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Adiponectin is associated with dynamic hyperinflation and a favourable response to inhaled glucocorticoids in patients with COPD

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Summary
Objectives: Adipokines are protein mediators first described as products of adipose tissue regulating energy metabolism and appetite. Recently, adipokines have also been found to modulate inflammation and smooth muscle cell responses. Therefore we investigated the association of two adipokines, adiponectin and leptin, with the degree of emphysema, pulmonary function, symptoms and glucocorticoid responsiveness in patients with COPD.
Methods: Plasma adiponectin and leptin levels, spirometry, body plethysmography and symptoms were measured in 43 male COPD patients with smoking history $\geq$ 20 pack-years, post bronchodilator $FEV_1/FVC < 0.7$ and pulmonary emphysema on HRCT. The measurements were repeated in a subgroup of patients after 4 weeks' treatment with inhaled fluticasone.
Results: In patients with COPD, plasma adiponectin levels correlated positively with airway resistance (Raw) ($r = 0.362$, $p = 0.019$) and functional residual capacity (FRC) ($r = 0.355$, $p = 0.046$). Furthermore, the baseline adiponectin concentration correlated negatively with

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the fluticasone induced changes in St George's Respiratory questionnaire (SGRQ) symptom score ($r = -0.413$, $p = 0.040$) and in FRC % pred ($r = -0.428$, $p = 0.003$), i.e. a higher baseline plasma adiponectin level was associated with more pronounced alleviation of symptoms and dynamic hyperinflation. Plasma leptin levels were not related to the measures of lung function, symptoms or glucocorticoid responsiveness.

Conclusions: Plasma adiponectin levels were associated with peripheral airway obstruction and dynamic hyperinflation in patients with COPD. A higher adiponectin level predicted more favourable relief of symptoms and hyperinflation during glucocorticoid treatment. Adiponectin may have a role in the COPD pathogenesis; it may also be a biomarker of disease severity and treatment responses in this disease.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a persistent airflow limitation with extrapulmonary manifestations [1]. Inflammatory activity is present not only in the lungs [2], but there is also a low-grade systemic inflammation [3] associated with the development of the comorbidities of COPD such as ischaemic heart disease, osteoporosis, diabetes, cachexia and depression [4–6]. It is uncertain whether the systemic inflammation in COPD is a spillover of the inflammation present in the lungs or if pulmonary manifestations are only one form of expression of this systemic disease [5].

It is known that a subset of patients with COPD benefits from inhaled glucocorticoid (GC) therapy, and GCs have been shown to reduce the markers of systemic inflammation in COPD [7]. Unfortunately, current measurements of lung function or pulmonary imaging cannot distinguish the steroid responders from the non-responders, and therefore novel systemic or local markers for steroid-sensitive phenotype of COPD are critically needed.

Adipose tissue releases a variety of factors, also called adipokines, which regulate energy metabolism and appetite and, based on the recent studies, also inflammatory responses [8]. The two best characterized adipokines are adiponectin and leptin. Adiponectin improves insulin sensitivity and, accordingly, plasma adiponectin levels are decreased in obese individuals, especially in those with the metabolic syndrome, type 2 diabetes and atherosclerosis [9]. Adiponectin acts through two specific receptors (AdipoR1 and AdipoR2) and exerts a variety of anti-inflammatory effects [10,11]. On the other hand, adiponectin has also reported to enhance the production of pro-inflammatory cytokines in airway epithelium [12] and to mediate pro-inflammatory and tissue matrix degrading effects in arthritis [13–15].

Discovered in 1994 leptin is another important adipokine [16]. Leptin controls appetite through its regulatory effects in the central nervous system, and it has also a significant role as an effector and regulator in inflammatory responses [17]. Leptin increases the production of many pro-inflammatory mediators and tissue matrix degrading enzymes, and supports the Th1-type immune response [18–20]. Circulating leptin levels directly correlate with the amount of body fat [21] and leptin is linked to several obesity associated inflammatory conditions like cardiovascular [22] and rheumatic diseases [14].

Both adiponectin and leptin are produced in the human lung [12,23,24]. There is recent experimental data indicating that they may also play a role in asthma and COPD by modulating the inflammatory responses [25] and airway smooth muscle cell functions [26]. Adipokines have also been reported to be associated with fibrosing lung diseases [27,28]. Furthermore, adipose-tissue related inflammation has been proposed to represent a link connecting pulmonary damage with the systemic inflammation in COPD [3] but the mechanisms remain poorly understood.

