

COPD and metabolic disorders: role of adiponectin

Andrea Bianco^{1,2}
 Viviana Turchiarelli^{1,2}
 Federica Fatica^{1,2}
 Ersilia Nigro³
 Gianluca Testa²
 Carolina Vitale¹
 Theodoros Thanassoulas¹
 Olga Scudiero^{3,4}
 Aurora Daniele^{3,5}

¹ Chair of Diseases of the Respiratory Apparatus, University of Molise, Campobasso, Italy

² Department of Medicine and Health Sciences, University of Molise, Campobasso, Italy

³ CEINGE - Advanced Biotechnologies 'Scarl', Napoli, Italy

⁴ Department of Biochemistry and Medical Biotechnologies, University of Napoli "Federico II", Napoli, Italy

⁵ Department of Sciences and Environmental, Biological and Pharmaceutical Technologies, II University of Napoli, Caserta, Italy

Address for correspondence:

Andrea Bianco, MD, PhD
 Department of Medicine and Health Sciences
 University of Molise
 Via de Sanctis
 86100 Campobasso, Italy
 E-mail: andrea.bianco@unimol.it

Summary

Metabolic disorders are common conditions associated to chronic obstructive pulmonary disease (COPD) contributing to lung function impairment and mortality. Evidence suggests that systemic inflammation may be the link between COPD and metabolic alterations, but this issue is still poorly investigated. This review focuses on the adipocyte-derived cytokine adiponectin which has been shown to have a role in the airway patho-physiology and therefore represents an attractive marker to link COPD and metabolic disorders.

KEY WORDS: COPD; adiponectin; metabolic disorders; inflammation.

Background

Chronic obstructive pulmonary disease (COPD) is a complex inflammatory disorder characterized by progressive airflow limitation (1). There is a growing awareness that

COPD is a lung disease with heterogeneous systemic inflammatory consequences and extrapulmonary comorbidities.

Like other complex diseases, COPD is due to a variety of processes that contribute to the onset and progression of the disease including immune response, influence of hormones and environmental factors that represent both initiators and causative agents.

Extrapulmonary comorbidities are common and significantly impact disease severity and mortality. Cardiovascular disease, hypertension, musculoskeletal disorders, lung cancer, diabetes mellitus II, and metabolic disorders are among the most prevalent and relevant, although the molecular mechanisms linking COPD and its comorbidities are still poorly understood (2).

Unexplained weight loss, changes in body composition as well as alterations in caloric intake, basal metabolic rate and intermediate metabolism are commonly reported in COPD. In parallel, a consistent number of COPD patients experience overweight and obesity, although the nature of this association remains

to be clarified (3).

A close association between metabolic syndrome biomarkers and impairment of respiratory function as been recently reported, suggesting a key role for systemic inflammation in development of both metabolic disorders and lung function impairment. In this regard, scientific interest has been recently focused on adipocyte-derived cytokines including adiponectin whose receptors have been identified on lung tissue.

Adiponectin is an adipocyte-derived cytokine whose receptors have been identified on lung tissue.

Airway epithelium, environmental factors and inflammation

Airway epithelium represents a critical site for the mechanisms involved in the complex interaction between environmental triggers, airway inflammation (4-6) and specific metabolic pathways.

In addition to environmental air pollution, smoking habit is the most relevant risk factor not only for COPD but also for many other chronic diseases. Smoking triggers a local inflammatory response throughout the whole tracheobronchial tree and pathological changes characteristic of COPD are found in the proximal large airways, peripheral small airways, lung parenchyma and pulmonary vasculature. Evidence indicates that airway inflammatory cell trafficking at epithelium level is mainly coordinated by adhesion molecules expression (7-10). The cellular pattern is quite heterogeneous, involving macrophages, neutrophils, T and B lymphocytes and mast cells. Beside these local effects, smoking may significantly contribute

to systemic inflammation, acting on the stimulation of the hematopoietic system and the consequent release of polymorphonuclear leukocytes and generation of systemic oxidative stress. These systemic effects of smoking could explain why patients with COPD often concomitantly suffer from other chronic diseases such as cardiovascular diseases or metabolic disorders with or without other risk factors such as arterial hypertension, hyperlipidemia and obesity (2). The chronicity of the inflammatory state in COPD is sustained by an increased production of several pro-inflammatory cytokines at both serum and airway levels. Indeed, C-reactive protein (CRP), fibrinogen, IL-1, TNF-, MCP-1, IL-8, IL-6 have been associated with disease progression and exacerbation (11, 12), whilst an inverse correlation between anti-inflammatory cytokine IL-10 and COPD has been demonstrated.

Inflammation and metabolic disorders

Around 50% of patients with severe COPD and chronic respiratory failure and 10 to 15% of patients with mild to moderate disease experience unexplained weight loss (13, 4).

