Role of adipokines in obstructive airway disease and diabetes mellitus

Seema Singh¹, Sunita Singh², Santosh Kumar¹, S K Verma¹, and Surya Kant¹

Department of Respiratory Medicine¹, Department of Microbiology², King Georges Medical University, Lucknow, India

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ABSTRACT: This review summarizes the state of the current literature relating to the associations of lung disease and adipokines (proteins produced by adipose tissue) in humans. The mechanistic basis for these associations in humans is not established, although a possible role for adipokines has been invoked. Leptin, a pro-inflammatory adipokine, and adiponectin, an anti-inflammatory adipokine, are causally associated with asthma in mice. Although human studies are currently inconclusive, high-serum leptin and low-serum adiponectin concentrations predict asthma, independent of obesity, in select population groups, such as premenopausal women in the United States. In contradistinction, low-serum leptin and high-serum adiponectin concentrations are associated with stable COPD, although these associations are likely confounded by fat mass. Interestingly, leptin may promote systemic and airway inflammation in stable COPD patients. On the other hand, COPD may upregulate systemic and lung adiponectin expression. The precise mechanism and significance of the associations between these adipokines and lung disease at the current stage are confusing and frankly paradoxical in places. It is now known that adipose tissue is not an inert organ simply for energy storage, but regulates systemic inflammation via a variety of secreted proteins (called adipokines). While the associations of obesity and adipokines with cardiovascular, endocrine, and rheumatological diseases are well described, the respiratory effects of obesity and adipokines are less well known. This review will focus on the effect of obesity and adipokines on asthma and chronic obstructive pulmonary disease (COPD) in humans. This area of research needs additional study that may open up novel therapeutic strategies for these lung diseases.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is considered a major health problem and 3rd leading cause of death which profoundly affects worldwide mortality and morbidity [1]. The severity of COPD worsens the lung function and increased systemic inflammation that contributes to the development of extrapulmonary complications such as cardiovascular disease, osteoporosis, depression, and weight loss [2], [5-7] which ultimately affects the survival rate. Adipose tissue mainly composed of white adipose tissue and brown adipose tissue, mainly white adipose tissue is responsible for the production of a large number of circulatory, includes chemokines, cytokines, and hormones like adiponectin, leptin, and resistin.

Adiponectin and leptin both are adipokines mainly produced by adipocytes cell found in white adipose tissue, they perform several metabolic and inflammatory-related functions [3] [5]. Recent researches suggested that adiponectin and leptin play a major role in inflammation of lung conditions such as COPD and asthma. In this review, we focus on adiponectin, leptin, and their role in COPD [4], [6]. Adipose tissue is a highly active organ and there is evidence that it secretes a large variety of proteins, including cytokines, chemokines, and hormone-like factors such as leptin, adiponectin, and resistin [3]. Leptin is a circulating hormone produced by adipose tissue acting both centrally and peripherally to regulate several metabolic and inflammation-related functions [5].
Adiponectin is the adipokine that is mainly involved in the regulation of insulin sensitivity [6]. Adiponectin has also anti-inflammatory properties, by reducing inflammatory cytokines and inducing anti-inflammatory ones [7,8]. Increased levels of leptin were reported in stable COPD as well as in ECOPD [9,10]. However, limited data are available on the role of adiponectin in COPD, except for an increase in its levels in underweight COPD patients and a marginal difference between stable phase and exacerbation [11,12].

Exacerbations of COPD (ECOPD) are associated with worsening of lung function, decreased health-related quality of life, increased systemic inflammation, and significant impact on survival [13].