1Since adiponectin and leptin both seem to be involved in the regulation of inflammation and smooth muscle function as well as in the tissue matrix destruction, we hypothesized that they may play a role in COPD. Therefore, we investigated if plasma levels of adiponectin and leptin would be associated with the degree of obstruction, hyperinflation and emphysema, with other markers of inflammation, with the degree of symptoms and/or with the response to inhaled glucocorticoids in patients with COPD.

Methods

Subjects and study design

We recruited forty-three steroid-naïve male patients with COPD among subjects referred from primary care for diagnostic assessment to the Department of Respiratory Medicine at Tampere University Hospital. COPD diagnosis was based on GOLD strategy paper [1] and the inclusion criteria were smoking history of at least 20 pack-years, symptoms of COPD (cough, sputum production and dyspnoea), post bronchodilator $FEV_1/FVC < 0.7$, reversibility of FVC or FEV_1 induced by β_2-agonist $< 12\%$ and 200 ml and pulmonary emphysema visible on high-resolution computed tomography (HRCT) of the lungs. None of the subjects had a diagnosis or a clinical history of asthma. Forty-one age-matched non-smoking healthy males with normal lung function served as controls.

Spirometry and body plethysmography were measured, high-resolution computed tomography (HRCT) of the lungs was performed and symptoms were scored with the St George's Respiratory Questionnaire (SGRQ) in patients with COPD. A venous blood sample was drawn in both groups. The same measurements excluding HRCT were repeated in

twenty-seven patients with COPD after 4 weeks of treatment with inhaled fluticasone propionate (Flixotide Diskus 500 μg b.i.d.; GlaxoSmithKline, Ware, UK).

Adipokines and inflammatory markers

Plasma concentrations of adiponectin, leptin, myeloperoxidase (MPO), interleukin 6 (IL-6) and matrix metalloproteinase 9 (MMP-9) were determined by enzymeimmunoassay by using the following reagents: adiponectin, leptin and MMP-9: R&D Systems Europe Ltd, Abingdon, UK; MPO: Hycult Biotechnology, Uden, Netherlands; and IL-6: Sanquin, Amsterdam, Netherlands. The detection limits and inter-assay coefficients of variation, were 31.3 pg/ml and 6.7% for adiponectin, 15.6 pg/ml and 4.5% for leptin, 0.4 ng/ml and 8.7% for MPO, 0.3 pg/ml and 7.6% for IL-6, and 7.8 pg/ml and 6.0% for MMP-9.

Lung function and HRCT

Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were measured with the Vmax 20 C spirometer (Sensor-Medics, Yorba Linda, CA, USA) before and after 400 μg of inhaled salbutamol. Airway resistance (Raw) and functional residual capacity (FRC) were measured with Autobox 6200 body plethysmography (Sensor-Medics, Yorba Linda, CA, USA).

In the HRCT examinations (Siemens Somatom Plus 4, Siemens Medical, Erlangen, Germany), a section thickness of 1 mm was used with a 10-mm inter-slice spacing at 140 kV and 206 mA s. The subjects were lying in the supine position and performing full inspiration. The HRCT images were scored according to a consensus by two experienced thoracic radiologists (RJ and LK) blinded to the medical information of the patients.

The extent of emphysema was estimated visually to the nearest 5% on each image section excluding the two most cranial and caudal images, as described by Desai and colleagues [29]. The mean value of emphysema percent on all image sections was taken as the final emphysema score for each subject. In the evaluation of the airway wall thickness, the external diameter (D) and the luminal diameter (L) of the right upper lobe bronchus were measured in each subject. Only images showing the bronchus as a cross-section without an angle were selected. Airway wall thickness (T) was calculated as $(D-L)/2$. The thickness-to-diameter ratio (TDR) and the percentage wall area (PWA) were calculated as $\mathrm{TDR} = T/D$, and $\mathrm{PWA} = (D/2)^2\pi - (L/2)^2\pi/(D/2)^2\pi \times 100\%$ [30]. TDR and PWA were used in statistical analysis.

Symptom scoring

The subjects filled in the Finnish translation of the St George's Respiratory Questionnaire (SGRQ) containing questions and scoring on three aspects of the disease (symptom frequency and severity, activities that cause or are limited by breathlessness, and the impact of the disease on social functioning including psychological disturbances resulting from the disease) to obtain a total score. The scale has a range from 0 to 100, with higher scores representing more severe disease.

