REVIEW

Endocrinological derangements in COPD

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ABSTRACT: Chronic obstructive pulmonary disease (COPD) is no longer considered to affect only the lungs and airways but also the rest of the body. The systemic manifestations of COPD include a number of endocrine disorders, such as those involving the pituitary, the thyroid, the gonads, the adrenals and the pancreas.

The mechanisms by which COPD alters endocrine function are incompletely understood but likely involve hypoxaemia, hypercapnia, systemic inflammation and glucocorticoid administration. Altered endocrine function can worsen the clinical manifestations of COPD through several mechanisms, including decreased protein anabolism, increased protein catabolism, non-enzymatic glycosylation and activation of the rennin-angiotensin-aldosterone system.

Systemic effects of endocrine disorders include abnormalities in control of breathing, decreases in respiratory and limb-muscle mass and function, worsening of respiratory mechanics, impairment of cardiac function and disorders of fluid balance.

Research on endocrine manifestations of COPD embraces techniques of molecular biology, integrative physiology and controlled clinical trials. A sound understanding of the various disorders of endocrine function associated with COPD is prudent for every physician who practices pulmonary medicine.

KEYWORDS: Aldosterone, diaphragm contractility, insulin-like growth factor-I, oestrogens, testosterone, thyroid

Patients with chronic obstructive pulmonary disease (COPD) have a chronic illness. They are commonly hypoxaemic, hypercapnic or both, have increased levels of systemic inflammatory markers, and receive glucocorticoids. Each of these factors can affect endocrine function. In turn, altered endocrine function can worsen COPD through several mechanisms. Systemic effects of endocrinopathies triggered by COPD (or therapies used in COPD) include abnormalities in control of breathing, decreases in respiratory and limb-muscle mass and function, worsening of respiratory mechanics, impaired cardiac function, and abnormal fluid balance. In this review, we discuss endocrinopathies triggered by COPD, such as those involving the pituitary, the thyroid, the gonads, the adrenals and the pancreas. Areas of active research and controversial topics are specifically highlighted.

COPD AND THE SOMATOTROPIC AXIS

Weight loss and muscle wasting are present in about 20% of stable outpatients with COPD [1], 40% of patients with acute respiratory failure and 70% of patients requiring mechanical ventilation [2]. A decrease in fat-free mass is accompanied by

a decrease in muscle mass (sarcopenia) [2, 3]. The control of muscle mass is complex and includes the action of inflammatory cytokines, mechanical load on the muscles and anabolic hormones [4–6]. There are four main anabolic axes: somatotropic, gonadal, adrenal and insulin [4–8].

Central to the somatotropic axis are growth hormone (GH) and insulin-like growth factor (IGF)-I. GH is released by the hypophysis and stimulates production of IGF-I. The major source of GH-dependent (and insulin-dependent) IGF-I production is the liver (circulating isoforms) [9]; however, other tissues, including the skeletal muscles and the adipose tissue, produce both local and circulating isoforms of IGF-I [6].

Although the GH/IGF-I axis is often considered a major regulator of muscle mass, there is accumulating evidence that IGF-I also acts independently of GH [10]. The role of locally *versus* systemically produced IGF-I in determining muscle mass is not clear [11, 12]. IGF-I stimulates muscle protein synthesis and hypertrophy, and inhibits protein catabolism *via* the phosphatidylinositol 3-kinase (PI3K)/Akt (also called protein kinase B) pathway (fig. 1) [16].

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COPD and depression of the somatotrophic axis: risk factors

Advanced age, malnutrition, inactivity and administration of glucocorticoids are associated with downregulation of the GH/IGF-I system. In contrast, hypoxaemia and hypercapnia probably increase GH levels in patients with COPD [18, 19].

Ageing

Most patients with COPD are old, and ageing is associated with progressive decrease in muscle mass [20]. The mechanisms responsible for age-related decrease in muscle mass probably include decreases in GH/IGF-I [21–23], testosterone [21, 23, 24] and dehydroepiandrosterone sulfate (DHEAS) [7].

Inactivity

In animal models of inactivity, loss of muscle mass has been associated with a decrease in IGF-I mRNA [25]. In patients with COPD, inactivity has been implicated in the reduction of quadriceps muscle expression of IGF-I and of myogenic differentiation protein (MyoD): a transcription factor required to maintain stable skeletal muscle differentiation and to induce proliferation and repair by satellite cells in response to muscle injury [10].

Malnutrition

Malnutrition can decrease serum levels of IGF-I [11, 26, 27]. In laboratory animals, malnutrition can also decrease IGF-I

FIGURE 1. Insulin-like growth factor (IGF)-I mediates many of the actions of growth hormone. IGF-I can originate from the liver (endocrine function of IGF-I) or locally (autocrine/paracrine function). a) IGF-I stimulates muscle protein synthesis and hypertrophy via the phosphatidylinositol 3-kinase (PI3K)-Akt pathway. (PI3K can also be activated by insulin and other extracellular signals [13].) Akt, activated by PI3K-induced phosphorylation, stimulates several hypertrophic pathways including glycogen synthase kinase-3 β (not shown) and the mammalian target of rapamycin (mTOR). mTOR itself can promote protein synthesis through activation of 70-kD ribosomal S6 protein kinase and by inhibiting eukaryotic translation initiation factor 4E binding protein-1 (not shown) [14]. IGF-I also reduces net protein breakdown by inactivation of the forkhead box class O (FoxO) transcription factors 1, 3 through Akt-mediated phosphorylation. Inactivation of FoxO factors 1, 3 decreases the expression of atrophy-related genes or "atrogenes" including atrogin-1 (also known as muscle atrophy F-box or MaF-bx) and muscle ring finger 1 (MuRF-1) both E3-ubiquitin ligases in the ubiquitin-proteasome proteolytic pathway [15] and other atrophy-related genes such as poly-ubiquitin, metallothionein, and cathepsin-L (not shown) [16]. In addition to its anabolic and anti-catabolic effects, the IGF-I activation of Akt and inhibition of FoxO increases the resistance of many cells to apoptosis (programmed cell death) [17]. b) When IGF-I levels are low, as during administration of glucocorticoids, the protein synthesis triggered by the IGF-I/PI3K/Akt pathway is reduced and protein degradation is increased. Not shown is a second IGF-I intracellular signaling pathway that potentiates proliferation of myoblasts and satellite cells through the activation of the mitogen-activated protein kinase cascade [17].

mRNA expression in the liver and limb muscles but not in the diaphragm [11]. Nutritional supplements can increase levels of IGF-I [27].

Glucocorticoids

Steroid myopathy results, at least in part, from a perturbation of the GH/IGF-I system [28, 29]. Steroid myopathy can affect respiratory and limb muscles and produce a wide range of manifestations [15]. On one end of the spectrum, usually associated with chronic moderate doses of glucocorticoids, is a mild-to-moderate weakness, mild myosin loss, and atrophy of type II fibres and less-so of type I fibres (table 1). On the opposite end, usually associated with acute administration of large doses of glucocorticoids in critically ill patients, is severe paresis, sarcomeric disarray, profound atrophy and acute myonecrosis [15].

Studies suggest that glucocorticoid-induced depression of the GH/IGF-I system contributes to the development of steroid myopathy [11, 16, 30–32] (fig. 1). In healthy subjects, the combination of prednisone ($0.8 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) plus recombinant human GH for 7 days increased protein synthesis but did not decrease proteolysis [33]. Whether administration of recombinant human GH prevents myopathy in patients is unknown. In laboratory animals, administration of recombinant human GH may [34] or may not [35] attenuate steroid myopathy. In contrast to the conflicting effects of the administration of recombinant human GH on myopathy, administration of IGF-I in laboratory animals with [32] or without emphysema [36] attenuates [36] or totally prevents [32] steroid myopathy.

Hypoxaemia

In patients with COPD and moderate-to-severe hypoxaemia, muscle wasting is associated with depressed protein synthesis [37]. Whether or not the depressed protein synthesis is caused by impairment in the somatotrophic axis is controversial. SCALVINI *et al.* [18] recorded GH levels in 17 stable patients with COPD (eight of whom were hypoxaemic). In nonhypoxaemic patients, GH levels were 3-fold greater than GH levels recorded in healthy subjects. In hypoxaemic patients, GH levels were 5-fold greater than GH levels recorded in healthy subjects. The investigators speculated that increased levels of GH in COPD might reflect a nonspecific response of the body to stress. Such upregulation of GH could play a role in pulmonary vasculature remodelling and right-sided hypertrophy of patients with pulmonary hypertension [18]. That hypoxaemia can increase GH levels is supported by a recent study of BENSO *et al.* [38], which recorded an increase in GH concentration, as well as an increase of total IGF-I, in athletes after 7 weeks of high-altitude exposure to hypoxia. Despite higher levels of IGF-I, hypoxia was associated with a decrease in body weight [38]. In contrast to the data in healthy subjects, hypoxaemic children with cyanotic congenital heart diseases have depressed IGF-I [39]. Depressed IGF-I is independent from nutritional status [39]. In animal models, IGF-I administration only partially reverses the catabolic effects of hypoxaemia [40].

