The Metabolic and Inflammatory Profile in Obese Patients with Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease (COPD) and obesity are major causes of morbidity and mortality worldwide and, according to current data, the global burden of these conditions will increase further. Obesity plays a major role in the development of the metabolic syndrome and has been identified as an important risk factor for chronic diseases such as type 2 diabetes mellitus and cardiovascular disease. Adiposity is associated with insulin resistance even over relatively normal ranges of body fatness. There is strong evidence that altered adipose tissue function plays a crucial role in the pathogenesis of obesity-related insulin resistance and type 2 diabetes, as has recently been reviewed. Obesity is linked to respiratory diseases such as obstructive sleep apnea syndrome and obesity hypoventilation syndrome and accumulating evidence suggests an association between obesity and asthma. A potential link between obesity and COPD is also increasingly recognized although little data is known about the mechanisms underlying this association. The inflammatory and metabolic profile differs between obese with COPD and normo or underweight with COPD in part due to dysfunction of adipose tissue.

Key words: COPD, obesity, adipocyte, inflammatory cytokine, metabolic syndrome.

Chronic obstructive pulmonary disease (COPD) and obesity are major causes of morbidity and mortality worldwide and, according to current data, the global burden of these conditions will increase further. While spirometry is used for diagnosis and gradation of COPD severity according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1], classification of overweight and obesity is based on body mass index (BMI) as defined by the World Health Organization (WHO) [2]. According to the Burden of Obstructive Lung Disease (BOLD) Initiative [3] the estimated international prevalence of stage II or higher COPD is currently 10.1% in individuals aged 40 years and older. COPD was the fifth leading cause of mortality around the world in 2001 and will be the third most frequent cause of death by the year 2020 [4]. The prevalence of obesity, defined as BMI >30 kg/m² [2], has multiplied during the last decades and varies from 10–20% in most European countries to >32% in the USA [2]. According to the most recent global WHO projections, 400 million adults were obese in 2005 and it is estimated that this number will exceed 700 million by the year 2015 [5]. Obesity plays a major role in the development of the metabolic syndrome and has been identified as an important risk factor for chronic diseases such as type 2 diabetes mellitus and cardiovascular disease. It is linked to respiratory diseases such as obstructive sleep apnea syndrome and obesity hypoventilation syndrome [6] and accumulating evidence suggests an association between obesity and asthma [7]. A potential link between obesity and COPD is also increasingly recognized [8], although little data is known about the mechanisms underlying this association. The risk of developing obesity is increased in patients with COPD as a result of a reduced level of physical activities in daily life in these patients compared with healthy age-matched controls [9]. In addition, in theory, patients with COPD who receive repeated courses of systemic glucocorticosteroids are at increased risk of truncal obesity as a result of glucocorticoid mediated redistribution of stored energy and the stimulatory effect on intake [10].
COMBINED DELETERIOUS EFFECTS OF OBESITY AND COPD