Statistics

The distributions of both adiponectin and leptin levels were skewed but they became normal after log-transformation, which was used in the statistical analyses. t-Test was used to examine differences between healthy controls and patients with COPD. To test if adiponectin or leptin correlate with markers of disease severity, partial correlation controlling for body mass index (BMI) was used as both log-adiponectin and log-leptin correlated with BMI. Changes in plasma levels of adipokines and other measures during fluticasone treatment were analyzed with paired t-test. The results are presented as mean ± SEM. A p-value < 0.05 was considered as significant. SPSS 19 software (SPSS Inc., Chicago, Illinois, USA) was used in the statistical analysis.

Ethics

The study was approved by the ethics committee of Tampere University Hospital, Tampere, Finland and complies with the declaration of Helsinki. All subjects provided their written informed consent.

Results

The subject characteristics are shown in Table 1. There were no differences with respect to the age or BMI between the patients with COPD and the controls but, as expected, plasma MMP-9 levels were higher in those individuals with emphysematous COPD. The adiponectin level correlated negatively with BMI ($r = -0.588$, $p < 0.001$), while there was a positive correlation between leptin concentration and BMI ($r = 0.700$, $p < 0.001$), as expected. There were no statistically significant differences in plasma adiponectin

Table 1 Characteristics of the subjects.

	COPD	Controls	p-Value
N	43	41	
Age (yrs)	59.5 ± 1.2	62.5 ± 1.0	0.057
BMI (kg/m^2)	25.8 ± 0.6	26.7 ± 0.6	0.332
FEV_1 (% pred)	53 ± 2	[a]	—
Raw (% pred)	213 ± 14	N.A.	—
FRC (% pred)	123 ± 5	N.A.	—
TLC (% pred)	108 ± 2	N.A.	—
MPO (ng/ml)	158.9 ± 11.6	139.6 ± 4.9	0.131
IL-6 (pg/ml)	1.5 ± 0.2	1.5 ± 0.2	0.888
MMP-9 (ng/ml)	40.6 ± 2.7	33.9 ± 2.0	0.048
Adiponectin[b] (ng/ml)	3034 ± 328	2538 ± 191	0.210
Leptin[b] (ng/ml)	7.5 ± 0.9	7.1 ± 1.0	0.703

Values are presented as mean ± SEM.
N.A., not analyzed.
BMI, body mass index; FEV_1, forced expiratory volume in 1 s; Raw, airway resistance; FRC, functional residual capacity; TLC, total lung capacity; MPO, myeloperoxidase; IL-6, interleukin 6; MMP-9, matrix metalloproteinase 9.
[a] Normal in every subject.
[b] Because distributions of adiponectin and leptin were skewed, log-transformed values were used in the statistical analysis.

and leptin levels between COPD patients and healthy controls, or between ex-smokers ($n = 10$) and current smokers ($n = 33$) in the COPD group.

In the COPD patients, body plethysmography was carried out to evaluate small airway obstruction (measured as airway resistance, Raw) and dynamic hyperinflation (measured as functional residual capacity, FRC). Interestingly, adiponectin levels correlated positively with airway resistance (Raw % predicted, $r = 0.362$, $p = 0.019$, Table 2) and functional residual capacity (FRC % predicted, $r = 0.355$, $p = 0.046$, Table 2), i.e. high plasma adiponectin concentrations were associated with peripheral obstruction and hyperinflation. Neither adiponectin nor leptin levels correlated with FEV_1 or FEV_1/FVC, with the inflammatory markers measured in plasma, with the degree of emphysema or airway wall thickness on HRCT or with SGRQ scores at baseline.

The effect of 4 weeks' fluticasone treatment on the adipokine levels and other parameters are shown in Table 3. St George's Respiratory Questionnaire (SGRQ) total and symptom scores decreased and leptin levels increased during the treatment, but there were no other significant changes. Interestingly, the baseline adiponectin level correlated negatively with fluticasone induced changes in SGRQ total score ($r = -0.410$, $p = 0.042$), SGRQ symptom score ($r = -0.413$, $p = 0.040$) and FRC % predicted ($r = -0.428$, $p = 0.003$), indicating that high baseline adiponectin level was associated with favourable relief of symptoms and hyperinflation in response to fluticasone treatment.

Discussion

The main findings of the present study were that high plasma adiponectin levels were associated with obstruction in peripheral airways and predicted a favourable effect of inhaled fluticasone treatment on both symptoms and dynamic hyperinflation in patients with COPD. This indicates that adiponectin may have a role in the pathogenesis of COPD and in addition, it may serve as a biomarker of disease severity.