Hypercapnia

In nine patients with COPD who had hypoxaemia, hypercapnia and peripheral oedema, GH concentrations were 11-fold

greater than normal [41]. In that study, it was not possible to dissect the potential effects of hypoxaemia [18, 38] from those of hypercapnia on the circulating levels of GH. An independent effect of hypercapnia on GH was suggested by the observation that, acute normoxic hypercapnia in mechanically ventilated patients increased levels of GH [19].

Inflammatory cytokines

Circulating and local levels of tumour necrosis factor (TNF)- α and other inflammatory cytokines can be increased in patients with COPD [42]. In cultured myoblasts, TNF- α at low concentrations induces a state of IGF-I receptor resistance [43]. Such resistance is responsible for inhibition of protein synthesis stimulated by IGF-I [43] and IGF-I-stimulated expression of myogenin, a key myogenic transcription factor [43].

COPD and depression of the somatotrophic axis: prevalence

Limited information is available on the interaction between COPD and the somatotrophic axis. In 87 patients with COPD enrolled in a rehabilitation program, CASABURI *et al.* [44] reported that levels of IGF-I were about half the values recorded in healthy subjects. In a follow-up study, they reported that levels of IGF-I were low in 47 men with COPD and low testosterone (mean total testosterone concentration $320 \text{ ng} \cdot \text{dL}^{-1}$) [45]. As in the studies by CASABURI and colleagues [44, 45], other investigators have reported a high prevalence of decreased IGF-I in stable patients with COPD [46, 47] and in patients experiencing an exacerbation [47]. The high prevalence of decreased IGF-I in several investigations [44–48] raises the possibility that a depression of the somatotrophic axis may contribute to the decreased muscle mass in some patients with COPD.

In contrast to the preceding studies [44–48], other investigators [14, 49] found that IGF-I in patients with COPD and muscle atrophy is equivalent to that in healthy subjects. These contrasting results may be reconciled by the variable concentration of ghrelin, a novel GH-releasing peptide synthesised by the stomach, anterior pituitary and hypothalamus [22]. Levels of ghrelin can be higher in underweight patients with COPD than in normal-weight patients with COPD and healthy volunteers [46]. Decreased levels of IGF-I in patients with COPD and muscle atrophy [14, 49], despite higher levels of ghrelin [46], might indicate that the somatotrophic axis in these underweight patients has developed resistance to the biological functions of ghrelin. The aforementioned studies [14, 49] are limited by the failure to determine whether the local expression and function of IGF-I, and its downstream pathways (fig. 1), are affected by COPD.

The pathways downstream of IGF-I have been recently assessed by DOUCET *et al.* [14]. Patients with COPD and muscle atrophy had greater expression of some components of the catabolic pathways in the quadriceps than healthy subjects, including increased levels of atrogen-1 and muscle ring finger protein (MuRF)1 mRNA and of forkhead box class O protein (FoxO)-1 (fig. 1). What role the IGF-I system has in determining muscle atrophy is difficult to assess. First, serum levels of IGF-I in patients with COPD and muscle atrophy were similar to the corresponding levels in healthy subjects [14]. Yet, muscle IGF-I mRNA expression in hospitalised and in stable patients with COPD measured by other investigators [10] was lower than in healthy elderly subjects. Secondly, compared with

TABLE 1 Characteristics of the different types of muscle fibres

	Type I	Type IIa	Type IIx	Type IIb
Contractile properties				
Velocity of shortening	+	++	+++	++++
Tetanic force	+	+	++	++
Endurance	++++	+++	++	+
Work efficiency [#]	+++	++	++	+
Histochemistry				
Mitochondrial volume density	+++	+++	++	+
ATP consumption rate	+	++	+++	++++
Oxidative enzymes	+++	+++	++	+
Glycolytic enzymes	+	++	+++	++++
Glycogen	+	++	++	+++
Capillary supply	+++	+++	++	+
Diameter	+	++	++	+++

ATP: Adenosine triphosphate. [#]: amount of work performed per unit of ATP consumed. +: relative expression of a given characteristic of the muscle fibre. A single myosin heavy chain isoform is typically expressed within an adult skeletal muscle fibre. Fibres classified as type I, IIa, IIx and IIb express myosin heavy chain isoform I (or slow), IIa, IIx and IIb, respectively. Type IIx fibres have been reported in peripheral muscles of humans and animals and in the diaphragm of animals. Type IIx fibres have not been reported in the human diaphragm. More than one myosin heavy chain isoform is expressed in a few fibres (~14% of adult rat diaphragm co-expresses myosin heavy chain isoforms IIb and IIx and <1% co-expresses myosin heavy chain isoforms I and IIa). While the velocity of muscle contraction depends primarily on the myosin heavy chain isoform, the velocity of muscle relaxation is mainly determined by troponin C calcium binding and release and by calcium re-uptake by the sarco-endoplasmic reticulum calcium-adenosine triphosphatase (SERCA). Several SERCA iso-enzymes have been identified: SERCA 1 is expressed in type II fibres (fast calcium re-uptake) and SERCA 2a is expressed in type I fibres (slow calcium re-uptake). The density of pumping sites largely accounts for different rates of calcium uptake in fast- and slow-twitch muscle fibres. Despite this separation of tasks, velocity of contraction and velocity of relaxation tend to parallel each other; type II fibres contract and relax with a greater velocity than type I fibres. Slower velocity of relaxation allows fusion of repetitive twitches at lower frequencies of stimulation compared with fast relaxations. Impairment of SERCA activity has been implicated in the development of fatigue and in disease states, including heart failure and corticosteroid myopathy. Reproduced from [15] with permission from the publisher.

patients with COPD who have muscle atrophy, patients with preserved muscle mass showed similar activation of the atrophying factors and increased expression of some components of the anabolic pathways. It is possible that patients with muscle atrophy are not able to respond to the upregulated hypertrophy signalling pathways [14]. Possible mechanisms include ageing and dysfunction of translational efficiency or capacity [14]. This mechanism is also supported by the observation that levels of GH are higher in cachectic patients with COPD than in noncachectic patients [50]. The latter finding suggests that acquired GH resistance contributes to the cachexia [50].

Upregulation of the IGF-I system within the fibres of the diaphragm has been reported within 4 days after lung-volume reduction surgery in hamsters [51]. This upregulation is likely to be an anabolic response to passive stretch of the diaphragm and ultrastructural sarcomeric injury [51].

COPD and depression of the somatotrophic axis: functional consequences

Decreased muscle mass

In patients with COPD, decreased muscle mass reduces respiratory muscle function, limb muscle function, exercise capacity and life expectancy [15]. As already stated, whether a depression of the somatotrophic axis contributes to decreased muscle mass in COPD, however, is unclear, and administration of recombinant human GH has produced mixed results.

In seven patients with COPD and ideal body weight (Metropolitan height-weight tables for adults) of <90%, 3 weeks of recombinant GH increased weight, improved nitrogen balance and maximal inspiratory pressure [52]. These results contrast with the negative results of BURDET *et al.* [48], the only randomised-controlled trial in malnourished patients with COPD. Several factors may explain the negative results of BURDET *et al.* [48]: first, redistribution of protein toward central organs rather than toward the muscles [48]; secondly, small dose and short duration of therapy (3 weeks) [48]; thirdly, uncoupling of Akt (activated by IGF-I) and the downstream anabolic and catabolic pathways (fig. 1) [14]. Lack of beneficial effect of recombinant GH on muscle function has also been reported in patients requiring prolonged mechanical ventilation, half of whom had COPD [53]; recombinant GH can increase mortality of critically ill patients [54].

In the study of BURDET *et al.* [48], maximal power output and oxygen consumption at the conclusion of a symptom-limited exercise test were not affected by recombinant GH administration. The response to six-minute walk was decreased in the treated patients [48]. A potential mechanism for this decrease in submaximal tests is an increase in oxygen consumption and carbon dioxide production induced by GH [48]. This possibility, however, is not supported by data recorded in young patients with COPD caused by cystic fibrosis in whom recombinant GH administration produced a significant increase in exercise capacity [55, 56].

In adults, chronic recombinant GH therapy can be associated with significant side effects including arthralgia, carpal tunnel syndrome, oedema and abnormal glucose tolerance [57, 58]. The potential risk of development and progression of common cancers including colon, breast and prostate cancers with chronic use of IGF-I [59] raises important questions on selection criteria, monitoring and safety of any study of recombinant GH/IGF-I supplementation in COPD.