The physiological derangements that occur at rest and during exercise in obesity and in COPD are well understood when each is considered in isolation. However, no mechanistic studies have explored the pathophysiological interactions that occur when both conditions coexist in the same individual, as is increasingly the case. Given the vast pathophysiological heterogeneity of COPD, the concomitant effects of aging and sex on physical performance, and the existence in many of serious co-morbidities in conjunction with obesity, the mechanisms of exercise intolerance in obese patients with COPD are necessarily complex. Clinical experience indicates that the combined restrictive/obstructive deficits evident in obese patients with COPD culminate in worsening symptoms and activity limitation [11][12]. Obesity would be expected to amplify the abnormalities of dynamic ventilatory mechanics and ventilatory demand that characterise COPD. Thus, ventilatory requirements are predictably higher in obese patients with COPD compared with those of normal weight as a result of the increase in chemo-stimulation that arises from the combination of increased metabolic loading, high fixed physiological dead space and possibly earlier metabolic acidosis due to impairment in oxygen uptake from de-conditioning or cardiac dysfunction. The increased recoil of the chest wall and lung in patients with central obesity may increase expiratory flow rates at a given operating lung volume compared with non-obese patients with COPD. However, the relatively reduced absolute end-expiratory lung volume in obese patients with COPD may worsen expiratory flow limitation and air trapping during exercise, particularly in the setting of the relatively increased ventilatory requirement [13][14]. The net effect of these abnormalities is an earlier mechanical limitation of ventilation with greater dyspnea and exercise curtailment in the obese patient with COPD. The accompanying rapid shallow breathing pattern (at a relatively low power output and ventilation) may compromise dynamic inspiratory muscle function and deleteriously affect alveolar ventilation [13][14]. In obese patients with COPD the increased contractile muscle effort required to sustain ventilation during exercise in the face of serious mechanical constraints on tidal volume expansion would be expected to cause significant neuro-mechanical uncoupling of the respiratory system and lead to incapacitating dyspnea earlier in exercise than in non-obese patients with COPD.

EFFECTS OF BODY COMPOSITION ON EXERCISE PERFORMANCE IN OBESI WITH COPD

In addition to ventilatory limitations, alterations in body composition contribute to exercise intolerance in patients with COPD. It is well accepted that loss of fat-free mass (FFM) contributes to muscle weakness [15] and reduced exercise capacity [16] in patients with moderate to severe COPD. Available data in these patients suggest that the contribution of alterations in fat mass to exercise intolerance is limited compared with the impact of muscle wasting. The degree of physical impairment, assessed by the 12 minute walking test, was greater in normal weight patients with depleted FFM and relatively enhanced fat mass than in underweight patients with preserved FFM [17]. Less is known about effects of obesity or relatively increased fat mass on physical performance in patients with less severe COPD. In patients with early stage COPD, obesity, decreased lean-to-fat mass ratio and increased sagital abdominal diameter were associated with functional limitation on the six minute walk test [18]. The accumulation of fat mass and not the loss of lean mass had a particularly negative impact on performance. This observation is not unique for patients with early stage COPD. In a cohort of elderly individuals from the general population, high body fatness was associated with increased risk of self-reported mobility-related disability, while low FFM was not predictive of disability [19]. In another community-based cohort study of older individuals, higher fat mass was related to an increased risk of functional limitation assessed by walking speed [20]. Although absolute lean mass was not related to physical performance, a higher ratio of lean mass to fat mass was predictive of walking speed. Thus, it seems that both absolute and relative accumulation of fat mass contribute to functional limitation in the elderly and early in the course of COPD, while the influence of muscle wasting on physical performance becomes apparent in patients with more severe COPD when FFM falls to very low levels [17][21].
OBSTRUCTIVE SLEEP APNEA SYNDROME

The prevalence of obstructive sleep apnea in the general population is highly variable, ranging from 25% to 58% among men and from 10% to 37% among women, depending on ethnicity and the geographic area studied [22]. Obstructive sleep apnea is characterized by intermittent upper airway obstruction due to the inability of pharyngeal musculature to maintain upper airway patency in the presence of alterations in airway shape and diameter [23]. This conducts in a fall in arterial oxygen content, a rise in carbon dioxide levels and increased inspiratory efforts that lead to abrupt awakenings as the person struggles to breathe [24]. The final result is profoundly disturbed sleep.

Obesity is a well-recognized risk factor for obstructive sleep apnea. Increased fat tissue deposition in the pharyngeal region and reduced operating lung volumes in obesity act together to reduce upper airway caliber, modify airway configuration and increase their collapsibility; airways are thus predisposed to repetitive closures during sleep [25]. About 70% of people with obstructive sleep apnea are obese, and, conversely, the prevalence of the disorder among obese people is approximately 40% [26]. Indeed, almost all men with class III obesity also have obstructive sleep apnea [27]. Obstructive sleep apnea is associated with excess mortality from accidents related to daytime sleepiness and to the high incidence of cardiovascular disorders reported in this condition [28–31]. Therefore, obstructive sleep apnea is one of the life-threatening sequelae of obesity.