### Leptin and COPD

Leptin, a protein mainly synthesized by white adipose tissue [14]. The concentration of leptin increases with the meal, pregnancy, and inflammatory infectious state [15]. Leptin is a primarily pro-inflammatory adipokine that affects both innate and adaptive immune responses. Leptin differentially increases the production of TH1 cytokines (Interleukin or IL-2, interferon-γ and Tumor Necrosis Factor or TNF-α) and suppresses the production of TH2 cytokines (IL-4, IL-5, and IL-10). Leptin also increases the release of Vascular Endothelial Growth Factor (VEGF) by airway smooth muscle cells [16]. VEGF may stimulate subepithelial neovascularization and vascular permeability, key findings in the pathogenesis of various lung inflammatory states such as asthma [9]. Leptin further increases natural killer cell function [23, 24] [10, 11]: CD4+ T-lymphocyte proliferation; macrophage phagocytosis and monocyte proliferation [17].

The expression of leptin is increased in bronchial epithelial cells and alveolar macrophages in ex-smokers with or without severe COPD as compared to never smokers [18], and the level of leptin expression is associated with the severity of COPD [19]. As in asthma, high circulating leptin levels have been reported especially in female and overweight patients with COPD [20] suggesting that sex and BMI are significant confounding factors also in the association between leptin and COPD. On the other hand, some groups have not found any differences in serum leptin levels between patients with COPD and healthy controls or any associations between leptin levels and the severity of COPD [21]. The circulating leptin levels in COPD may also be affected by the phenotype of the patient, as lower leptin levels have been reported in COPD patients with either osteoporosis [22] or emphysema [23]. However, these results may be affected by the lower fat mass and BMI in the subjects with osteoporosis or emphysema as lower circulating leptin levels have been reported in COPD patients with either low [24] or normal [25] BMI. Higher circulating leptin levels are also related to systemic inflammatory activity [26] and COPD exacerbations [27]. Thus, the precise role of leptin in the pathogenesis of COPD, particularly in different phenotypes remains unresolved.

### Leptin in asthma

Because epidemiological studies have shown that the prevalence of both asthma and obesity have increased concomitantly during recent decades [28], it was interesting to investigate if an obese gene product leptin would be associated with asthma. Several human studies have indicated that a high serum leptin concentration is associated with asthma [29], especially in premenopausal women [30], and in children [31], especially in obese children [32]. Interestingly, Sood et al., reported that adjustment for leptin did not affect the association between asthma and BMI in women suggesting that the relationship between obesity and asthma was not mediated solely via leptin [33]. Besides, the severity of asthma symptoms has been associated with serum leptin levels [33]. Shore et al., have demonstrated that in leptin-deficient mice the exogenous administration of leptin can increase airway hyperreactivity and the allergen-specific IgE levels in serum [34], pointing to a causal role for leptin in murine asthma. However, in humans with mild atopic asthma, inhalation allergen challenge did not acutely affect the serum leptin concentration [35]. Leptin itself did not promote smooth muscle proliferation [36], but it has been reported to increase the release of vascular endothelial growth factor (VEGF) from airway smooth muscle cells, and leptin could therefore in this way influence angiogenesis and airway remodeling [37]. Although many reports are supporting a role for leptin in asthma, some studies have not shown an association between asthma and circulating leptin levels [38]. Thus, the current knowledge on the association between leptin and asthma is still controversial and the relationship between leptin and asthma in non-obese adults is not known.

### Leptin in Diabetes mellitus

Obesity is not only influenced by the lack of leptin but also leptin resistance. Leptin has been proven to increase with increasing adiposity in humans and rodents [39]. Given that the presence of leptin reduces food intake and body weight, elevated levels of leptin in obese persons are viewed as leptin resistance [40]. In these cases, humans lack the responsiveness to the appetite-reducing effects of leptin [41]. The effects of leptin resistance are however reversible. If the fat content of obese mice is reduced, the mice will recover leptin sensitivity and glycemic control. It is believed that decreased leptin sensing in the melanocortin circuits influences the pathology of leptin resistance [42]. Research done on mice found that the diet-induced resistance to leptin occurs in stages [43]. In the first stage, in response to a high-fat diet, the mice were sensitive to exogenous leptin. The second stage conveyed reduced food consumption, increased leptin production, and central leptin sensitivity. The final stage conveyed increased food intake and reduced central leptin sensitivity [44]. The leptin resistance caused by high-fat diet results from a defect in access to sites of action in the hypothalamus, which significantly decreases the ability of peripheral leptin to activate hypothalamic signaling [45]. The resistance is also caused by an intracellular signalling defect in leptin-responsive hypothalamic neurons [46].