Recently, NAGAYA *et al.* [60] investigated a novel pharmacological strategy to modulate the somatotrophic axis in patients with severe COPD. Administration of ghrelin for 3 weeks produced increased appetite, increased circulating GH, increased peripheral and respiratory muscle strength, increased six-minute walking distance and decreased plasma norepinephrine; levels of IGF-I were unaffected by ghrelin. These positive findings [60] must be interpreted with caution because the study was open labelled and lacked a control arm.

In patients with severe COPD, nonpharmacological upregulation of anabolic signals in the vastus lateralis muscle, including IGF-I and MyoD proteins and mRNA of IGF-I, and its load-sensitive splice variant (mechanogrowth factor), can be induced by pulmonary rehabilitation [61]. This favourable response is associated with a reduction in the proportion of type IIb muscle fibres (table 1), increases in the mean cross-sectional area of all fibre types and improved peak exercise work rate [61]. The anabolic effect occurred despite the fact that rehabilitation did not decrease plasma levels of inflammatory mediators [61, 62] and it did not decrease mRNA expression of TNF- α [61, 62] and interleukin (IL)-6 in the muscle [61].

COPD and depression of the somatotrophic axis: treatment

Despite the plausibility of linking derangements of the somatotrophic axis and decreased muscle mass in COPD, it is premature to recommend the use of recombinant GH, IGF-I or ghrelin in patients with COPD and decreased muscle mass.

COPD AND GONADAL AXIS

In men and women, the gonadal axis is a complex network of hormones that includes testosterone, an important anabolic hormone [63]. In men, the main production site of androgens is the testicle [63]; in women, the adrenals and the ovaries [64]. Secretion is stimulated by luteinising hormone (LH), one of the pituitary gonadotropins [65]. Under physiological conditions, about 44% of circulating testosterone is strongly bound to the sex hormone binding globulin; 54% is weakly bound to albumin and other lower affinity, high-capacity binding sites, such as α_1 acid glycoprotein and transcortin [66]. About 2% of circulating testosterone is nonprotein bound, *i.e.* free testosterone. Together, weakly bound testosterone and free testosterone are referred to as “bioavailable testosterone” [66]. Women have much lower levels of circulating testosterone than men. In both men and women, testosterone is responsible for libido, sexual hair and anabolic functions that affect muscle and bone [64, 67].

In patients with COPD, testosterone supplementation can increase leg muscle mass [45] and vastus lateralis mRNA for slow/ β -myosin heavy chain [68]. These anabolic responses are accompanied by increases in vastus lateralis IGF-I protein and myogenin mRNA [68]. In these patients, circulating levels of IGF-I [45] and intramuscular expression of MyoD mRNA and myostatin mRNA [68] are not affected by testosterone supplementation. Taken together, these data suggest that androgens produce an enhanced local anabolic milieu, driven in large part by the muscle's IGF system. Increased size of motor neurons [69] is an additional mechanism through which androgens may exert their anabolic action.

The concentration of serum testosterone [70, 71] and other androgens, such as the adrenal steroid dehydroepiandrosterone (DHEA), a testosterone precursor [72], decline in middle-aged and elderly men. When excessive, this decline may contribute to various signs and symptoms, including decreased energy level, libido, bone density and muscle mass and, possibly, reductions in cognitive function and memory [73]. This constellation of signs and symptoms has been termed late-onset hypogonadism, symptomatic late-onset hypogonadism, androgen deficiency in the ageing male or andropause

[67]. The observation that many men with COPD fit the profile of late-onset hypogonadism [74–76] has spurred a flurry of research on the incidence [76–78], functional impact [49, 76, 78] and possible treatment [45] of this abnormality.

As in men, levels of testosterone and of other androgens, such as DHEA, decline in women with ageing [24]. This process starts before, and continues after, the menopause [24]. Little is known about the impact of declining levels of testosterone and other androgens in women with COPD. Accordingly, most of our discussion will focus on late-onset hypogonadism in men with COPD.

COPD and late-onset hypogonadism: risk factors

Several risk factors that may decrease testosterone in patients with COPD have been reported. These include ageing, chronic disease, hypoxaemia, hypercapnia, smoking, administration of glucocorticoids, systemic inflammation and obesity.

Ageing

Purported mechanisms by which old age causes hypogonadism in men include decreased responsiveness of the testes to human chorionic gonadotropin (which acts as LH), increased testosterone feedback at the hypothalamic-pituitary level, decreased responsiveness of the pituitary to gonadotropin releasing hormone, and asynchronous (chaotic) release of gonadotropin releasing hormone from the hypothalamus [79]. In men, sex hormone binding globulin increases with age [23] and reduces the biological availability of testosterone [23].

The mechanisms responsible for age-related decrease in testosterone in women include decreased adrenal production of DHEA and DHEAS [80], decreased ovarian production of androgens [80] and increased specific activity of aromatase in the adipose tissue [81].

Chronic illness

Chronic illnesses, including diabetes, cardiovascular disease and hypertension, have been associated with a decline in serum testosterone [82]. An important contributor to this decline is a decrease in LH (hypogonadotrophic hypogonadism) [82], the most common presentation of late-onset hypogonadism in men with COPD [45, 76]. Whether COPD is a “chronic illness” that can cause, by itself, hypogonadism is controversial considering that among ambulatory men with COPD severity of lung disease does not predict the hormonal abnormality [76, 78]. Also, the number of comorbid conditions in hypogonadal and eugonadal men with COPD is similar [78].

While the prevalence of hypogonadism seems to be unaffected by severity of COPD when patients are in a stable clinical condition [76, 78], acute exacerbations [83] and, possibly, the need for prolonged mechanical ventilation [84], can (further) decrease testosterone.

Hypoxaemia/Hypercapnia

In 1980, SEMPLE *et al.* [85] assessed serum levels of testosterone and gas exchange in 22 men with COPD. When the partial pressure of arterial oxygen (P_{aO_2}) dropped below 55 mmHg, there was a strong correlation between the degree of hypoxia and the degree of testosterone reduction. Lack of association between testosterone and hypoxia (when P_{aO_2} is >55 mmHg)

has been confirmed by more recent studies [49, 76, 78]. SEMPLE *et al.* [85] also reported a correlation between the degree of hypercapnia and testosterone.

Smoking

In men, both testosterone and sex hormone-binding globulin are greater in smokers than in nonsmokers, yet, levels of bioavailable testosterone are similar [86]. These results suggest that smoking modulates total testosterone through changes in the concentration of sex hormone-binding globulin but has no significant impact on the biologically active fraction of the hormone.

Glucocorticoids

The effect of glucocorticoids on testosterone concentration is controversial [49, 76–78]. In 36 men with COPD, 16 of whom were taking oral glucocorticoids, KAMISCHKE *et al.* [77] found that free testosterone was inversely related to glucocorticoid dosage. Mechanisms that may explain the decrease in levels of testosterone include a reduction in gonadotropin releasing hormone, decrease in adrenal precursors and reduction of testosterone biosynthesis [77]. In addition, glucocorticoids may compete with testosterone for the same receptor sites in the peripheral tissues [87]. Despite these results [77], three groups of investigators have more recently reported no correlation between testosterone and glucocorticoid therapy in men with COPD [49, 76, 78].

Systemic inflammation

In laboratory animals [88] and healthy men [89], TNF- α can lead to decreased testosterone. Mechanisms through which TNF- α and other inflammatory cytokines, such as IL-1 and IL-6, could decrease testosterone include increased expression of aromatase, the enzyme that irreversibly converts testosterone to oestradiol (*via* the testosterone–oestradiol shunt) [90], a reduction in gonadotropin releasing hormone [65] and a cytokine-mediated testicular defect [88, 91]. Despite the biological plausibility, a recent investigation in more than 100 men with COPD [83] suggested that the increased levels of inflammatory cytokines in patients with stable COPD were insufficient to decrease testosterone concentrations.

Obesity

Body mass index of men with COPD and late-onset hypogonadism is greater than that of eugonadal men with COPD with similar age and severity of lung disease [76]. Increased body mass index could result from a positive feedback between obesity and hypogonadism. Hypogonadism is associated with a preferential deposition of adipose tissue in the abdomen [92]. A state of leptin resistance may contribute to this increased adipose deposition [93]; in men, levels of leptin have been reported to be inversely related to testosterone [94]. A second mechanism is a decrease in serum concentrations of ghrelin [95] resulting in less fat utilisation [96]. Irrespective of the mechanism, greater adipose tissue accumulation increases aromatase activity and, thus, the conversion of testosterone to oestradiol (testosterone–estradiol shunt) [90]. Such an upregulation could produce a vicious cycle where depression of testosterone concentration causes deposition of abdominal fat that, in turn, worsens the hypogonadal state [97].

