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Endocrinological disturbances in chronic obstructive pulmonary disease

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ABSTRACT: In this overview, the available literature on endocrinological disturbances in chronic obstructive pulmonary disease (COPD) is reviewed, with stress on growth hormone/insulin-like growth factor I (IGF-I), thyroid hormone and the anabolic steroids.

In COPD, little is known about circulating growth hormone or IGF-I concentrations. Some authors find a decrease in growth hormone or IGF-I, others an increase. An increase of growth hormone might reflect a nonspecific response of the body to stress (for instance, hypoxaemia). Until now, only one controlled study on growth hormone supplementation has been published, which however did not reveal any functional benefits. Before growth hormone supplementation can be advised as part of the treatment in COPD, further controlled studies must be performed to investigate its functional efficacy. The prevalence of thyroid dysfunction in COPD and its role in pulmonary cachexia has not been extensively studied. So far, there is no evidence that thyroid function is consistently altered in COPD, except perhaps in a subgroup of patients with severe hypoxaemia. Further research is required to more extensively study the underlying mechanisms and consequences of disturbed thyroid function in this subgroup of COPD patients.

A few studies have reported the results of anabolic steroid supplementation in chronic obstructive pulmonary disease. Although some studies have discerned that low circulating levels of testosterone are common in males with chronic obstructive pulmonary disease, little is known about the prevalence, the underlying causes or functional consequences of hypogonadism in these patients. The use of systemic glucocorticosteroids and an influence of the systemic inflammatory response have been suggested as contributing to low testosterone levels. It can be hypothesised that low anabolic hormones will reduce muscle mass and eventually result in a diminished muscle function. Further evidence is required before testosterone replacement can be recommended for males with chronic obstructive pulmonary disease.

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Chronic obstructive pulmonary disease (COPD) is characterised by chronic airflow limitation that progresses slowly over time and, by definition, the airflow obstruction is largely irreversible [1]. At present, medical treatment of COPD is predominantly focused on the primary organ dysfunction. Despite optimal medication, there is a weak relationship between the primary organ impairment on the one hand and disability and experienced handicap on the other. The most important complaints of patients with COPD are dyspnoea [2] and an impaired exercise performance. The latter is clearly related to the diminished muscle function [3]. Diminished muscle function is commonly the result of muscle wasting in COPD; its prevalence increases from 20% in clinically stable outpatients [4] up to 35% in patients presenting for pulmonary rehabilitation [5].

Since selective wasting of fat-free mass (FFM), despite relative preservation of fat mass, has been reported in COPD [6], the presence of underlying disturbances in energy or intermediary metabolism is suggested. There is indeed evidence for a relationship between an enhanced systemic inflammatory response and FFM depletion [7]. Furthermore, disturbances in the anabolic hormone system may also impair the anabolic responses needed for skeletal muscle performance. Because anabolic steroids can be exogenously supplemented, this is an important area of research.

In this overview, the contribution of endocrinological disturbances to the muscle wasting and weakness in COPD will be discussed. Disturbances in the growth hormone/insulin-like growth factor-I (IGF-I) system, in the thyroid hormone system and in the hypothalamic-pituitary-gonadal axis will be discussed.

Growth hormone/insulin-like growth factor-I in chronic obstructive pulmonary disease

Growth hormone provides stimulation for muscle growth and development. Growth hormone exerts its effects primarily by increasing levels of insulin-like growth factors. Healthy elderly individuals have decreased levels of IGF-I, the major mediator of growth hormone's anabolic action on muscle [8]. In addition to increasing age, systemic corticosteroids (commonly used to treat COPD exacerbations) are known to down-regulate the growth hormone system. In rats, corticosteroid treatment decreases IGF-1 and IGF-2 expression in the diaphragm and the gastrocnemius [9].

Little information is available regarding circulating growth hormone or IGF levels in COPD. Pituitary growth hormone secretion is pulsatile; circulating levels vary substantially over the course of the day. For this reason, growth hormone level in a single blood sample has limited importance. Although some investigators have serially sampled growth hormone levels over a 24-h period in order to calculate average growth hormone levels, most inferences about the function of the growth hormone axis have been inferred from measurement of IGF-I levels which are considered to reflect integrated growth hormone secretion. The data that exist suggest that IGF-I levels in stable COPD patients tend to be low [10, 11], consistent with the impression that the growth hormone axis is suppressed by chronic disease. On the other hand, a few studies suggested increased growth hormone concentrations in COPD and especially in hypoxaemic COPD [12]. An increase of growth hormone might reflect a nonspecific response of the body to stress or, alternatively, it may play a role in the development of right-sided hypertrophy present in patients with pulmonary hypertension. In COPD, physiological stress like chronic hypoxia and bronchoconstriction could possibly induce an increase in growth hormone.