It has been suggested that the potential causative factors of cachexia are energy imbalance, disuse atrophy of the muscles, arterial hypoxaemia and hormonal insufficiency (14). In addition, it has been reported that COPD patients present an increased basal metabolism leading to protein catabolism, resistance to anabolic hormones (insulin) and to increased levels of catabolic molecules (cortisol, glucagon and catecholamines) (15). This so called "Hypermetabolic syndrome" (HS) has the consequence of skeletal and cardiac muscle protein breakdown (16-18) and loss of fat mass contributing to a lesser extent, although body composition alterations can occur also in the absence of clinically significant weight loss (13).

Systemic inflammation has become the primary focus to link COPD and cachexia (13, 19, 20, 14) and to explain the development of COPD as a syndrome in susceptible subjects (2).

Several inflammatory markers, such as TNF-, PCR, IL-6, IL-8, Fas, Fas-L, Lipopolysaccharide Binding Protein have receiving great attention for their role in increased metabolism, weight loss and asthenia (21), although there is still no direct evidence for a cause-and-effect relationship between them (14).

Whilst weightloss has been the traditional nutritional concern in patients with COPD, a great number of COPD patients is affected by overweight and obesity, but the nature of this association remains to be clarified (3).

Clinical evidence indicates that in any given individual obesity decreases chest wall and lung compliance, reduces the diaphragm motility and increases work and oxygen cost of breathing (22, 23).

On the other side, COPD patients are at increased risk of developing obesity because of reduced level of physical activities in daily life and the repeated courses of systemic glucocorticosteroids, which cause truncal obesity as a result of glucocorticoid mediated redistribution of stored energy. (24). However, the pathophysiological interactions that occur when both COPD and obesity coexist in the same individual are still poorly understood.

It has been recently shown that the metabolic syndrome can precede reductions in lung function. The results by

Naaved et al. indicate that dyslipidemia, elevated heart rate, elevated insulin resistance and leptin levels were independent risk factors of subsequent FEV1 decline within six months of World Trade Center irritant exposure (13). However, evidence also indicates a possible protective role of obesity in COPD mortality. In mild and moderate COPD patient, the low-grade systemic inflammation associated with visceral fat accumulation contributes to develop cardiovascular complications and type 2 diabetes and may contribute to mortality; in contrast, in severe COPD obese patients mortality risk is reduced: this condition is described as "Obesity Paradox" (24, 25).

Systemic inflammation may represent a common background for abnormal adipose tissue function and lung function impairment and may provide new insight into the pathogenesis and reversibility of systemic involvement of COPD (26).

Recent studies have provided evidence for a link between adipose tissue and circulating concentrations of TNF-, IL-6, leptin and adiponectin that play a part in metabolic changes associated with COPD and reduced/impaired lung function (17).

Adiponectin as a potential target for COPD-related metabolic disorders

In physiologic condition, adipose tissue synthesizes and secretes a variety of proteins known as "adipokines" involved in several biological functions as immunity, insulin resistance, lipid and glucose metabolism, inflammation. Among the adipokines, adiponectin is a proteic hormon that structurally belongs to the complement 1q family and is found at high concentrations (~0.01% of the total protein) in serum of healthy individuals (25). Adiponectin is synthesized and secreted by adipose tissue as a 30 KDa monomer that, due to post-translational modifications, forms characteristic homomultimers. A peculiar structural feature of adiponectin is its ability to assemble into several characteristic oligomeric multimers including trimers known as low molecular weight (LMW), hexamers known as medium molecular weight (MMW), and higher-molecular weight (HMW) multimeric complexes. Growing evidences associate the oligomerization process with multiple biological activities of adiponectin.

In humans, the gene encoding adiponectin (ACDC) is located on chromosome 3q27; single-nucleotide polymorphisms (SNPs) and haplotypes in ACDC gene have been associated with obesity as well as with metabolic syndrome (MS) and CAD (26-28). Adiponectin acts through binding and activation of two receptors, AdipoR1 and AdipoR2 that are ubiquitous expressed in several organs, tissues and cell lines (29-31). In particular, it is reported that AdipoR1 is mainly implicated in the metabolic functions of adiponectin, whereas AdipoR2 is more involved in anti-inflammatory and anti stress-oxidative activities (32, 33). Downstream of these two receptors, the biological effects of adiponectin are mediated by different signal pathways involving the following molecules: AMPK, ERK, AKT and P38 (34).

Adiponectin may play a role in metabolic changes associated with COPD.