COPD and late-onset hypogonadism: prevalence

LAGHI *et al.* [76] tested 101 men with stable COPD for late-onset hypogonadism. Late-onset hypogonadism was present in 38% of the men. This value falls between the prevalence of 69% reported by KAMISCHKE *et al.* [77] and 22% reported DEBIGARE *et al.* [49].

The 47% difference in the prevalence of hypogonadism between the studies of KAMISCHKE *et al.* [77] and DEBIGARE *et al.* [49] cannot be ascribed to age or severity of COPD. It may be related to patient selection: 84% of the patients in the first study had concurrent chronic diseases [77], whereas patients with chronic diseases were excluded in the second study [49]. A difference in comorbidities can explain only 15% of the 47% difference [49]. Sample size is a more likely explanation. When data from the two investigations [49, 77] are combined, 35 (43%) of 84 patients exhibit hypogonadism; similar to that in the study of LAGHI *et al.* [76].

VAN VLIET *et al.* [78] reported a prevalence of late-onset hypogonadism in 51% of 78 men with COPD and 26% of 21 age-matched controls. These results do not necessarily mean that late-onset hypogonadism is more prevalent in men with COPD than in the general population. The prevalence of hypogonadism in the small control group [78] was much lower than the 34–40% prevalence of hypogonadism for subjects in their 60s and the near 70% prevalence for subjects in their 70s, reported in large population studies [23, 70]. Levels of testosterone did not correlate with severity of airway obstruction [76, 78] or with a $Pa_{O_2} > 55$ mmHg or glucocorticoid therapy [49, 76, 78].

COPD and late-onset hypogonadism: functional consequences

Sexual function

In a study of 36 men with COPD, 25 of whom were hypogonadal, the prevalence of sexual difficulties was not associated with the level of free testosterone [77].

Quality of life

COPD [98–100] and late-onset hypogonadism [101] can decrease quality of life. To determine whether the occurrence of late-onset hypogonadism had an additive effect on reduced quality of life in COPD, LAGHI *et al.* [76] compared the results of the St George's Respiratory Questionnaire (SGRQ), a respiratory-specific questionnaire, and of the Veterans Short Form (SF)-36 Health Survey, a general health questionnaire, in 38 men with COPD and late-onset hypogonadism and 63 eugonadal men with similar severity of airway obstruction [76]. The questionnaire scores were similar in the two patient groups. Free testosterone was not associated with the perceived impact of COPD on health and well being [76].

Women with COPD report worse health-related quality of life than men [102]. Whether menopause and hormone supplementation in women with COPD could affect the health-related quality of life is untested.

Depression

Decreased testosterone levels [103, 104] and COPD [105] have been associated with depressed mood. Yet, the SGRQ impact score [106] and the SF-36 mental health domain [107], which

are affected the presence of depression are equivalent in eugonadal and hypogonadal men with COPD [76].

Respiratory muscles

Recently, LAGHI *et al.* [108] reported that diaphragmatic contractility was similar in hypogonadal and eugonadal men with COPD (fig. 2). When performing a progressive inspiratory threshold loading protocol, hypogonadal and eugonadal patients had similar respiratory muscle endurance times, perceived inspiratory effort and perceived air hunger [108]. Neither group of patients developed diaphragmatic fatigue after loading (fig. 2). The lack of fatigue was similar to its absence after failed weaning from mechanical ventilation [109] and under more extreme conditions in laboratory animals [110].

The equivalent performance of the respiratory muscles in hypogonadal and eugonadal men [108] is consistent with the observations of CASABURI *et al.* [45], who found that inspiratory muscle strength was not altered by the administration of testosterone enanthate to patients with COPD who had variable serum testosterone levels.

Several mechanisms may protect the respiratory muscles against the deleterious effects of low testosterone levels. First, a conditioning effect of the increased inspiratory load [111] may counterbalance the catabolic effects [112, 113]. Secondly, in the investigation of LAGHI *et al.* [108], most patients were not underweight. Thirdly, respiratory muscles may be less sensitive to testosterone (and lack thereof) than the limb muscles considering that administration of massive doses of testosterone ($20 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ for 14 days) to rabbits did not produce increased diaphragmatic strength or endurance [110].

Limb muscles

It is unclear whether late-onset hypogonadism in men with COPD affects limb muscle strength and endurance. In 78 men with COPD, VAN VLIET *et al.* [78] recorded a correlation

between quadriceps strength and testosterone concentrations. Conversely, LAGHI *et al.* [108] recorded no difference in quadriceps strength (and endurance) between hypogonadal and eugonadal men with COPD. This equivalent limb muscle performance in the two patients groups is in line with the observation that testosterone has no effect on leg-muscle endurance when administered at physiological doses in otherwise healthy hypogonadal men [114] or in healthy eugonadal men receiving a long-acting gonadotropin-releasing hormone agonist [115]. Likewise, the equivalent limb-muscle performance in the two groups is consistent with the observation that physiological doses of testosterone had no effect on leg-muscle strength in some hypogonadal men [116–118]. Similarly, when BHASIN *et al.* [119] administered a long-acting gonadotropin-releasing hormone agonist to induce hypogonadism in elderly men and then supplemented the men with sub-therapeutic doses of testosterone enanthate, they recorded no difference in fat free mass or muscle strength. When they doubled the circulatory levels of total and free testosterone using higher doses of testosterone enanthate, the increases in fat free mass and strength were within the noise of the measurement. They, however, reported a 17% increase in quadriceps strength (and endurance) when administering $100 \text{ mg} \cdot \text{week}^{-1}$ of testosterone enanthate for 10 weeks in men with COPD who had variable testosterone levels [45]. It is not known why low testosterone should cause a decrease in strength in some studies and not in others, nor whether the statistical differences in quadriceps strength, when present, are clinically important. The same investigators reported preliminary results on testosterone supplementation (12.5 and 25 mg testosterone enanthate weekly for 10 weeks) in women with COPD [120]. Only modest changes in body composition and strength without evidence of virilisation were observed.

Exercise capacity

Exercise capacity in men with COPD with and without late-onset hypogonadism has been found to be equivalent [76, 78, 108]. During cycle exercise to exhaustion, exercise performance, gas exchange and respiratory muscle recruitment (estimated by oesophageal and gastric pressure swings during tidal breathing) were similar in both groups [108]. Equivalent exercise capacity has been recorded even when quadriceps strength among hypogonadal patients with COPD was less than in eugonadal patients with COPD [78].

The similar exercise performance in patients with COPD with or without late-onset hypogonadism [76, 78, 108] is consistent with the observation that administration of anabolic steroids to unselected patients with COPD [121, 122] or testosterone enanthate to men with COPD and variable testosterone levels [45] produced no improvement in whole body exercise capacity.

Risk for cardiovascular disease

Several case-control studies suggest an association between low testosterone levels and excess cardiovascular risk in men [123–125], while the opposite may be true in women [126]. It is not known whether late-onset hypogonadism has an additive effect on the already increased risk of cardiovascular disease associated with COPD [127–131].

FIGURE 2. Potentiated (●, ■) and nonpotentiated (○, □) transdiaphragmatic twitch pressure (twitch P_{di}) in 10 hypogonadal (●, ○) and 10 eugonadal (■, □) men with COPD recorded before (baseline) and 20 min after conclusion of inspiratory threshold loading to task-failure. Potentiated and nonpotentiated twitch P_{di} values were not affected by hormonal status or by threshold loading. Data are presented as mean $\pm$ SE. Reproduced and modified from [108] with permission from the publisher.

Bone density

Reduced bone mineral density is common in COPD [74]. Reduced bone mineral density has not been associated with low testosterone levels in two studies [132, 133], possibly because the risk of osteoporosis is already so high in COPD that the additional effect of late-onset hypogonadism does not further affect bone mineral density.

COPD and late-onset hypogonadism: therapy

If patients are deficient in a hormone, it might seem self-evident to replenish normal levels. Before recommending hormone supplementation, however, it is critical to weigh potential risks and benefits. Stated differently, does it matter if a man with COPD develops late-onset hypogonadism? The question entails whether clinically important functional differences between hypogonadal and eugonadal patients do exist, which, in turn, could have important therapeutic implications. For some clinical aspects, the accumulating evidence suggests that men with COPD and late-onset hypogonadism are not different from their nonhypogonadal counterparts. Therefore, if testosterone is administered, it would be unclear what should be the therapeutic effects to monitor.

The caution about whether to advocate testosterone replacement in men with late-onset hypogonadism and COPD needs to reflect the ongoing controversy regarding indications for testosterone replacement in older men in general [67, 73, 134]. Long-term testosterone supplementation can be associated with side effects, including increase in haematocrit, sleep apnoea, prostatic hypertrophy (fig. 3) [67, 73]. Long-term effects of testosterone administration on the risk of atherosclerotic heart disease and prostate cancer remain unknown [67, 73]. More than 6,000 elderly hypogonadal men, randomly assigned to receive testosterone or placebo for 6 years, would be necessary to determine whether testosterone treatment increases the risk of prostate cancer by 30% [73]. The Institute of Medicine (Washington DC, USA) recently concluded that, unless more convincing studies are published, there is currently insufficient evidence to support testosterone therapy in older men [135].