Originally, adipose-tissue derived adipokines were found to regulate energy metabolism and be associated with the chronic low-grade inflammation present in obesity-related metabolic disturbances and inflammatory diseases [11,31]. More recently, adiponectin and leptin have also been linked with inflammatory lung diseases like asthma and COPD [25]. The majority of the studies have hinted that high circulating leptin and low adiponectin levels seem to be associated with asthma independently of the presence of obesity [25,32]. Accordingly, we have recently found that increased leptin levels were associated with more severe asthma also in non-obese patients [33]. The data on adiponectin and leptin levels in human COPD are less conclusive [25]. Breyer et al. hypothesized that adipokine metabolism is altered in patients suffering from COPD, particularly in women [34]. Some human studies have demonstrated higher plasma or serum adiponectin concentrations also in male patients with COPD when they are compared to healthy controls [34–37]. Carolan et al. found increased levels of adiponectin especially in subjects with very severe COPD [38]. In the present study, the mean adiponectin level was somewhat higher in COPD patients than in healthy controls although the difference was not statistically significant. There was variation in the adiponectin levels in COPD patients, and interestingly, higher adiponectin levels were associated with more severe airway obstruction and hyperinflation in patients with COPD.

It is thought that there are many causes for the airway obstruction in COPD such as mucosal oedema, contraction of the airway smooth muscle, small airway fibrosis and loss of

Table 2 BMI-adjusted partial correlations between adiponectin and leptin and other parameters in COPD patients ($n = 43$).

	Adiponectin[a]	Leptin[a]
FEV_1 (% pred)	$r = 0.058$	$r = 0.000$
	$p = 0.717$	$p = 0.999$
Raw (% pred)	$r = 0.362$	$r = -0.089$
	$p = 0.019$	$p = 0.576$
FRC (% pred)	$r = 0.355$	$r = -0.225$
	$p = 0.046$	$p = 0.216$
Emphysema percentage (%)	$r = 0.208$	$r = -0.217$
	$p = 0.186$	$p = 0.167$
MPO	$r = 0.117$	$r = 0.160$
	$p = 0.483$	$p = 0.338$
IL-6	$r = -0.012$	$r = 0.172$
	$p = 0.942$	$p = 0.276$
MMP-9	$r = -0.121$	$r = 0.029$
	$p = 0.463$	$p = 0.860$

FEV_1, forced expiratory volume in 1 s; Raw, airway resistance; FRC, functional residual capacity; MPO, myeloperoxidase; IL-6, interleukin 6; MMP-9, matrix metalloproteinase 9.
Statistically significant p-values ($p < 0.05$) are bolded.
[a] Because distributions of adiponectin and leptin were skewed, log-transformed values were used in the statistical analysis.

Table 3 Adipokines and other parameters before and after fluticasone treatment in COPD patients.

	Before treatment	After treatment	p-Value
Adiponectin[a] (ng/ml)	3594 ± 486	3460 ± 457	0.598
Leptin[a] (ng/ml)	6.0 ± 1.0	7.1 ± 1.2	**0.018**
FEV_1 (% pred)	53 ± 3	56 ± 3	0.288
Raw (% pred)	214 ± 19	210 ± 16	0.656
FRC (% pred)	123 ± 6	121 ± 6	0.467
MPO (ng/ml)	166 ± 16	171 ± 17	0.768
IL-6 (pg/ml)	1.62 ± 0.29	1.67 ± 0.26	0.747
MMP-9 (ng/ml)	39.1 ± 3.5	44.9 ± 4.2	0.268
SGRQ total score	36.4 ± 3.1	30.8 ± 3.1	**0.015**
SGRQ symptom score	55.2 ± 4.3	38.0 ± 4.5	**<0.001**

Values are presented as mean ± SEM, $n = 27$.
FEV_1, forced expiratory volume in 1 s; Raw, airway resistance; FRC, functional residual capacity; MPO, myeloperoxidase; IL-6, interleukin 6; MMP-9, matrix metalloproteinase 9; SGRQ, St George's Respiratory Questionnaire.
Statistically significant p-values ($p < 0.05$) are bolded.
[a] Because distributions of adiponectin and leptin were skewed, log-transformed values were used in the statistical analysis.