Adiponectin plays an important role in energy homeostasis, regulating both glucose and lipid metabolism. In humans, down regulation of adiponectin and its receptors are associated with obesity, metabolic syndrome, insulin resistance, hyperinsulinemia, and type 2 diabetes, as well as with cardiovascular diseases (25, 35, 36). Moreover, adiponectin seems implicated in the development and progression of several local and systemic inflammatory processes. In fact, it has been recently outlined that adiponectin could play an important role in anti-inflammatory responses in several tissues and cell cultures such as pancreatic beta cells and endothelial cells (37, 38). Mouse models of adiponectin deficiency develop lung function impairment and systemic inflammation. In fact, Summer et al. reported a protective role of adiponectin on lung through inhibition of alveolar macrophage function and vascular homeostasis regulation (39, 40). On the other hand, it was also reported that adiponectin plays an important pro-inflammatory role in experimental tobacco smoke-induced COPD (29). All these *in vitro* and *in vivo* evidences support the idea of an anti-inflammatory role of adiponectin. Furthermore, in several pathological conditions, adiponectin serum levels have been found elevated: osteoarthritis, rheumatoid

In humans, adiponectin serum levels are elevated in COPD patients but the biological effects of adiponectin on human lung are not yet fully clarified.

arthritis, lupus erythematosus, Crohn's disease, cystic fibrosis, pulmonary emphysema, myotonic dystrophy and COPD (41, 42). In all these diseases, adiponectin levels correlated with increased inflammatory cytokines (TNF- β , IL-6, IL-1 β and CRP) suggesting that adiponectin attenuates or modulates inflammation. Additionally, while the role of adiponectin in energy metabolism has been studied in several tissues, organs and cells, little is known about its role in inflammatory lung diseases.

While the role of adiponectin in energy metabolism has been widely studied, little is known about its role in inflammatory processes of lung (25). Different studies indicate that adiponectin can exert pro-inflammatory rather than anti-inflammatory lung properties. Recent data have revealed an anti-inflammatory role in the lung: mice lacking adiponectin spontaneously develops a COPD-like phenotype with extrapulmonary effects, including systemic inflammation, body weight loss and osteoporosis. This finding highlights the key role of adiponectin in lung pathologies and the novel link between COPD and metabolic disorders (43, 44). In humans, adiponectin serum levels are elevated in COPD patients but the biological effects of adiponectin and of its oligomers on human lung and even less in lung diseases are not fully clear (42). In fact, it is known that low levels of total adiponectin are present in smokers without COPD, while high levels are observed in COPD patients (45-47). Recently, different studies showed that total serum levels of adiponectin represent a significant diagnostic and prognostic marker of COPD. Recently, it has demonstrated that the oligomerization pattern of adiponectin is altered in COPD; in particular the higher levels of adiponectin are associated with a specific increase of HMW, the

most biologically active isoforms (42). Protective anti-inflammatory role of HMW oligomers has been demonstrated both *in vivo* and *in vitro* studies (48). Pajavani reported that HMW oligomers improve insulin sensitivity, suppress apoptosis in endothelial cells, and their levels are inversely correlated to cardiovascular events and to the severity of coronary artery disease (49). Furthermore, *in vitro* evidences indicate that HMW oligomers are also involved in TNF- suppression. Daniele et al. found no detectable TNF- values in normal subjects and in COPD patients suggesting that the high levels of adiponectin and HMW could be involved in reducing the increase of circulating levels of this pro-inflammatory cytokine. As COPD is a disease characterized by inflammatory process and impairment of endothelial functions, the high levels of HMW found in this study may exert a protective role on both pathogenic mechanisms. These observations suggest that total levels of adiponectin and HMW oligomers can be considered useful complementary criteria to improve prognostic and therapeutic strategies for lung diseases (42).

The specific biological role of adiponectin in lung functions derives also from the observation that both AdipoRs are expressed in COPD and tumour lung (29, 50). Petridou et al. reported the presence of AdipoR1 and AdipoR2 in cancerous lungs and the association of AdipoR2 expression with the progression of lung cancer, while Miller et al. showed that only AdipoR1 was expressed in healthy and COPD lungs (29, 50).

A recent study demonstrated the expression of AdipoR1 and AdipoR2 at mRNA level as well as at protein level in lung tissues from COPD and from non small cell lung cancer (NSCLC) with a AdipoR1 expression higher than AdipoR2 in COPD suggesting a specific signaling pathway of adiponectin in this disease (42). The downregulation of AdipoR2 could be responsible for the worsening of inflammation state in COPD and related to lung NSCLS cancer. Accordingly, it was reported that AdipoR2 signaling pathway is mainly involved in adiponectin inhibition effects on inflammation and oxidative stress (32). Furthermore, epidemiologic as well as *in vitro* studies have associated adiponectin and AdipoRs with several malignancies (51). In fact, adiponectin has been shown to suppress tumor growth in mice and cell growth in various cell lines (52, 53). In contrast, adiponectin stimulated colonic epithelial cell proliferation and breast carcinoma cell lines (54, 55). Besides, because serum adiponectin is not significantly influenced by smoking status, it is a very promising biomarker of cardiovascular outcomes in COPD (56).

The adiponectin concentration and oligomeric isoform distribution, and the modulation of receptors add complexity to adiponectin system.

Conclusions

New insight into mechanisms underlying systemic inflammatory consequences and extrapulmonary comorbidities in COPD will contribute to identification of potential targets for new diagnostic and therapeutic approaches. Adiponectin appears to be an attractive biomarker in COPD and represents a promising disease indicator with implications for the treatment of COPD.

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