COPD AND ADRENAL AXIS

The adrenal glands produce a vast array of hormones with protean metabolic effects; among these are cortisol, DHEA and its metabolite, DHEAS, the most abundant steroid present in the blood [49]. The action of DHEAS at the tissue level is both direct, through specific binding sites of the hormone in peripheral tissues [136], and indirect. The indirect action occurs as a result of the conversion DHEAS to androstenedione or androstenediol, and finally to testosterone [137]. Reduced levels of DHEA and DHEAS and high cortisol/DHEA or cortisol/DHEAS ratios are thought to create an imbalance between protein synthesis and degradation favouring catabolism over anabolism [49].

In contrast to the anabolic properties of DHEA and DHEAS, cortisol (when in excess) has catabolic properties [138]. Cortisol mobilises glucose, free fatty acids and amino acids from endogenous stores [138]. In addition, cortisol increases appetite and induces insulin resistance [138].

COPD and imbalance of the adrenal axis: risk factors*Ageing*

Serum concentrations of DHEAS decrease with ageing [24, 72, 139], whereas concentrations of cortisol do not [71].

Severity of COPD/hypoxaemia/hypercapnia

Severe airway obstruction, hypoxaemia and hypercapnia have been associated with decreased serum levels of DHEAS [83]. Whether severity of lung disease affects serum levels of cortisol is unclear [18, 41, 140].

COPD and imbalance of the adrenal axis: prevalence

The limited available information suggests circulating levels of DHEAS are decreased in COPD [49, 83]. DEBIGARE *et al.* [49] found lower DHEAS levels in patients with COPD and decreased muscle mass than in those without decreased muscle mass or in control subjects. Similarly, KARADAG *et al.* [83] found lower DHEAS levels in patients with COPD than in controls. During acute exacerbations DHEAS levels decreased even further [83].

Whether cortisol levels are altered in patients with stable COPD is unclear [18, 41, 141, 142]. Systemic and possibly (high-dose) inhaled corticosteroids increase the risk of adrenal insufficiency [143].

During acute exacerbations, levels of cortisol are increased in patients not treated with systemic corticosteroids [144]. In these patients, the cortisol response to adrenocorticotrophic hormone (ACTH) is normal [144]. In contrast, patients treated with corticosteroids during an exacerbation have decreased circulating cortisol levels and commonly limited cortisol response to ACTH [145]. The limited response can last more than 3 weeks after corticosteroid withdrawal [145]. Neither glucocorticoid dose nor duration of treatment can be used to predict adrenal insufficiency [146].

COPD and imbalance of the adrenal axis: functional consequences*Decreased muscle mass/decreased muscle function*

In men with severe COPD, the cortisol/DHEAS ratio was greater among patients with decreased muscle mass than among those without decreased muscle mass [49]. Nevertheless, administration of DHEA, for 2 years, to elderly men and women without COPD and reduced DHEAS levels had no effect on body composition, exercise capacity, muscle strength or quality of life [147].

Osteoporosis

Among women who, for the most part did not have COPD, lower DHEA levels were associated with decreased bone-mineral density [139]. Yet, when administered to elderly men and women without COPD, DHEA had minimal and inconsistent effects on bone-mineral density [147].

COPD and imbalance of the adrenal axis: therapy

In elderly patients without COPD, DHEA administration had no significant benefit [147].

COPD AND DIABETES

Insulin is an anabolic hormone that exerts its effects by binding to its cognate receptor [148]. Many cells throughout the body,

FIGURE 3. Schematic representation of the mechanisms of action of testosterone, of the tissues affected by testosterone, and the potential effects of testosterone-replacement therapy. Testosterone has protean effects because it can act as three different hormones. In some tissues, testosterone binds to the androgen receptor and acts directly as an androgen. In tissues expressing the enzyme 5α-reductase, it is converted to dihydrotestosterone. Dihydrotestosterone binds to the androgen receptor with greater affinity than testosterone. Consequently, dihydrotestosterone has effects that a physiological concentration of testosterone does not have. Finally, in tissues expressing the enzyme aromatase, testosterone is terminally metabolised to oestradiol, which acts through the oestrogen receptor. Reproduced and modified from [73] with permission from the publisher.

including liver, lung, skeletal muscle, adipose tissue and vascular endothelial cells, express this transmembrane receptor [149, 150]. When insulin binds to the receptor in myocytes, it activates the intrinsic tyrosine protein kinase activity [8]. The activated receptor phosphorylates the insulin receptor substrates 1 and 2, which, in turn, activate PI3K and, with it, the mTOR signal transduction pathway (fig. 1) [8]. Insulin is a mitogen and growth factor of airway smooth muscle cells and of bronchial and alveolar epithelial cells [149]. *In vitro*, insulin improves hypoxia-induced vasoconstriction and causes pulmonary artery vasodilation [149].

Diabetes mellitus can result from destruction of the pancreatic β cells, which leads to absolute insulin deficiency (type 1) or, more often, from insulin resistance coupled with relative impairment in insulin secretion (type 2) [151]. Abnormalities of the insulin receptor and abnormalities downstream to the receptor contribute to insulin resistance in patients with type 2 diabetes [150].

COPD and diabetes: prevalence/risk factors

The prevalence of diabetes in patients with COPD is 10–14% [78, 152–154]. The relationship between impaired pulmonary function and increased risk of developing diabetes is controversial [131, 154–156]. Among almost 8,000 participants in the Framingham Heart Study [154] and the National Health and Nutrition Examination Survey [155], there was no association between COPD and the development of diabetes. In contrast to these studies, in which about half the participants were men, COPD was found to increase the risk of diabetes in the Nurses' Health Study (involving nearly 100,000 female nurses; multivariate relative risk 1.8, 95% CI 1.1–2.8) [156]. Likewise, among more than 20,000 participants (56% female) of the Atherosclerosis Risk in Communities Study (ARIC) and the Cardiovascular Health Study (CHS), the presence of moderate-to-severe COPD was shown to increase the risk of diabetes (multivariate relative risk 1.5, 95% CI 1.1–1.9) [131]. It is not

possible to reconcile the contrasting results. The mechanisms through which COPD might induce type 2 diabetes include systemic inflammation, oxidative stress, smoking and administration of glucocorticoids.

Smoking/systemic inflammation/oxidative stress

Cigarette smoking can increase the risk of insulin resistance and diabetes by triggering systemic inflammation [154, 157] and oxidative stress [158]; both of which are common in COPD [154, 157–159]. In nonhypoxaemic nondiabetic patients with COPD, insulin resistance was linked to systemic inflammation (*via* IL-6) and body mass index [160].

Glucocorticoids

In elderly patients, administration of systemic glucocorticoids more than doubles the risk of developing diabetes [161]. Potential mechanisms include direct inhibition of insulin release, reduction in the hepatic levels of insulin receptor substrate-1 and PI3K, decrease in glucose uptake and increase in hepatic glucose production [162, 163].

Systemic and topical glucocorticoids are used in patients with COPD during exacerbations and as maintenance therapy. Systemic corticosteroids can interfere with glycaemic control [161, 164] and poor glycaemic control in patients hospitalised for COPD exacerbation has been associated with increased length of hospital stay and increased mortality [165]. Diabetes is a risk factor for mortality, even after hospital discharge for COPD exacerbations [166]. It is unclear whether short- [165] and long-term survival [166] following an acute COPD exacerbation can be improved by tight glycaemic control.

In contrast to systemic glucocorticoids, administration of inhaled glucocorticoids is probably safe in patients with COPD and diabetes [161, 167]. In 10 patients with type 2 diabetes and asthma or COPD, inhaled glucocorticoids for 6 weeks caused no change in glycosylated haemoglobin [167].

COPD and diabetes: functional consequences

In patients who do not necessarily have COPD, diabetes can negatively affect respiratory muscle function, pulmonary mechanics, gas exchange and respiratory drive. Patients with diabetes are also at increased risk of infections and cardiovascular complications.

Respiratory muscles

Patients with diabetes exhibit a 20% decrease in global inspiratory strength [168] and a 30–50% decrease in diaphragmatic strength [168, 169]. Weakness might result from non-enzymatic glycosylation (glycation) of muscle fibres (fig. 4) [170, 171]. Rarely, diaphragmatic weakness results from diabetic neuropathy of the phrenic nerves [172, 173], which can occur despite the absence of peripheral neuropathy [173].