OBESITY HYPOVENTILATION SYNDROME

Hypercapnic respiratory failure and cor pulmonale are frequently observed in obesity. In the absence of other known causes of respiratory failure, this syndrome, which was first described 50 years ago [32], is now termed obesity hypoventilation syndrome [33]. Respiratory failure, severe hypoxemia, hypercapnia and pulmonary hypertension represent the syndrome’s most common symptoms [33][34]. Most patients with obesity hypoventilation syndrome also have obstructive sleep apnea [33], but that some patients have obesity hypoventilation syndrome but not obstructive sleep apnea suggests that obesity alone can lead to chronic hypoventilation. The diagnostic criteria for the syndrome are provided in Table I.

Table I

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<thead>
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<th>Diagnostic criteria for obesity hypoventilation syndrome</th>
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<td>• Body mass index &gt; 30 kg/m²</td>
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<tr>
<td>• Daytime PaCO₂ &gt; 45 mm Hg</td>
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<tr>
<td>• Associated sleep-related breathing disorder (obstructive sleep apnea–hypopnea syndrome or sleep hypoventilation or both)</td>
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<td>• Absence of other known causes of hypoventilation</td>
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ADIPOSE TISSUE – A SOURCE OF INFLAMMATION IN OBESE PATIENTS WITH COPD

The association between abdominal obesity, insulin resistance and cardiovascular disease is well recognized [35], but the underlying mechanisms are not yet fully understood. Adiposity is associated with insulin resistance even over relatively normal ranges of body fatness. There is strong evidence that altered adipose tissue function plays a crucial role in the pathogenesis of obesity-related insulin resistance and type 2 diabetes, as has recently been reviewed [36].

Until recently, fat was considered to function predominantly as the triglyceride reservoir of the body and was believed to have only a passive endocrine role. It is now recognized that white adipose tissue is a multifunctional organ. White adipocytes secrete several hormones and a diverse range of protein factors that have been given the collective name “adipocytokines” or “adipokines”. Adipocytes themselves have been found to secrete proteins involved in lipid metabolism, insulin sensitivity, the alternative complement system, vascular homeostasis, blood pressure regulation and angiogenesis, as well as the regulation of energy balance. Of particular interest, leptin and adiponectin have been linked to acute exacerbations and stable COPD.

Adipocytes express and secrete a variety of adipokines – including cytokines, growth factors, adiponectin, resistin, adipin, leptin, acylation stimulating protein (ASP), plasminogen activator inhibitor-I
(PAI-1), lipoprotein lipase (LPL) and components of the renin-angiotensin system [37] – which may exert local and systemic effects. Chronic low-grade inflammation is a hallmark of obesity, insulin resistance and type 2 diabetes [38][39]. Importantly, inflammatory pathways play a prominent role in the mechanisms underlying insulin resistance and type 2 diabetes in cultured cells and animal models [40–42], and this may also be the case in humans.

The inflammatory response that is often present in obesity appears to be triggered and to reside predominantly in the enlarged adipose tissue [43–46]. The expression and/or secretion of inflammatory molecules, including tumor necrosis factor α (TNFα) [45][47, 48], interleukin 6 [47–49], PAI-1[50] and leptin [48], are increased in the adipose tissue of obese insulin-resistant individuals. In contrast, the expression of the insulin-sensitising factor, adiponectin is reduced in obese and insulin-resistant subjects [51][52]. Interestingly, enlarged adipocytes seem to express pro-inflammatory and anti-inflammatory factors with a shift towards dominance of pro-inflammatory adipokines compared with smaller adipocytes [53].