In growth hormone-deficient adults, administration of growth hormone increases muscle mass and strength, and improves exercise performance [13]. However, while administration of growth hormone to healthy elderly individuals increases muscle mass, improvements in muscle strength and endurance have not generally been detected. Considering studies in patients with COPD, SUCHNER *et al.* [13] reported that 1 week treatment with growth hormone in six severely underweight ($\geq$10% weight loss in the previous year) patients with COPD resulted in a positive nitrogen balance, and also in increased fat oxidation and energy expenditure and decreased glucose oxidation. No changes in body weight, muscle function or lung function were found [14]. In seven underweight (<90% of ideal body weight) patients with COPD, in an uncontrolled study design, 3 weeks of recombinant human growth hormone administration increased weight and improved nitrogen balance and maximal inspiratory pressure, with no adverse effects [15].

A controlled study has examined whether administration of growth hormone enhances the benefits of exercise training in a study of 16 patients with COPD [10]. The group that received growth hormone plus endurance exercise training increased lean body mass, whereas the group that received exercise training alone did not. Despite the increase in muscle mass, no significant change in maximum inspiratory pressure was observed in either group. The only measure of peripheral muscle strength obtained was handgrip strength, which did not change in either group. There were no significant differences between groups in the improvements after training in peak oxygen uptake in an incremental exercise test; 6-min walk distance decreased in the growth hormone group but not the placebo group [10].

Another consideration is that growth hormone is quite expensive and must be administered by injections several times per week. Taken together with the failure to date to demonstrate appreciable functional benefits, it is difficult to find a rationale for the use of growth hormone in COPD at this time. Further controlled studies of a larger patient group must be performed in the future to investigate its functional efficacy in (cachectic) patients with COPD.

Thyroid hormone in chronic obstructive pulmonary disease

An important function of thyroid hormone is regulation of metabolism and thermogenesis. Abnormalities in thyroid function potentially influence energy balance and body composition. Hypermetabolism is commonly observed in patients with COPD; this has been attributed to increased energy expenditure both at rest [16] and during physical activities [17]. A hypermetabolic state in combination with insufficient dietary intake will result in a negative energy balance and may conceivably contribute to weight loss in COPD [18]. The prevalence of thyroid dysfunction in COPD and its role in pulmonary cachexia has not been extensively studied.

Thyroid hormone levels have been reported in a group of 11 clinically stable normal-weight patients with COPD [19]. DIMOPOULOU *et al.* [20] found that, as a group, patients with COPD had normal serum thyroid hormone levels. Serum total thyroxine (TT4), total triiodothyronine (TT3), resin T3 uptake (RT3U), reverse triiodothyronine (rT3) and thyroid stimulating hormone (TSH) levels were measured. The free thyroxine and free triiodothyronine indexes (FT4I=RT3U/30TT4 and FT3I=RT3U/30TT3, respectively) along with the TT3/TT4 ratio were calculated; the latter was used as a marker of peripheral conversion of thyroxine into triiodothyronine. In patients with forced expiratory volume in one second (FEV1) $\geq$50% predicted TT3, TT4, and TT3/TT4 ratio did not correlate with age, FEV1, arterial oxygen tension (P_{a,O_2}) or inhaled corticosteroid use. In patients with FEV1 <50% pred, however, there was a strong positive correlation between TT3/TT4 ratio and P_{a,O_2} [20]. Based on this work, hypoxaemia seems to be a determinant of the peripheral metabolism of thyroid hormones. Whether this constitutes an unfavourable adaptation in the metabolism of patients with COPD must be further studied. Another study investigated neuroendocrine function before and after at least 4 months of long-term oxygen treatment (LTOT) in 12 male, stable, hypoxaemic COPD patients [21]. Patients received thyroid releasing hormone challenge before and after this period. Pretreatment thyroid hormone levels were within normal range. Low FEV1 was associated with low basal and stimulated TSH levels. No significant hormonal changes were noted following an average of 8 months of LTOT for the entire study group. However, in a subgroup (n=6) with an increase in arterial oxygen saturation exceeding 7% points while receiving LTOT, nocturnal excretion of S-free thyroxin was reduced by 20%. Therefore, in patients with chronic hypoxaemia, thyroid function is not influenced by LTOT except for a subgroup with severe nocturnal hypoxaemia [21].