parenchymal support to small airways due to emphysema [2]. In the present study, we observed that plasma adiponectin levels correlated with Raw and FRC but not with FEV_1 and FEV_1/FVC. This is interesting, as FEV_1 and FEV_1/FVC are mostly reflecting obstruction in the larger airways and these parameters are not very sensitive to changes occurring in the small airways. Furthermore, in cases of severe small airway obstruction and airway closure during exhalation causing dynamic hyperinflation, FCV reductions in addition to FEV_1 and the ratio FEV_1/FVC may not reflect the severity of small airway obstruction. Raw is a more sensitive measure of small airway obstruction than FEV_1 or FEV_1/FVC, and FRC is believed to be a good marker of dynamic hyperinflation in COPD [39]. Thus, our results suggest that adiponectin may be more closely related to peripheral than central airway obstruction in COPD. This is in line with the earlier results of Tomoda and colleagues who reported that the plasma adiponectin level correlated with hyperinflation but not with FEV_1 in their sample of COPD patients [35].

The relation between adiponectin levels in plasma and small airway obstruction suggests that adiponectin may be a marker or even a mediator of parenchymal inflammation and the tissue destruction present in emphysematous COPD, which then leads to small airway obstruction and hyperinflation. Our results are supported by the data in a cohort of COPDGene study, in which Carolan et al. found an association between plasma adiponectin and CT-assessed emphysema in patients with COPD [38]. Interestingly, the degenerative cartilage changes seen in (osteo)arthritis seem to display similarities with tissue matrix degrading events leading to pulmonary emphysema in COPD. Adiponectin has been reported to contribute to cartilage matrix destruction in arthritis by inducing the production of the same pro-inflammatory cytokines and degrading metalloproteinase enzymes that are also involved in COPD and emphysema [2,14]. In addition, adiponectin may have a direct effect on airway function, as human airway smooth muscle cells express adiponectin receptors [26] and adiponectin is known to increase contractility in smooth muscle cells [40]. Thus, it may be that increased levels of circulating adiponectin enhance the contractility of airway smooth muscle and are involved in inducing the airway obstruction, and also contribute to the inflammation and tissue destruction which is evident in COPD.

We also found that high baseline levels of adiponectin predicted good symptom relief and alleviation of hyperinflation in response to inhaled fluticasone treatment. This finding also indicates that there is a relationship between lung inflammation and the circulating adiponectin levels and further suggests that adiponectin is related to the steroid-sensitive phenotype in COPD. On the other hand, specific inhibition of the adiponectin induced smooth muscle contraction might be one of the mechanisms through which glucocorticoids act to alleviate small airway obstruction and the symptoms in COPD. This is supported by the fact that glucocorticoids can inhibit the expression of adiponectin receptors (AdipoR1 and AdipoR2) as shown in rat [41] and human muscle cells [42]. Therefore it may be that the contractile effect of adiponectin on airway smooth muscle is alleviated if adiponectin receptor density is reduced during glucocorticoid treatment. In addition, glucocorticoids have been shown to decrease adiponectin expression under some conditions [41] and this might also be a potential mechanism linking adiponectin and the response to steroid treatment. However, most of the studies [43—45] have reported that glucocorticoids, delivered either orally or by inhalation, do not alter plasma levels of adiponectin. This is in line with our present finding that fluticasone treatment had no effect on the circulating adiponectin concentrations.

Based on data from animal studies, adiponectin has also been proposed to exert a protective role against emphysema, as adiponectin deficiency has been reported to lead to increased levels of two pro-inflammatory mediators, TNF-α and MMP-12, and to an emphysema-like phenotype in the mouse lung [46,47]. In addition, exposure to tobacco smoke has been reported to reduce the expression of adiponectin in both mice [48] and humans [12], but adiponectin is highly expressed in the lungs of patients with the emphysematous form of COPD [12]. However, we observed no correlation between the degree of emphysema on HRCT and plasma levels of adiponectin in these subjects with emphysematous COPD. Furthermore, there was no difference in plasma levels of adiponectin between healthy nonsmoking controls and patients with emphysematous COPD. This is in line with the results of the large ECLIPSE study [49], although there are also reports of increased serum levels of adiponectin in COPD [34—38].