Recent data indicate that adipose tissue of obese individuals is infiltrated by macrophages, which may be a major source of locally produced pro-inflammatory adipokines [54][55]. There seems to be cross-talk between adipocytes and macrophages within adipose tissue. For example, macrophage-secreted factors exert effects on adipocytes that may increase systemic inflammation and insulin resistance associated with obesity [56]. The mechanisms underlying the impaired adipokine secretion and macrophage infiltration in adipose tissue in obesity remain to be elucidated, but there is evidence to support a major role for adipose tissue hypoxia in these events.

**MOLECULAR CHARACTERISTICS OF ADIPOCYTES**

To elucidate the molecular mechanism of visceral obesity-related diseases, Matsuzawa et al. [57] have investigated the biological characteristics of adipose tissue by analyzing the gene expression profile in visceral and subcutaneous fat. They found unexpectedly high frequency of the genes encoding secretory proteins in adipose tissue, most of which are important bioactive substances [58]. In subcutaneous adipose tissue, approximately 20% of all known genes were the genes encoding secretory protein. Furthermore, its frequency came up to approximately 30% in visceral adipose tissue. Leptin and tumor necrosis factor (TNF)-α have been well recognized as bioactive substances from adipose tissues, which control the functions of other organs.

The gene that expressed most abundantly and specifically in adipose tissue was also a novel gene [59]. The molecule encoded by this gene, adipose most abundant gene transcript-1, possesses a signal peptide, collagen-like motif and globular domain, and has the significant homology with collagen X and VIII and complement factor C1q [59]. This matrix-like protein was termed adiponectin. Interestingly, plasma levels are negatively correlated with body mass index (BMI), whereas leptin, another adipose tissue-specific secretory protein, is known to increase with (BMI) [60]. The negative correlation is stronger between adiponectin levels and visceral adiposity than between the protein and subcutaneous adiposity. The mechanism of reduction in plasma adiponectin levels in the subjects with visceral fat accumulation has not been clarified yet. It has been reported that TNF-α is a strong inhibitor of adiponectin promoter activity [61].

**ADIPONECTIN AND COPD**

In healthy subjects, adiponectin carries out its roles for preventing development of vascular changes and the impairment of glucose and lipid metabolism, which may be induced by a variety of attacking factors, such as chemical subjects, mechanical stress, or nutritional loading. A large amount of adiponectin flows with the blood stream inside of vascular walls. It would be interesting to know whether adiponectin can enter the vascular walls. Adiponectin has potential inhibitory activities of these atherogenic cellular phenomena. Adiponectin was shown to inhibit the TNF-α-induced nuclear factor-kB activation through the inhibition of I kB phosphorylation, which might be a major molecular mechanism for the inhibition of monocyte adhesion to endothelial cells [64]. Adiponectin also inhibits the expression of the scavenger receptor type A-1 of macrophages, resulting in markedly decreased uptake of oxidized LDL and inhibition of foam cell formation [65]. In addition, adiponectin inhibits the proliferation and migration of smooth muscle cells. From these vascular cellular functions, adiponectin may have a potential antiatherogenicity.
Hypoadiponectinemia together with the increase of TNF-α or PAI-1 induced by the accumulation of visceral obesity might be a major background of vascular changes as well as metabolic disorders, including insulin resistance, which are the characteristics of the so-called metabolic syndrome. In patients with metabolic syndrome, plasma adiponectin levels were inversely correlated with body weight. COPD is characterized by systemic inflammation; therefore, decreased BMI is one of the important prognostic markers in COPD. In COPD there are two major phenotypes; emphysema-dominant type and airway disease-dominant type. Usually, patients with emphysema-dominant type show lower BMI than those with airway disease-dominant type.

Considering the above mentioned the normal question is: does adiponectin play a role in obese patients with COPD?