Pulmonary mechanics/gas exchange

Lung specimens in patients with diabetes demonstrate several abnormalities that are reminiscent of those described in the glomeruli. These abnormalities include intraseptal nodular fibrosis, microangiopathy, thickening of the basal laminae of pulmonary capillaries and loss of alveolar microvascular bed associated with increased extracellular matrix and connective tissue [149]. Thickening of the basal laminae of pulmonary capillaries and loss of alveolar microvascular bed [149] may contribute to increased work of breathing, decreased diffusing capacity [149] and dyspnoea in patients with diabetes [174].

Respiratory drive

The ventilatory response to hypercapnia is normal in diabetic patients without autonomic neuropathy, reduced in patients with parasympathetic neuropathy and increased in patients with combined parasympathetic and sympathetic neuropathy [175]. The differences have been attributed to proportional variation in cerebrovascular reactivity (velocity of blood flow in the middle cerebral artery) to hypercapnia [175]. Parasympathetic neuropathy, with secondary depression of vagal tone, may contribute to diminished bronchodilator

response to anticholinergic drugs in some patients with diabetes [149].

Infections

Diabetes increases the risk of lower respiratory tract infections [176]. In patients with COPD exacerbations requiring non-invasive ventilation, hyperglycaemia is associated with pulmonary infections and is an independent risk factor for failure of noninvasive ventilation [177]. In euglycaemic subjects with airway inflammation or in hyperglycaemic patients, glucose concentrations in airway secretions are increased [178]. Mechanically ventilated patients with detectable glucose in bronchial aspirates have increased likelihood of pathogenic bacteria, particularly *Staphylococcus aureus* [179]. Airway glucose may promote bacterial growth or interfere with local immune defences [165].

Osteoporosis

Diabetes has been associated with higher bone mineral density in both women and men [180, 181]. The higher bone mineral density could result from the hyperinsulinaemia that precedes overt type 2 diabetes [181]. In turn, hyperinsulinaemia could exert an anabolic effect on bone tissue [181]. Hyperinsulinaemia has been reported in nondiabetic patients with COPD [160]. Despite a higher bone mineral density, patients display an increased risk of fractures, mainly attributable to the increased risk of falling [182].

COPD and diabetes: therapy

The goal of diabetic care is to achieve glucose levels close to normal without inducing significant hypoglycaemia [183]. With the exception of inhaled insulin [184], strategies to reach this goal in COPD should be the same as for diabetic patients without COPD [183, 185, 186]. Detailed reviews of this topic are available elsewhere [183, 185, 186].

In 2006, US and European Drug Agencies (the US Food and Drug Agency and the European Medical Association) approved inhaled insulin for clinical use in nonsmoking adults with type

FIGURE 4. Effect of nonenzymatic glycosylation on the speed of actin filaments sliding over a) slow myosin (soleus muscles) and b) fast myosin (extensor digitorum longus) in control muscle fibres of rats incubated with low-salt buffer (○) and with 6 mM glucose (●). Incubation of muscle fibres for 30 min in low-salt buffer had no effect on motility speed in the slow (a) and fast (b) myosin preparations. In contrast, incubation with glucose for 30 min caused a progressive decrease in motility speed both in the slow (a) and fast (b) myosin preparations ($p < 0.05$). Data are presented as mean $\pm$ SD. Reproduced and modified from [170] with permission from the publisher.

1 and type 2 diabetes [187]. Inhaled insulin can cause small but significant decreases in diffusing capacity and FEV₁ [184]. In addition, absorption of inhaled insulin in COPD is unpredictable [184] and, at least in ex-smokers, inhaled insulin might increase the rate of bronchogenic carcinomas [187]. Whether inhaled insulin should be even considered in diabetic patients with COPD has become a moot point: in 2007 inhaled insulin was discontinued as a result of poor market acceptance [187].

The oral anti-hyperglycaemic agent, metformin, is thought to increase the risk of lactic acidosis, and is considered contraindicated in chronic hypoxaemic conditions [188]. Despite these concerns, a recent meta-analysis of 206 trials revealed no cases of fatal or nonfatal lactic acidosis in 47,846 patient-yrs of metformin use or in 38,221 patients-yrs in the non-metformin group [188].

COPD AND THYROID DISEASES

The thyroid hormone regulates the metabolism of proteins, lipids and carbohydrates, and controls the activity of membrane-bound enzymes [189, 190]. This hormone can also regulate the transcription of numerous genes encoding both myofibrillar and calcium-regulatory proteins in myofibres (table 2) [191, 192]. The thyroid hormone enhances mitochondrial oxidation and, thus, augments metabolic rate [193]. This effect on metabolic rate is probably responsible for the association between the thyroid hormone and respiratory drive [194].

Limited data on the prevalence of thyroid diseases among patients with COPD are available [195, 196]. Yet, several characteristics of patients with COPD could potentially increase their likelihood of developing hypothyroidism and hyperthyroidism.

COPD and hypothyroidism: prevalence/risk factors

Impaired thyroid function can present as subclinical hypothyroidism, overt hypothyroidism and nonthyroidal illness syndrome. Of these, nonthyroidal illness syndrome is the most common in COPD [195], being reported in 20% of stable patients [195] and 70% of patients experiencing an exacerbation [195]. Patients with nonthyroidal illness syndrome have decreased levels of the biologically active hormone triiodothyronine (T₃) and normal or decreased levels of the prohormone thyroxine (T₄) [197]. Serum levels of the TSH are

usually normal, though they can be low in the most severely ill patients [197]. In the past, patients with nonthyroidal illness syndrome were said to have euthyroid sick syndrome. The latter nomenclature, however, is now considered inappropriate because it is not clear whether these patients are in fact euthyroid in those tissues that are targets for the action of the thyroid hormone [197]. To date it is impossible to state which patient with nonthyroidal illness syndrome, if any, might benefit from treatment, nor what that treatment should be [198]. It is not known if nonthyroidal illness syndrome is a favourable compensatory mechanism to offset catabolism and protein breakdown or if it is an unfavourable adaptation with resultant biochemical hypothyroidism [195]. Severity of airway obstruction, hypoxaemia, systemic inflammation and glucocorticoids may predispose to develop subclinical hypothyroidism, overt hypothyroidism and nonthyroidal illness syndrome.

Severity of airway obstruction

Compared with moderate COPD, patients with severe COPD (FEV₁ <50%) demonstrate reductions in total T₃ and in the T₃/T₄ ratio (a marker of peripheral conversion of the prohormone (T₄) to the active cellular form of the thyroid hormone (T₃)) [195]. In addition, low FEV₁ is associated with low basal and stimulated levels of thyroid stimulating hormone (TSH) [199].

Chronic hypoxaemia

It is controversial whether hypoxaemia impairs the TSH response to exogenous thyroid releasing hormone (TRH) in COPD [141, 200]. In patients with stable severe COPD, chronic hypoxaemia is associated with a decrease in the peripheral conversion of T₄ to the biologically active hormone T₃ [196].

Systemic inflammation

Patients with COPD can present with increased systemic levels of inflammatory cytokines such as IL-6, IL-1 and TNF- α [42, 195]. These cytokines can inhibit the synthesis or secretion of TSH, T₃ and thyroid hormone-binding proteins, and can decrease the mRNA for the hepatic enzyme iodothyronine deiodinase type 1; an enzyme that converts T₄ to T₃ [197, 198]. Notwithstanding these observations, the impact of inflammatory cytokines on thyroid function in patients with COPD is controversial [195, 196].

Glucocorticoids

In 25 patients with stable COPD, serum T₄ levels were inversely related to the dose of oral prednisone [201]. Glucocorticoids may decrease circulating thyroid hormone by decreasing serum TSH [202–205], by redistributing T₄ and T₃ in the vascular and tissue compartments [206] and by decreasing peripheral conversion of T₄ to T₃ [207]. Hypothyroidism, when present, can interfere with the metabolism of glucocorticoids by increasing the area-under-the-curve and by delaying the time-to-peak of plasma concentrations of oral prednisone [208]. In contrast, inhaled glucocorticoids do not appear to affect thyroid function [196].

COPD and hypothyroidism: functional consequences

When present, hypothyroidism can decrease respiratory drive, respiratory muscle function, exercise capacity, and increase the risk for sleep disordered breathing in COPD.