We detected no difference in plasma levels of leptin between controls and subjects with emphysematous COPD. Previous data on leptin is controversial, as some studies have shown increased [50], others decreased [51,52] and some unchanged [34,36] circulating leptin levels in patients with COPD. These differences are most likely attributable to the heterogeneity of the COPD patient populations and, may also be affected by the gender-dependent differences in adipokine metabolism. As in the present study, Kirdar et al. found no significant differences in plasma leptin levels between male patients with stable COPD and healthy controls [36]. In the study of Breyer et al., leptin levels did not differ between subjects with COPD and healthy controls, but in both groups, the leptin levels were higher in females than in males [34]. In addition, leptin levels correlated with CRP, IL-6 and fibrinogen only in females but not in males with COPD [34]. This is evidence of an important gender-related difference in leptin metabolism and it may be explained by different proportions of adipose tissue of the body composition and possibly also partly by an interesting finding indicating that androgens can inhibit leptin secretion whereas it is stimulated by oestradiol [53].

Leptin may also be associated with some features or comorbidities of COPD. In fact, alterations in leptin levels are often associated with COPD exacerbations [54,55]. Leptin has been shown to stimulate the production of vascular endothelial growth factor (VEGF) in human airway smooth muscle in vitro and leptin could therefore affect angiogenesis and promote airway remodelling in COPD [26]. On the other hand, leptin does not evoke contractile responses in human airway smooth muscle cells [56], and this is in line with our findings that the leptin level did not correlate with the markers of airway obstruction. Interestingly, we found that treatment with inhaled fluticasone increased plasma levels of leptin in the COPD patients. Glucocorticoids have been reported to stimulate leptin

expression in adipose tissue [57] and to increase plasma leptin levels in patients with polymyalgia rheumatica [58]. This may be attributable to a direct effect of glucocorticoids on leptin gene expression, as the glucocorticoid responsive element (GRE) has been identified in the leptin gene promoter [59].

In the present study, high plasma levels of adiponectin were associated with peripheral airway obstruction and dynamic hyperinflation in patients with COPD. Furthermore, higher plasma levels of adiponectin also predicted more favourable relief of symptoms and hyperinflation during glucocorticoid treatment, supporting the experimental data that adiponectin is a pro-inflammatory mediator able to induce tissue matrix degradation and to evoke smooth muscle contraction. However, further studies will be needed to confirm the role of adiponectin in the pathogenesis of COPD and whether it is useful as a marker of the steroid-sensitive phenotype in this disease.

Conflict of interest

The authors declare that there are no conflicts of interest.

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References

[1] Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007;176:532—55.
[2] Barnes PJ, Shapiro SD, Pauwels RA. Chronic obstructive pulmonary disease: molecular and cellular mechanisms. Eur Respir J 2003;22:672—88.
[3] Wouters EF, Reynaert NL, Dentener MA, Vernooy JH. Systemic and local inflammation in asthma and chronic obstructive pulmonary disease: is there a connection? Proc Am Thoracic Soc 2009;6:638—47.
[4] Agusti AG, Noguera A, Sauleda J, Sala E, Pons J, Busquets X. Systemic effects of chronic obstructive pulmonary disease. Eur Respir J 2003;21:347—60.
