidenced the positive effect of oxandrolone at the dose of 20 mg/day as a treatment standard in alcoholic hepatitis of medium-high severity [71].

In preliminary studies in 1967, Bengmark, et. [74] found no influence of testosterone treatment on liver regeneration after partial hepatectomy. However, later, it was shown that both sex hormones stimulated the mammalian liver. In both sexes, the liver contains estrogen receptors, and the serum estrogen concentration may initiate or facilitate liver regeneration after resection [75] through the activation of estrogen receptor α (ERα) [76].

Androgens accelerated the regenerative process in the liver after partial surgical resection [10,77-79]. Vic e coll. [80] demonstrated a complete regeneration of the liver in rats with a surgical hepatectomy of 90% of the liver with testosterone administration.

Oxandrolone in Menopause

Androgens have a generally positive effect on women's health, and the decline in plasma androgen levels plays a significant role in affecting perimenopausal and menopausal symptomatology and quality of life [18]. Oxandrolone therapy finds applications in menopausal women to treat or prevent the clinical effects due to the loss of circulating levels of androgens, such as loss of libido, vasomotor symptoms, mood and well-being, bone structure, and muscle mass [81], who experience natural menopause and premenopausal loss of libido from diminished free testosterone levels. Androgens excess appears to participate as an independent parameter, which further aggravates the cardiovascular and metabolic aberrations in women with PCOS [82]. However, studies on the effect of increased androgen levels on cardiovascular outcomes in postmenopausal women indicate no deleterious effect or increased cardiovascular risk [83]. Free androgen levels were negatively correlated with waist circumference, insulin resistance, and lipids [84] and predicted all-causes mortality events [63]. A low SHBG level has an independent predictive value for CVD risk [16,85]. Among post-menopausal women, a higher testosterone/estradiol ratio was associated with an elevated risk for incident CVD [86]. These data suggest that the evaluation of cardiovascular disease risk in women should include the androgen plasma levels [84]. The benefits of low-dose testosterone therapy, typically combined with estrogen therapy, include positive impacts on body composition, functional capacity, insulin sensitivity, inflammatory markers, and cholesterol [87]. However, although well indicated, there are no studies on the effect of oxandrolone in menopausal and young women.

Effect on Bone Metabolism

Osteoporosis is a significant public health problem associated with fracture risk [88]. In menopausal women, a major cause is correlated with estradiol deficiency and was correlated with changes in the periosteal diameter [3]. However, there is evidence that estrogens are also a major regulator of bone metabolism in men [89]. Sex hormones promote bone mass acquisition and consolidation in different manners during puberty and maintain it for all of life [90].

On several cell types in bone, such as mesenchymal and myeloid precursors to osteoblasts and osteoclasts, estrogen receptor alpha (ER α), estrogen receptor beta (ERβ), and AR have been detected. Androgens protect men against osteoporosis, maintaining the cancellous bone mass and expansion of cortical bone, and this action is mediated by the AR and ERα [91]. Men with homozygous mutations in the estrogen receptor ERα gene, resulting in a nonfunctional ER, had unfused epiphyses and osteopenia, with a spine BMD that was more below the standard [92]. This data demonstrated that estrogen was essential for epiphyseal closure and the acquisition of bone mass during puberty in males.

In women, the decline in serum estradiol levels through menopause is closely associated with increased osteoclastic bone resorption [93]. There is a different effect of estradiol versus testosterone on cancellous and cortical bone. In women, estrogen activates cancellous and cortical bone mass; in men, androgens stimulate the cancellous bone, while estrogens the cortical bone. Both sex steroids play essential roles in reducing osteoporosis. Declining sex steroid levels and other hormonal changes likely contribute to age-related bone loss, as do impairments in osteoblast number and/or activity [89]. 17β-estradiol inhibits bone resorption, whereas both hormones regulate bone formation. 17β-estradiol in men derived from the activity of aromatase on testosterone.

AR deletion in osteoblast lineage cells in male mice leads to reduced cancellous bone volume and cancellous number associated with increased osteoclast numbers [94]. One of the major secondary causes of osteoporosis in men is hypogonadism, which is found in up to 20% of men with symptomatic vertebral fractures and 50% of elderly men with hip fractures [68] testosterone replacement in hypogonadism and explore other options for the treatment of osteoporosis secondary to loss of sex steroids in men. Androgens may act as pro-hormones for estrogens so that, can no longer be considered exclusively "male" or "female" hormones [95]. Androgens can be converted into estrogens expressing the most relevant cellular and biological actions on bone [96]. Other important regulatory variables include mechanical loading and innervation/neuroregulation [97]. In hypogonadal individuals, and

nonpharmacologic measures such as good nutrition (especially adequate intake of protein, calcium, and vitamin D) and regular physical activity.