TABLE 2 Muscle genes responsive to thyroid hormone

Na ⁺ /K ⁺ ATPase
Myosin heavy chain isoforms
Sarcoplasmic reticulum Ca ²⁺ ATPase (SERCA 2)
Phospholamban
Adenylyl cyclase
Voltage-gated K ⁺ channels (Kv 1.5, 4.2, 4.3)
β_1 -adrenergic receptors
Guanine nucleotide regulatory protein (G _s)
Na ⁺ /Ca ²⁺ exchanger (NCX)

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Respiratory muscle function/respiratory drive

Hypothyroidism can cause inspiratory and expiratory muscle weakness in patients with [209] and without COPD [210]. Weakness is proportional to the severity of hypothyroidism [210] and is reversed by replacement therapy [209, 210]. Weakness might result from decreased expression of Type IIb myosin heavy chains (table 1) [192], phrenic nerve neuropathy [211] or decreased neuromuscular transmission secondary to a decrease in the planar areas of nerve terminals and end-plates of type I and IIa fibres [212]. Although neuromuscular transmission is decreased at rest, transmission is increased during repetitive contractions [212].

It is unclear whether the respiratory muscle weakness can cause chronic or acute-on-chronic alveolar hypoventilation [209], or even need for prolonged mechanical ventilation [213, 214]. In the few series of hypothyroid patients who developed ventilatory failure [213, 214] it is impossible to differentiate the contributions of respiratory muscle weakness and decreased respiratory drive [215]. Several mechanisms have been postulated as risk factors for the development of alveolar hypoventilation in hypothyroidism (table 3) [213, 216].

Exercise capacity

Exercise tolerance and maximal oxygen uptake are decreased in patients with COPD and overt [209] or subclinical hypothyroidism [217]. Impaired muscle energy metabolism, resulting from a defect in glycogen breakdown or mitochondrial function [217], hypothyroid myopathy with the characteristic type II fibre atrophy and large type I fibres [218], and impaired gas exchange [209], systolic function [219] and ventricular relaxation [219], probably contributes to the reduced exercise capacity in these patients.

Sleep-disordered breathing

High prevalence of sleep-disordered breathing (mainly obstructive in nature) has been reported in hypothyroid patients with [209] and without COPD [220–222]. In these patients, sleep-disordered breathing is largely reversible with replacement therapy [222]. Potential mechanisms of sleep-disordered breathing include obesity, mucoprotein deposition

in the upper airway, upper airway myopathy and decreased ventilatory drive [220–224].

COPD and hypothyroidism: treatment

Hypothyroidism in patients with COPD should be treated in the same manner as in patients without COPD [225]. Patients who also have obstructive sleep apnoea and coronary artery disease require particular attention. In this situation, thyroid replacement should be implemented with care because it causes an increase in myocardial oxygen consumption [226]. During an apnoeic episode, hypoxaemia is further increased in patients with COPD. In the presence of coronary artery disease, these changes can trigger ischaemic events [224].

COPD and hyperthyroidism: prevalence/risk factors

The prevalence of subclinical [219] and overt hyperthyroidism among patients with COPD is unknown. That hyperthyroidism is more prevalent among former and current smokers [227] raises the possibility that hyperthyroidism may be more prevalent in COPD than in the general population [228].

COPD and hyperthyroidism: functional consequences

Hyperthyroidism may impair respiratory muscle function, respiratory mechanics and exercise capacity in COPD.

Respiratory muscle function

Hyperthyroidism causes inspiratory and expiratory muscle weakness in COPD [210, 229–231]. The weakness is proportional to the severity of hyperthyroidism [210] and it can be reversed by 3–9 months of antithyroid therapy [210, 229, 231–233].

Enhanced proteolysis through the activation of a proteasome-dependent pathway (fig. 5) [234] and oxidative modification of myofibrillar proteins contribute to diaphragmatic atrophy [235] and weakness in hyperthyroidism [235, 236]. Proteolysis triggered by excess T3 levels [234, 236] can be enhanced by administration of glucocorticoids [16]. β -Adrenergic blockade can rapidly reverse much of (limb) muscle weakness in hyperthyroidism [237], suggesting that reversible changes in calcium handling and cyclic adenosine monophosphate-mediated contractile function contributes to hyperthyroid-associated myopathy [191]. Lastly, hyperthyroid-associated neuropathy may contribute to the weakness [191, 238].

Respiratory mechanics

Some [233, 239] but not all investigators [229, 240] have reported decreased lung compliance in hyperthyroidism. The mechanisms are unclear [233, 239]. Decreased lung compliance [233, 239] and muscle strength [210, 229–231] probably contribute to the mild reduction in vital capacity seen in some patients [210, 229, 230, 233, 239–242]. The reduction in vital capacity is reversed by antithyroid therapy [210, 229, 230, 233, 241]. It is not known if hyperthyroid patients with COPD experience worsening in airway obstruction, as reported in some patients with severe asthma [243–245].

Respiratory failure

Hyperthyroid patients are at increased risk for respiratory failure [246] because of decreased respiratory muscle performance [210], decreased lung compliance [233, 239], increased ventilatory requirements [241], increased peripheral and central chemoreceptor sensitivity [231], increased respiratory

TABLE 3	Potential risk factors for the development of alveolar hypoventilation in hypothyroidism
Decreased pressure output from the respiratory muscles	
Decreased hypoxic and hypercapnic ventilatory drive	
Respiratory muscle weakness (neuropathy, neuromuscular junction abnormality, myopathy, decreased muscle perfusion caused by myocardial impairment)	
Increased mechanical load	
Upper airway obstruction/sleep apnoea	
Pleural effusions	
Ascites	
Increased bronchial reactivity	
Impaired gas exchange	
Reduction in pulmonary capillary bed	
Increased permeability of the pulmonary capillaries	
Increased alveolar and capillary wall thickness

FIGURE 5. Ubiquitin–proteasome degradation of contractile proteins. The first step in degradation of actin and myosin is activation of ubiquitin (Ub) by a first enzyme, E_1 ; a process requiring ATP. Activated Ub interacts with a second enzyme, E_2 , a carrier protein. Ub and E_2 join a third enzyme, E_3 . E_3 transfers activated Ub to actin and myosin. The cycle is repeated until a chain of Ub is bound to the contractile proteins. The chain of Ub binds to one end of a proteasome complex in a process requiring ATP. The Ub chain is subsequently removed (allowing reuse of Ub), and actin and myosin are unfolded and pushed into the core of the proteasome. Multiple enzymes within the core degrade actin and myosin into small peptides. The peptides are extruded from the proteasome and degraded to amino acids by peptidases in the cytoplasm. The ubiquitin–proteasome pathway degrades many proteins other than actin and myosin. Reproduced and modified from [15] with permission from the publisher.

effective impedance [231], and impaired cardiovascular performance [247].

Exercise capacity

Exercise capacity is decreased in subclinical [248] and overt hyperthyroidism [229, 242], and can be improved by treatment [241, 242, 248]. Potential mechanisms include decreased limb

muscle strength [230, 232], reduced muscle mass [232], decreased fatigue-resistant myofibres [249], reduced skeletal muscle L-carnitine (a carrier of fatty acids in the mitochondria for subsequent oxidation [250]), decreased efficiency of oxygen utilisation [241], reduction in cardiac functional reserve [247, 251], excessive increase in respiratory drive [242], decreased lung volumes [230, 240] and excessive lactate production [247].

COPD and hyperthyroidism: treatment

Hyperthyroidism in patients with COPD should be treated in the same manner as in patients without COPD [225].

COPD AND RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The renin–angiotensin–aldosterone system is central to the control of sodium reabsorption by the kidney [252]. Decreases in glomerular filtration rate and sodium delivery to the distal nephron cause release of renin. Renin cleaves angiotensinogen to form angiotensin I [252]. Angiotensin I is then cleaved into angiotensin II by the angiotensin-converting enzyme. Angiotensin II can increase sodium retention through three mechanisms. First, it enhances sodium reabsorption in the proximal tubule. Secondly, it decreases the filtered load of sodium. Thirdly, it stimulates the adrenal cortex to secrete aldosterone. Aldosterone, in turn, increases sodium reabsorption through multiple mechanisms. While activation of the renin–angiotensin–aldosterone system causes sodium retention, sodium excretion is controlled by several natriuretic factors [252]. These factors include a number of natriuretic peptides such as the atrial natriuretic peptide, and the B-type and C-type natriuretic peptides [253]. Natriuretic peptides are primarily synthesised in the heart and brain. Atrial natriuretic peptide and B-type natriuretic peptide increase in response to overload of the extracellular volume. They cause natriuresis, vasodilation and suppress activity of the renin–angiotensin–aldosterone system. The C-type natriuretic peptide is primarily vasodilatory.

In the 1970s and 1980s, the group of Farber and Manfredi was among the first to demonstrate that clinically stable hypercapnic patients with COPD often exhibited impaired excretion of sodium and water [254], which was aggravated when oedema was present [255]. They reported upregulation of the renin–angiotensin–aldosterone system and vasopressin (which increases water reabsorption in the distal nephron) in COPD [255, 256]. Increased renin–angiotensin–aldosterone may contribute to sodium retention and increased vasopressin may contribute to hyponatraemia and water retention [255–257]. (Sodium and fluid homeostasis in COPD is reviewed in detail by DE LEEUW and DEES [252].)