[5] Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? Lancet 2007;370:797—9.
[6] Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J 2009;33:1165—85.
[7] Sin DD, Lacy P, York E, Man SF. Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004;170:760—5.
[8] Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol 2005;115:911—9.
[9] Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 1999; 257:79—83.
[10] Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, et al. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature 2003;423:762—9.
[11] Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006;6:772—83.
[12] Miller M, Cho JY, Pham A, Ramsdell J, Broide DH. Adiponectin and functional adiponectin receptor 1 are expressed by airway epithelial cells in chronic obstructive pulmonary disease. J Immunol 2009;182:684—91.
[13] Lago R, Gomez R, Otero M, Lago F, Gallego R, Dieguez C, et al. A new player in cartilage homeostasis: adiponectin induces nitric oxide synthase type II and pro-inflammatory cytokines in chondrocytes. Osteoarthr Cartil 2008;16:1101—9.
[14] Gomez R, Conde J, Scotece M, Gomez-Reino JJ, Lago F, Gualillo O. What's new in our understanding of the role of adipokines in rheumatic diseases? Nat Rev Rheumatol 2011;7:528—36.
[15] Koskinen A, Juslin S, Nieminen R, Moilanen T, Vuolteenaho K, Moilanen E. Adiponectin associates with markers of cartilage degradation in osteoarthritis and induces production of proinflammatory and catabolic factors through mitogen-activated protein kinase pathways. Arthritis Res Ther 2011;13:R184.
[16] Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994;372:425—32.
[17] Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol 2011; 11:85—97.
[18] Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, Lechler RI. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. Nature 1998;394:897—901.
[19] Santos-Alvarez J, Goberna R, Sanchez-Margalet V. Human leptin stimulates proliferation and activation of human circulating monocytes. Cell Immunol 1999;194:6—11.
[20] Koskinen A, Vuolteenaho K, Nieminen R, Moilanen T, Moilanen E. Leptin enhances MMP-1, MMP-3 and MMP-13 production in human osteoarthritic cartilage and correlates with MMP-1 and MMP-3 in synovial fluid from OA patients. Clin Exp Rheumatol 2011;29:57—64.
[21] Maffei M, Fei H, Lee GH, Dani C, Leroy P, Zhang Y, et al. Increased expression in adipocytes of ob RNA in mice with lesions of the hypothalamus and with mutations at the db locus. Proc Natl Acad Sci U S A 1995;92:6957—60.
[22] Scotece M, Conde J, Gomez R, Lopez V, Pino J, Gonzalez A, et al. Role of adipokines in atherosclerosis: interferences with cardiovascular complications in rheumatic diseases. Mediators Inflamm 2012;2012:125458.
[23] Bruno A, Chanez P, Chiappara G, Siena L, Giammanco S, Gjomarkaj M, et al. Does leptin play a cytokine-like role within the airways of COPD patients? Eur Respir J 2005; 26:398—405.
[24] Vernooy JH, Drummen NE, van Suylen RJ, Cloots RH, Moller GM, Bracke KR, et al. Enhanced pulmonary leptin expression in patients with severe COPD and asymptomatic smokers. Thorax 2009;64:26—32.
[25] Ali Assad N, Sood A. Leptin, adiponectin and pulmonary diseases. Biochimie 2012;94:2180—9.
[26] Shin JH, Kim JH, Lee WY, Shim JY. The expression of adiponectin receptors and the effects of adiponectin and leptin on airway smooth muscle cells. Yonsei Med J 2008;49:804—10.
[27] Leivo-Korpela S, Lehtimaki L, Nieminen R, Oksa P, Vierikko T, Jarvenpaa R, et al. Adipokine adipsin is associated with the degree of lung fibrosis in asbestos-exposed workers. Respir Med 2012;106:1435—40.