Taken together, no evidence has been presented so far that thyroid function is substantially altered in COPD, except perhaps in a subgroup of patients with severe hypoxaemia. Further research is required to more extensively study the underlying mechanisms and functional consequences of disturbed thyroid function in hypoxaemic COPD.

Testosterone in chronic obstructive pulmonary disease

In males, testosterone is secreted mainly by the gonads. Secretion is stimulated by luteinising and follicle stimulating hormones, which are produced in the pituitary. In females, circulating testosterone levels are much lower; the main sites of secretion are the adrenals and the ovaries. Testosterone has long been recognised for its anabolic properties, which are mediated by the androgen receptor and can be attributed to increases in the fractional synthesis rates of actin and myosin heavy chains [22]. In the presence of sufficient amino acids, fibre hypertrophy occurs [23]. Total testosterone consists of ~30% of testosterone strongly bound to sex hormone binding globulin (SHBG); the remaining 70% denoted bioavailable

testosterone includes testosterone weakly bound to albumin (68%) and free testosterone (2%) [24].

Aging is accompanied by changes in the hypothalamic-pituitary-gonadal axis resulting in detectable declines in testosterone and oestrogen. In males, testosterone levels decline with age; this decline has been hypothesised to be linked to sexual dysfunction, muscle weakness and atrophy, osteopenia and memory loss. In females, testosterone levels decrease even before the menopause. This decline continues after the menopause [25] due to decreased ovarian production, adrenal secretion and peripheral conversion from its major precursor, androstenedione [8].

Since testosterone circulates mainly in bound form, changes in binding proteins (principally SHBG) alter biological availability. SHBG increases with age and in females its concentration is higher after the menopause. Therefore, free testosterone is often substantially reduced in the aging males and post-menopausal females [24]. From cross-sectional studies, low testosterone and high SHBG predict low bone density and low muscle strength [8].

Several chronic wasting diseases have been found to be associated with decreased anabolic hormone levels and, perhaps as a consequence, with muscle wasting and osteoporosis. In patients infected with human immunodeficiency virus (HIV), the prevalence of hypogonadism ranged from 17% in normal-weight patients up to 25% in patients suffering from nutritional depletion [26]. Accumulating data indicate that anabolic hormone levels are low in COPD. The mechanism of these alterations is unclear, but it has been speculated that chronic hypoxia, disease severity, smoking, corticosteroid therapy and chronic (inflammatory) illness contribute to low testosterone levels.

One of the suggested underlying factors for hypogonadism is hypoxaemia, which is present in a portion of the COPD population. SEMPLE *et al.* [27] found low testosterone levels in acutely ill, hospitalised COPD patients with hypoxaemia (P_aO_2 ranging from 5–10 kPa). The degree of testosterone depression was correlated to the severity of arterial hypoxaemia and hypercapnia [27]. Whether hypogonadism is correlated to disease severity in terms of low FEV1 or impaired diffusing capacity, remains to be determined.

Studies on the effects of cigarette smoking on total testosterone concentrations have been conflicting. A recent work reported that healthy male smokers had higher total and free testosterone and SHBG concentrations compared to non-smoking males matched by age and body mass index, while bioavailable testosterone was similar. This suggests no significant effect of smoking on the biologically active fraction of testosterone [28].

Given the clinical impression that patients with COPD may demonstrate signs compatible with hypogonadism, KAMISCHKE *et al.* [29] investigated the relationship between testosterone deficiency and corticosteroid use. Thirty-six males with COPD of whom 16 were receiving oral glucocorticoid medication (mean±SD dose 9.4±4.4 mg prednisolone) were cross-sectionally investigated. No differences were seen between the groups, except for a shorter 6-min walking distance in patients receiving glucocorticoids compared to patients without oral steroid therapy. Serum levels of testosterone were below normal (<12 nM) in 15 of 36 patients. Serum levels of free testosterone (free T) were decreased (<200 pM) in 25 of the 36 patients, including all patients receiving glucocorticoid treatment. In the 16 patients taking glucocorticoids, free T was inversely correlated with current glucocorticoid dosage and positively correlated with body mass index. Therefore, glucocorticoid treatment appears to aggravate hypogonadism. Systemic glucocorticoids have been shown to contribute to respiratory as well as peripheral muscle weakness in COPD [30], independent of the extent of muscle wasting [31].

A study in asthmatic males treated with maintenance systemic glucocorticoids showed reduced total and free testosterone concentrations, which could be restored by 12 months therapy with intramuscular testosterone [32]. Systemic glucocorticoids can reduce the normal nocturnal increase in testosterone by lowering testosterone biosynthesis. In addition, they decrease adrenal precursors and affect the pituitary response to gonadotropin releasing hormone, resulting in decreased luteinising hormone secretion and low plasma testosterone [29]. A binding competition between testosterone and glucocorticoids for the same receptor site is proposed as the mechanism for the deleterious effects of systemic glucocorticoids on testosterone levels [33].