It is known that acute exacerbations of COPD (most often in response to bacterial infection) are associated with increased serum of CRP, IL-6, TNF-α, leptin, and adiponectin, as well as with increases in other factors associated with bacterial inflammation and infection. Recently, differences in body weight and serum adiponectin levels have associated with the two clinical major phenotypes found in COPD. In a Japanese study of normal and underweight patients with emphysema, serum levels of adiponectin were elevated in both groups and were correlated with increased serum of TNF-α and IL-6 levels, as well with the severity of lung disease. Plasma adiponectin levels in patients with COPD were elevated and correlated with body weight loss, hyperinflation, and systemic inflammation [66]. Increased adiponectin may reduce cardiovascular events in underweight patients with COPD.

In conclusion, serum adiponectin can be a prognostic and subtype discriminative marker in COPD.

LEPTIN AND COPD

Leptin is a peptide hormone that is produced predominantly by white adipose cells [67]. Circulating leptin is proportional to the amount of adipose tissue in any given individual. Leptin exerts most of its energy metabolism effects through effects on the central nervous system, namely on the hypothalamic nuclei. These effects include decreases in food intake, increases in energy expenditure, and decreases in metabolic efficiency. In addition, leptin has been shown to influence a wide spectrum of biological functions, including lipid and glucose metabolism, synthesis of glucocorticoids and insulin, regulation of the hypothalamic–pituitary–adrenal axis, maturation of the reproductive system, hematopoiesis, angiogenesis, and fetal development [68–76].

It is therefore not surprising that, during acute exacerbations of COPD, leptin concentrations have been shown to relate to disturbances in the energy balance and the systemic inflammatory response [27].

Furthermore, the almost universal distribution of leptin receptors reflects the multitude of leptin’s biological effects outside the central nervous system.

Recently published studies demonstrate that leptin has a potentiating role in the function of both innate and adaptive immunity [77]. Leptin stimulates neutrophils and macrophage chemotaxis [78], and enhances their functional capacities such as oxidative burst [78], phagocytosis [79], and cytokine secretion [80][81]. In addition, leptin exerts activating [82] and proliferating [83] effects on T lymphocytes and promotes Th1 cell differentiation [84]. Furthermore, leptin enhances host responses to inflammation and infection by stimulating tissue repair via its mitogenic and angiogenic effects on epithelium and endothelium [72][85].

All of the above has led to the general consensus that leptin has a proinflammatory role in the regulation of inflammation and immunity.

In both experimental and human study increased levels of circulating leptin may contribute to anorexia and weight loss in COPD because administration of TNF-α or IL-1 produced a prompt and dose-dependent increase in serum leptin levels (86). Circulating levels of leptin levels were significantly lower in patients with COPD than in healthy controls. Circulating levels of the leptin are not controlled by the TNF-α system and physiologic regulation of leptin is maintained despite the weight loss in patients with COPD. However, decreased levels of circulating leptin may have some pathophysiologic role in obese patients with COPD.

More research is needed to better our understanding of the role of elevated concentrations of leptin during exacerbations of COPD, particularly regarding the role of leptin in local respiratory defense [87][88].

In summary, leptin does function as a proinflammatory cytokine and is involved in the pathogenesis of inflammatory and autoimmune diseases, including acute exacerbations of COPD.
The cytokine TNF-α was one of the first mediators found to be elevated in COPD [89]. TNF-α produced by macrophages, epithelial cells, and lymphocytes increases IL-8 levels through activation of NF-kB pathways. The chemokine IL-8, which is elevated in the sputum of COPD patients, is a potent chemoattractant and activator of neutrophils and associated with disease severity. IL-8 also activates the lipid mediator 5-lipoxygenase to form leukotriene B4 (LTB4), which results in further neutrophilia. It has been suggested that TNF-α may be related with systemic inflammation in COPD and elevated levels of TNF-α were associated with increased leptin levels and poor nutritional status [90]. During an acute exacerbation of COPD, the involvement of the systemic inflammatory response may be more pronounced than in the stable patient. A recent study found no statistically significant difference in serum leptin levels between COPD patients during stable stage and acute exacerbation, and there was no significant correlation between TNF-α and leptin during the regulation of the energy balance in COPD patients [91].