Testosterone replacement to improve bone mass or prevent bone loss is routinely recommended because it was shown to improve bone mass [98]. In men with symptomatic hypogonadism, testosterone replacement, if indicated, can improve BMD and the anabolic therapy is superior to bisphosphonates for high-risk patients [8]. Randomized, double-blind, placebo-controlled clinical trials showed that in children with Klinefelter syndrome, oxandrolone improved bone mass. Since these individuals are at risk for osteoporosis, age-appropriate androgen replacement and future studies on bone health in children with KS should be further explored [99].

Watts using the association of estrogen plus androgen (esterified estrogen mg 1.25 plus methyltestosterone mg. 2.5) in menopausal women evidenced the benefits of this association with increased vertebral bone mineral density, relieved somatic symptoms and safety during two years of treatment [100]. Various studies evidenced the importance of androgen associated with estrogen in the hormonal replacement HRT program in postmenopausal women [101-104].

Oxandrolone in Neurodegenerative Diseases

Neurodegenerative diseases, including Alzheimer disease (AD), Parkinson disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and Huntington disease, are characterized by the loss of neurons and myelin as well as neuronal function in multiple regions of the central and peripheral nervous systems. The role of androgens in maintaining brain health and preventing neurodegeneration is essential [105].

Androgens are active in the brain and peripheral neural system due to the widespread distribution of androgen receptors (AR) and estrogen receptors (ER) in neurons [106]. ARs are primarily expressed in the hypothalamus [107], telencephalon, and amygdala and also in the majority of the brainstem and spinal cord areas associated with sensory functions [106]. suggesting that androgens may have an essential and novel extranuclear role in neuronal function. ARs are also present in axons and dendrites within the mammalian central nervous system. The observation that ARs are present in axons and dendrites highlights the possibility that androgens play an important and novel extra-nuclear role in neuronal function [108]. The loss of AR function could contribute to motor neuron degeneration [31] and motor neuron vulnerability increases when AR expression is reduced [109] enhancing neurodegeneration. These data reinforce a novel potential link between ALS and spinal bulbar muscular atrophy (SBMA), another motor neurodegenerative disease mediated by reduced AR function in motor neurons [110].

The activation of the nuclear hormone receptors by their ligands also promotes the synthesis of myelin proteins and lipids in mouse models of demyelination [111]. However, there are limited clinical studies that focus on how the activation of these nuclear hormone receptors could alleviate demyelination in patients with diseases such as multiple sclerosis (MS). The treatment of demyelination in neurodegenerative diseases is cricial, and the activation of nuclear hormone receptors is a potential therapeutic target for demyelinating diseases. Neuroactive steroids, (progesterone, dihydroprogesterone, dihydrotestosterone, testosterone, and 3alpha-diol), stimulate both *in vivo* and *in vitro* (Schwann cell cultures) [112]. The neural brain AR is required for the remyelination effect of testosterone. In knockout AR in neuron and macroglial cells, testosterone did not stimulate the formation of new myelin sheaths. The potent synthetic testosterone analog 7alpha-methyl-19-nortestosterone, which has been developed for long-term male contraception and androgen replacement therapy in hypogonadal males and does not stimulate prostate growth, also efficiently promotes myelin repair [113]. Brooks et al. [114] demonstrate, in a cell culture, a direct trophic effect of androgens on lower motor neurons, mediated through the AR expressed in this population of neurons.

In Alzheimer's Disease (AD)

Recent studies support epigenetic dysfunctions in neurodegenerative and psychiatric conditions, such as Alzheimer's disease (AD). These dysfunctions in epigenetic mechanisms also play crucial roles in the transgenerational effects of the environment on the brain and, subsequently, in the inheritance of pathologies. The possible role of gonadal steroids in the etiology and progression of neurodegenerative diseases, including AD, has become the subject of a growing body of research over the last 20 years. Recent scientific findings suggest that epigenetic changes, driven by estrogen and androgens, play a vital role in brain functioning. Therefore, exploring the role of estrogen and androgen-based epigenetic changes in the brain is critical for understanding AD and the possible therapeutic strategies for AD [115]. The neuroplastic effects of androgens exerts a particular emphasis on the hippocampus, which has been the focus of much of the research in this field [116].

Androgen deprivation therapy for prostate cancer is associated with an increased risk of dementia, including AD [117]. Testosterone and dihydrotestosterone, but not estradiol, enhance the survival of new hippocampal neurons in adult male rats. Through an androgen-dependent mechanism, testosterone enhances hippocampal neurogenesis via increased cell survival in the dentate gyrus [118]. The therapy with testosterone has shown some benefit in patients with dementia and AD [17].