Additional factors besides hypoxaemia and chronic use of systemic glucocorticoids may be involved in hypogonadism in COPD. There is evidence for an enhanced systemic inflammatory response associated with FFM wasting in COPD [7]. Although little information is yet available on the involvement of the systemic inflammatory response in testosterone metabolism, experimental data in healthy males showed that a single dose of recombinant human tumour necrosis factor induced an increase in luteinising hormone followed by a 50% decrease in serum total testosterone [34]. These data suggest that tumour necrosis factor affects the hypothalamic-pituitary-testicular axis at multiple levels and might be involved in hypogonadism in systemic diseases.

Leptin, a hormone involved in energy balance homeostasis that is suggested to be up-regulated by the systemic inflammatory response [35], has also be proposed to play a role in hypogonadism. NYSTROM *et al.* [36] found an inverse correlation between serum testosterone and the natural logarithm of leptin in healthy males, which persisted after correction for body mass index.

Hypogonadism, accompanied by chronic disease or not, is associated with wasting of body cell mass [37, 38]. In healthy, elderly males, no association was found between functional tests (isometric strength of upper and lower extremities, up-and-go test) and testosterone concentrations. In contrast, it was found that a good performance on the up-and-go test (controlled for age, height and body mass index) was associated with higher serum levels of SHBG [39]. From this study's results, one would also expect an association with free testosterone, since free testosterone decreases with age due to an increase in SHBG. Furthermore, since the biological functions of testosterone are predominantly mediated by free testosterone [24], it can be hypothesised that free testosterone will predominantly influence functional performance.

Reports on the role of hypogonadism in osteoporosis are conflicting. MEDRAS *et al.* [40] found associations between free testosterone and bone mass content in healthy younger and elderly subjects. However, IQBAL *et al.* [41] detected no correlation between serum testosterone and bone mass in a group of 130 patients with COPD.

The effects of testosterone supplementation have been studied in health and in certain diseases. BHASIN *et al.* [42] performed a randomised, double-blind, placebo-controlled study in 43 healthy males with experience in weight-lifting. They were randomised into four groups: placebo-no strength training, placebo-strength training (weight-lifting three times daily), testosterone (600 mg intramuscularly weekly for 10 weeks)-no strength training and testosterone-strength training. Protein and energy intake were standardised. Of the males in the no-strength training groups, those with testosterone treatment had greater increases in FFM (3.2 kg *versus* 0.8 kg), in triceps and quadriceps muscle size and in muscle strength. The males in the testosterone-strength training group had greater increases in FFM (6.1 kg,

$p<0.001$), muscle size and muscle strength than those in the two no-strength training groups. The males in the placebo-strength training group achieved an increase in FFM of 2.1 kg ($p=0.017$). It can be concluded from this well-designed study that supraphysiological doses of testosterone, especially when combined with strength training, increase FFM and muscle size and strength in healthy males.

In 74 males with symptomatic human immunodeficiency virus illness, RABKIN *et al.* [43] evaluated the efficacy of testosterone supplementation in alleviation of hypogonadal symptoms (diminished libido, depressed mood, low energy, and depleted muscle mass). Patients were enrolled in a double-blind, placebo-controlled 6-week trial with bi-weekly testosterone injections, followed by 12 weeks of open-label maintenance treatment. With testosterone treatment, average increase in muscle mass over 12 weeks was 1.6 kg for the whole group ($p<0.001$), and 2.2 kg for the 14 males with wasting at baseline ($p<0.001$). Improvement in all parameters was maintained during subsequent open-label treatment for up to 18 weeks.

Only a few studies of anabolic steroid supplementation in chronic obstructive pulmonary disease have been reported. SCHOLS *et al.* [44] administered a relatively low dose of nandrolone every 2 weeks for 8 weeks to males and females with chronic obstructive pulmonary disease; increases in lean body mass and respiratory muscle strength were observed. Six months of stanozolol administration to males with chronic obstructive pulmonary disease resulted in increased body weight, lean body mass, but no endurance exercise changes [45]. Forty-nine subjects completed a 4-month uncontrolled observational study of oxandrolone; body weight increased, but 6-min walk did not [46]. It seems appropriate to conclude that further evidence has to be gathered before testosterone repletion can be routinely recommended for patients with chronic obstructive pulmonary disease.

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