In conclusion, we can easily observe that data are not clear about the relationship between TNF-α, circulating leptin and nutritional parameters.

Other potentially important cytokines associated with pulmonary inflammation in COPD include monocyte chemotactic protein-1 [92] and IL-6 (a potential mediator of systemic effects of the disease) [93]. Additionally, transforming growth factor (TGF) β1 is increased in epithelial cells and macrophages in peripheral airway tissue of smokers and COPD patients [92]. TGF-β1 may be an important mediator of the peripheral airway fibrosis associated with progressive airflow obstruction.

### CRP AND INFLAMMATION IN COPD

During the latest decade, there has been compelling evidence that CRP is not just a marker of disease but it also contributes to pathogenesis. Further expansion of our knowledge of the structure and function of CRP is crucial if we are to improve our understanding of the pathogenesis and heterogeneity of COPD.

Plasma CRP is produced mainly by hepatocytes, predominantly under transcriptional control by IL-6. The plasma half-life of CRP is about 19 hours and is constant under all conditions of health and disease, so that the sole determinant of circulating CRP concentration is the synthesis rate, which thus directly reflects the intensity of the pathologic process stimulating CRP production. Subjects in the general population have stable CRP concentrations that are characteristic for each individual. The complement system is a powerful effector mechanism, which, upon activation, generates activation fragments (C3a and C5a) responsible for the initiation of a local inflammatory response by recruitment of leukocytes to the area of infection or injury. Few studies have reported that the complement system may participate in the inflammatory process of COPD [59][60]. One study evaluated C5a concentrations in the induced sputum of patients with COPD. Significantly elevated levels of C5a were found in the induced sputum of patients with COPD. C5a concentrations in patients with COPD correlated negatively with diffusing capacity [95].

Slightly CRP levels have been shown to associate with the presence of inflammation in atherosclerosis and with increased risk of coronary heart disease and myocardial infarction. There are a lot of studies which suggest that increased CRP levels also associate with lung inflammation in stable COPD and levels of CRP correlate with the degree of pulmonary inflammation. It is therefore possible that serum CRP as a systemic marker of ongoing lung inflammation could be used as a predictor of future COPD outcomes [96].

The relation between CRP and lung function in patients with COPD was the strongest in underweight patients in the sense of inverse association between the level of FEV1 and CRP [97]. Patients with COPD have higher levels of CRP than the healthy patients and this relation is more expressed at obese with COPD and metabolic syndrome [98].

In summary, the role of CRP and pro-inflammatory cytokine may extend beyond the lung and play an important role in the systemic effects of the disease and associated co-morbidities like diabetes, cardiovascular diseases and osteoporosis.

### DISCUSSION AND CONCLUSIONS

Increasing evidence now points toward a role of proinflammatory cytokines such as C-reactive protein, interleukin-6, and tumor necrosis factor in
the pathogenesis of insulin resistance and type 2 diabetes. Due to the upregulation of proinflammatory cytokines in COPD one might hypothesize that these chronic inflammatory diseases would increase risk for type 2 diabetes. The inflammatory and metabolic profile differs between obese with COPD and normo or underweight with COPD in part due to dysfunction of adipose tissue.

Airflow obstruction is an important risk factor for cardiac injury. In the presence of elevated CRP, the risk increases almost 2-fold, which suggests an important interplay of systemic inflammation with airflow obstruction in the development of ischemic heart disease.

Concerning the above mentioned we can easily speculate that an obese with COPD has a higher cardiovascular risk as compared with a lean COPD patient, mainly due to a higher metabolic risk and secondary to an exacerbated pulmonary and systemic inflammatory profile.

Further studies are needed to establish the cardio-metabolic risk of obese patients with COPD and to clarify the role of cytokine in prognosis of COPD.

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