### Adiponectin in COPD

Some human studies have detected higher circulating adiponectin levels in male patients with COPD in comparison to controls [47]. Besides, unchanged adiponectin levels have been reported in a mixed population of female and male patients with COPD, and in this same study, adiponectin levels were higher in females than in males in both patients with COPD and healthy controls [48]. Tomoda et al., showed that plasma adiponectin levels were elevated in both normal- and underweight patients with COPD [49] and the levels further increased during an exacerbation of...
COPD [50]. In a mouse model, adiponectin has been reported to protect against the development of emphysema in animals not exposed to tobacco, and adiponectin deficiency led to increased secretion of pro-inflammatory mediators TNF-α and matrix metalloproteinase (MMP)-12 from alveolar macrophages and to an emphysema-like phenotype [51]. Furthermore, Nakashiki et al reported that the adiponectin deficiency in adiponectin knockout mice was associated not only with an emphysema-like phenotype but also with systemic inflammation and extra-pulmonary effects such as weight loss, skeletal muscle atrophy and osteoporosis [52] and they postulated that the endothelial apoptosis resulting from adiponectin deficiency could be an underlying mechanism linking COPD with the comorbidities. On the contrary, adiponectin knockout mice are protected against tobacco-induced inflammation and increased emphysema, evidence that adiponectin plays a pro-inflammatory role in the lungs of tobacco exposed wild-type mice [53]. Exposure to tobacco smoke in subjects without COPD has been reported to downregulate adiponectin expression and this was proposed to be mediated via the increased production of reactive oxygen species [54]. Furthermore, previous smoking has been found to decrease serum adiponectin levels in a dose-dependent manner [55]. However, adiponectin is highly expressed in the lungs of patients with emphysematous COPD who have stopped smoking as compared to the levels in smokers or healthy controls [56]. Recently, it was claimed that higher plasma adiponectin levels were associated with pulmonary emphysema, decreased body mass index, female sex, older age, and lower bronchial reversibility in patients with COPD [57]. These findings suggest that adiponectin is associated with COPD but virtually nothing is known about the associations of adiponectin with important clinical parameters like lung function, symptoms, or treatment responsiveness.

Adiponectin in asthma

In mice, serum adiponectin levels decrease during allergic pulmonary reactions [58], but in human asthma inhalation of the allergen does not seem to affect serum adiponectin concentrations [59]. Some human studies have revealed an association between asthma and adiponectin such that lower circulating adiponectin concentrations have been measured particularly in female asthmatics [60]. On the other hand, some other publications have detected no associations between asthma and adiponectin [61]. High serum adiponectin levels seem to reduce the risk to develop asthma in women [62], and a positive relationship has been reported between serum levels of adiponectin [63] and improved asthma control [64]. This protective effect of adiponectin against asthma in humans is consistent with the findings in mice, in which treatment with adiponectin attenuated allergic airway inflammation and airway hyperresponsiveness [65]. On the other hand, adiponectin has also been related to more severe asthma in male patients [66], i.e. adiponectin may have both anti- and pro-asthmatic effects in different patient groups.

Adiponectin in diabetes mellitus

Diabetes types 2, as well as the impaired fasting glucose (IFG), are common among the Jordanian population. The estimated age-standardized prevalence rate of (IFG) and diabetes were 7.8% and 17.1%, respectively, with no significant gender differences according to a recent study [67]. To complicate things further, there are alarming rates of obesity and its associated co-morbidities among Jordanians, especially among women [68]. This study aims to evaluate the serum levels of adiponectin in type 2 diabetic patients and to establish a correlation between adiponectin serum levels and insulin resistance in those patients. In contrast, previous studies had investigated the association of adiponectin serum levels and obesity and DM type 2.

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