In Parkinson's Disease (PD), a neurodegenerative disorder that has a higher incidence in the male population. Sex hormones and genes encoded by the sex chromosomes could protect from the disease or reduce its development. underline the importance of considering sex when studying brain physiology and pathology in cellular and animal models to understand disease etiology better and develop novel tailored therapeutic strategies [119]. Testosterone administration (gel 5 gr/day) in PD patients for 3 months an improvement of nonmotor and motor symptoms was

observed [120]. Replacement therapy for men with PD and low testosterone levels may be an important addition to antiparkinsonian management strategies.

ALS

Amyotrophic lateral sclerosis (ALS) is a fatal motoneuron degenerative disease that is associated with demyelination. In animal models with motoneuron degeneration, Esperante et al. showed that testosterone reduced motoneuron degeneration and myelin deterioration, enhanced muscle mass and grip strength, and reduced paw abnormalities. Therefore, testosterone acts as a myelin protector and finds potential clinical translation. In CSF of ALS patients, the dihydrotestosterone (DHT) levels were significantly decreased in all male and female ALS patients, sustaining the hypothesis that DHT leads to motor neuron death, causing ALS [121]. Testosterone has been shown to promote myelin repair. Asbelaoui et al. [5] demonstrate that remyelination of axons by oligodendrocytes induced by testosterone was accompanied by an increase in astrocytes activation. The cooperation between testosterone and CXCR4 signaling involving astrocytes is required for myelin regeneration after focal demyelination produced in the ventral mouse spinal cord by the infusion of lysolecithin.

Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune inflammatory disease of the CNS that causes neuronal demyelination with subsequent loss of axonal function and paralysis. MS manifests itself with varied symptoms ranging from loss of vision to neuromuscular disorders with an evident predominance of women (ratio 3:1 to men) [122]. The neurologic decline in patients with MS is associated with an irreversible degeneration of axons and neurons that have lost their capacity for remyelination [61]. Low plasma androgen levels (T, DHEA, or DHEAS) were found in men and women affected by MS [53,123]. Estrogens [124] and androgens [113] contribute substantially to the remyelination process.

In patients with MS, AR and ER activation may represent important therapeutic strategies for myelin recovery and a viable strategy in future clinical trials. In patients with progressive MS, astrocytes expressing CXCR4 and AR surrounded myelin lesions, and their presence opposed the incursion of Schwann cells. These results highlight a mechanism of testosterone-promyelinating-induced signaling and the importance of normalizing its levels in combined myelin repair therapies [5].

There are recent advancements in the field of myelin biology to treat demyelinating disorders using various synthetic analogs of progesterone and testosterone [124]. Oxandrolone has neuroprotective properties used to prevent muscle loss and increase locomotor recovery, which is concomitant with reduced loss of cord tissue in a standard weight drop model of spinal cord contusion injury. Oxandrolone also increased axonal sprouting within the ventral horns distal to the injury, consistent with the formation of relay circuits mediating locomotor recovery [126]. Oxandrolone therapy in a patient with Charcot-Marie Tooth disease after three months induced an improvement in muscular strength and walking capacity. Muscle biopsy revealed a significant increase in the type grouping of muscle fibers, an expression of regeneration, and reinnervation processes [127]. These studies show that oxandrolone is a possible alternative to testosterone and methylprednisolone.

Conclusions

Oxandrolone is a potent anabolic steroid well tolerated with low side effects that found its indication in many clinical conditions characterized by sarcopenia, cachexia where the muscle protein synthesis is compromised, as observed in burned patients, and chronic diseases. Oxandrolone improves organ function, modulates the systemic inflammatory response, and accelerates wound healing in a murine burn injury model [128]. Oxandrolone effectively reduced complications and healing time in burned children and improved growth rate. Oxandrolone administration gives benefits in neurodegenerative disease and osteoporosis, particularly in women when associated with estrogens.

Although many clinical trials with anabolic androgenic steroids have shown the benefit in the treatment of chronic diseases, including HIV-wasting, chronic renal failure, chronic obstructive lung disease, muscular disease, alcoholic liver disease, and postoperative recovery, with clinically relevant results, further studies are necessary for the endpoint [129].

Trials explicitly looking at the use of oxandrolone in the cachectic population are even sparser. The most relevant study has confirmed that oxandrolone has potent anabolic effects in conditions associated with cachexia and wasting [20,21]. However, considering the safety and low cost of the drugs, oxandrolone should be considered as a therapeutic intervention in all patients with sarcopenia and chronic diseases.

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