COPD and imbalance of the renin–angiotensin–aldosterone system: risk factors/prevalence

Most studies of the renin–angiotensin–aldosterone system in COPD have focused on patients who already have evidence of fluid retention. Therefore, there are limited data on the frequency with which this system is activated in the general COPD population (table 4). Development of sodium and water retention in COPD implies poor prognosis [258].

COPD and imbalance of the renin–angiotensin–aldosterone system: functional consequences

Patients with COPD can develop fluid retention when stable [255, 257] or during exacerbations [41, 259]. Fluid retention can cause peripheral oedema, ascites and pleural effusions [260]. Right heart pressures can be normal or increased [259]. Cardiac output is often preserved or even increased [41, 259, 261].

The mechanisms responsible for development of fluid retention are complex [252]. The traditional view, that volume overload occurs as a result of right-ventricular failure, itself caused by hypoxia-induced pulmonary vasoconstriction, probably holds true only for certain patients. Growing evidence suggests that renal vasoconstriction is central in the development of fluid retention in patients with COPD [41, 252].

ANAND *et al.* [41] reported increased pulmonary artery resistance and decreased peripheral vascular resistance in nine hypoxaemic, hypercapnic patients experiencing an exacerbation of COPD and new-onset fluid retention. Cardiac output was normal and mean arterial pressure was reduced. Renal plasma flow and glomerular filtration rate were decreased. Plasma norepinephrine, renin activity, circulating vasopressin and atrial natriuretic peptide concentrations were all increased [41]. The investigators [41] argue that hypercapnia plays a central role by decreasing systemic vascular resistance through a direct effect on systemic arterioles [262, 263]. The increased vascular capacitance will decrease the effective circulating volume and renal blood flow (severe hypoxaemia can also contribute to reduced renal flow [264–267]). A second mechanisms by which hypercapnia may decrease effective circulating volume is through a reduction in precapillary tone [252]. The reduced tone will move the point of filtration equilibrium distally in the capillaries and, consequently, increase extravasation and the loss of plasma volume [252]. Reduction of effective circulating volume will stimulate the sympathetic nervous system, the renin–angiotensin–aldosterone system and vasopressin [260]. To restore intravascular volume and tissue perfusion, the kidney will respond with vasoconstriction and sodium retention (fig. 6) [260]. Hypercapnia may also increase sodium retention by accelerating the renal reabsorption of sodium bicarbonate [255]. The retention of salt and water, with the attendant expansion of the extracellular volume, may be sufficient to increase intracardiac pressures and, with it, it may increase circulatory levels of atrial natriuretic peptide [41]. The atrial natriuretic peptide, with its vasodilator properties, could further reduce systemic

vascular resistance. Two additional factors may contribute to fluid retention: GH, which can be increased in patients with COPD [18, 41], can itself activate the renin–angiotensin–aldosterone system [255]. Second, the carbon dioxide might directly or indirectly turn on the sodium–hydrogen antiporter in the luminal membrane of proximal tubules [252]. The sodium–hydrogen antiporter, also known as sodium–hydrogen exchanger, is primarily responsible for maintaining the balance of sodium and it is involved in the buffering of respiratory acidosis at the expense of sodium gain (fig. 6) [252]. ANAND *et al.* [41] argue that persistence of hypercapnia will produce vasodilatation and retention of sodium and water. Administration of diuretics may aggravate the vicious cycle by promoting sodium loss and, thus, further activation of the renin–angiotensin system [260].

The model proposed by ANAND *et al.* [41] has limitations. First, the investigators fail to reconcile the observation that, after the resolution of the congestive state and normalisation of peripheral vascular resistances, levels of renin, angiotensin and aldosterone remained the same as those recorded during the exacerbation [41]. Secondly, the vasoconstrictor effect of hypercapnia-associated activation of the sympathetic nervous system predominates over the direct vasodilatation effect of hypercapnia (indirect vasoconstriction is absent when the vasomotor centre cannot respond to hypercapnia-induced sympathetic activation or when the vasomotor centre is disconnected from peripheral parts of the sympathetic nervous system) [268]. Thirdly, although most patients with COPD and fluid retention are hypercapnic [269, 270], hypercapnia is not a necessary prerequisite for the development of fluid retention in these patients [257, 259]. Lastly, the investigators [41] did not control for sodium intake, and all medications, including diuretics, were continued. Therefore, it is difficult to decipher whether fluid retention was a primary event or secondary to relative cardiac impairment; in the study of ANAND *et al.* [41], patients did not compensate for the decreased blood pressure with supraphysiologic cardiac output.

Additional observations raise questions about the contributions of hypercapnia, aldosterone and vasopressin to fluid retention. In a study of saline loading of patients with COPD [257], only severity of parasympathetic neuropathy and renal blood flow independently influenced sodium excretion. In patients with stable COPD and fluid retention, normalisation of aldosterone by administration of angiotensin-converting enzyme inhibitors did not improve sodium excretion [271]. In

TABLE 4 Abnormalities of the renin–angiotensin–aldosterone system in chronic obstructive pulmonary disease (COPD)			
	Mild-to-moderate COPD plus hypoxaemia, normocapnia and no oedema (n=20)	Severe COPD plus hypoxaemia, hypercapnia and no oedema (n=20)	Severe COPD plus hypoxaemia, hypercapnia and oedema (n=25)
Elevated renin activity	5	80	80
Elevated aldosterone	15	10	44
Elevated vasopressin	0	10	56

Data are presented as % of patients. Reproduced and modified from [255] with permission from the publisher.

FIGURE 6. Hypothetical pathophysiology of sodium and water retention in chronic obstructive pulmonary disease (see text for details). Not shown are pathways through which atrial natriuretic peptide can modulate fluid homeostasis including dilation of the afferent glomerular arteriole and constriction of the efferent glomerular arteriole with consequent increased glomerular filtration (and thus greater excretion of sodium and water) and inhibition of renin and aldosterone secretion. SNS: sympathetic nervous system; RAAS: renin-angiotensin-aldosterone system; AVP: arginine vasopressin; ANP: atrial natriuretic peptide. Reproduced and modified from [252] with permission from the publisher.

seven mechanically ventilated patients with COPD, changes in plasma hormones during acute hypercapnia were associated with the haemodynamic changes induced by respiratory failure and not to acute hypercapnia *per se* [272].

A fall in renal blood flow and development of a subclinical parasympathetic neuropathy [273, 274], reported in >35% of patients with COPD [273], might be more important than aldosterone and vasopressin in causing fluid retention in nonhypoxaemic patients with COPD [257]. Interruption of the parasympathetic afferents can increase vasopressin [275] and, consequently, increase tubular reabsorption of solute-free water. Interruption of vagal pathways can increase intrarenal sympathetic activity with abolition of the reflex fall in sympathetic tone associated with an increase in effective blood volume [257]. A failure to correctly interpret this increase could partly explain the reported impaired sodium excretion [257].

The presence of sympathetic neuropathy [274, 276, 277] may explain why hypercapnia causes a (direct) decrease in peripheral vascular resistance rather than an (indirect) increase through hypercapnia-mediated sympathetic stimulation. A correlation between severity of autonomic neuropathy and hypoxaemia reported by some [273, 274], but not all [276]

investigators raises the possibility that autonomic neuropathy is caused by intraneural hypoxaemia [273].

COPD and imbalance of the renin-angiotensin-aldosterone system: therapy

Few investigators have assessed treatments aimed at reducing fluid retention in COPD [271, 278, 279]. Some suggest postponing diuretics as long as possible [252, 260]. Diuretics can aggravate retention of sodium and water [252, 260] through several pathways including hypoventilation-induced hypochloaemic metabolic alkalosis [280, 281]. Others suggest the use of angiotensin-converting enzyme inhibitors to increase sodium excretion [256]. These agents, however, have inconsistent effects and may increase [282] or have no effect on sodium excretion [271]. Vasopressin levels vary inversely with arterial oxygen tension [252] suggesting that oxygen supplementation may help.

CONCLUSION

Despite plausibility and increased research, little information is available whether patients with COPD are at increased risk for specific endocrinopathies. The role of the renin-angiotensin-aldosterone system in contributing to oedema in COPD has been studied for more than 30 years, yet our understanding of its contribution is rudimentary. Even less is known about the indications and contraindications for hormone-replacement therapy. No study to assess whether any specific replacement therapy has some effect on COPD progression has been conducted. Cross-fertilisation is source of much creativity in science: Pasteur was a skilled chemist and Darwin a published geologist before they embarked on biology; and Crick was a physicist and Watson a zoologist when they started to research DNA. The paucity of knowledge about the interactions between COPD and the endocrine system indicates that this would be a fertile territory for cross-fertilising collaboration.

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STATEMENT OF INTEREST

None declared.

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