[28] Sauni R, Oksa P, Lehtimaki L, Toivio P, Palmroos P, Nieminen R, et al. Increased alveolar nitric oxide and systemic inflammation markers in silica-exposed workers. Occup Environ Med 2012;69:256—60.
[29] Desai SR, Hansell DM, Walker A, MacDonald SL, Chabat F, Wells AU. Quantification of emphysema: a composite physiologic index derived from CT estimation of disease extent. Eur Radiol 2007;17:911—8.
[30] Orlandi I, Moroni C, Camiciottoli G, Bartolucci M, Pistolesi M, Villari N, et al. Chronic obstructive pulmonary disease: thin-section CT measurement of airway wall thickness and lung attenuation. Radiology 2005;234:604—10.
[31] Conde J, Scotece M, Gomez R, Lopez V, Gomez-Reino JJ, Lago F, et al. Adipokines: biofactors from white adipose tissue. A complex hub among inflammation, metabolism, and immunity. Biofactors 2011;37:413—20.
[32] Sood A. Obesity, adipokines, and lung disease. J Appl Physiol 2010;108:744—53.
[33] Leivo-Korpela S, Lehtimäki L, Vuolteenaho K, Nieminen R, Kankaanranta H, Saarelainen S, et al. Adipokine resistin predicts anti-inflammatory effect of glucocorticoids in asthma. J Inflamm (Lond) 2011;8:12.
[34] Breyer MK, Rutten EP, Locantore NW, Watkins ML, Miller BE, Wouters EF. ECLIPSE investigators (evaluation of COPD longitudinally to identify predictive surrogate endpoints). Dysregulated adipokine metabolism in chronic obstructive pulmonary disease. Eur J Clin Investig 2012;42:983—91.
[35] Tomoda K, Yoshikawa M, Itoh T, Tamaki S, Fukuoka A, Komeda K, et al. Elevated circulating plasma adiponectin in underweight patients with COPD. Chest 2007;132:135—40.
[36] Kirdar S, Serter M, Ceylan E, Sener AG, Kavak T, Karadag F. Adiponectin as a biomarker of systemic inflammatory response in smoker patients with stable and exacerbation phases of chronic obstructive pulmonary disease. Scand J Clin Lab Investig 2009;69:219—24.
[37] Chan KH, Yeung SC, Yao TJ, Ip MS, Cheung AH, Chan-Yeung MM, et al. Elevated plasma adiponectin levels in patients with chronic obstructive pulmonary disease. Int J Tuberc Lung Dis 2010;14:1193—200.
[38] Carolan BJ, Kim YI, Williams AA, Kechris K, Lutz S, Reisdorph N, et al. The association of adiponectin with CT phenotypes in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013.
[39] Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26:948—68.
[40] Ding M, Carrao AC, Wagner RJ, Xie Y, Jin Y, Rzucidlo EM, et al. Vascular smooth muscle cell-derived adiponectin: a paracrine regulator of contractile phenotype. J Mol Cell Cardiol 2012;52:474—84.
[41] de Oliveira C, de Mattos AB, Biz C, Oyama LM, Ribeiro EB, do Nascimento CM. High-fat diet and glucocorticoid treatment cause hyperglycemia associated with adiponectin receptor alterations. Lipids Health Dis 2011;10:11.
[42] Jang C, Inder WJ, Obeyesekere VR, Alford FP. Adiponectin, skeletal muscle adiponectin receptor expression and insulin resistance following dexamethasone. Clin Endocrinol (Oxf) 2008;69:745—50.
[43] Lewandowski KC, Szosland K, Lewinski A. Short-term dexamethasone administration does not alter serum adiponectin or resistin concentrations in overweight and obese subjects despite an increase in insulin resistance. Clin Endocrinol (Oxf) 2006;65:551—2.
[44] Patel JV, Cummings DE, Girod JP, Mascarenhas AV, Hughes EA, Gupta M, et al. Role of metabolically active hormones in the insulin resistance associated with short-term glucocorticoid treatment. J Negat Results Biomed 2006;5:14.
[45] Man SF, Xuekui Z, Vessey R, Walker T, Lee K, Park D, et al. The effects of inhaled and oral corticosteroids on serum inflammatory biomarkers in COPD: an exploratory study. Therap Adv Respir Dis 2009;3:73—80.
[46] Summer R, Little FF, Ouchi N, Takemura Y, Aprahamian T, Dwyer D, et al. Alveolar macrophage activation and an emphysema-like phenotype in adiponectin-deficient mice. Am J Physiol Lung Cell Mol Physiol 2008;294:1035—42.
[47] Nakanishi K, Takeda Y, Tetsumoto S, Iwasaki T, Tsujino K, Kuhara H, et al. Involvement of endothelial apoptosis underlying chronic obstructive pulmonary disease-like phenotype in adiponectin-null mice: implications for therapy. Am J Respir Crit Care Med 2011;183:1164—75.
[48] Miller M, Pham A, Cho JY, Rosenthal P, Broide DH. Adiponectin-deficient mice are protected against tobacco-induced inflammation and increased emphysema. Am J Physiol Lung Cell Mol Physiol 2010;299:834—42.
[49] Dickens JA, Miller BE, Edwards LD, Silverman EK, Lomas DA, Tal-Singer R. Evaluation of COPD longitudinally to identify surrogate endpoints (ECLIPSE) study investigators. COPD association and repeatability of blood biomarkers in the ECLIPSE cohort. Respir Res 2011;12:146.
[50] Breyer MK, Rutten EP, Vernooy JH, Spruit MA, Dentener MA, van der Kallen C, et al. Gender differences in the adipose secretome system in chronic obstructive pulmonary disease (COPD): a pivotal role of leptin. Respir Med 2011;105:1046—53.
[51] Takabatake N, Nakamura H, Abe S, Hino T, Saito H, Yuki H, et al. Circulating leptin in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159:1215—9.
[52] Eker S, Ayaz L, Tamer L, Ulubas B. Leptin, visfatin, insulin resistance, and body composition change in chronic obstructive pulmonary disease. Scand J Clin Lab Investig 2010;70:40—4.
[53] Machinal-Quelin F, Dieudonne MN, Pecquery R, Leneveu MC, Giudicelli Y. Direct in vitro effects of androgens and estrogens on ob gene expression and leptin secretion in human adipose tissue. Endocrine 2002;18:179—84.
[54] Creutzberg EC, Wouters EF, Vanderhoven-Augustin IM, Dentener MA, Schols AM. Disturbances in leptin metabolism are related to energy imbalance during acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;162:1239—45.
[55] Krommidas G, Kostikas K, Papatheodorou G, Koutsokera A, Gourgoulianis KI, Roussos C, et al. Plasma leptin and adiponectin in COPD exacerbations: associations with inflammatory biomarkers. Respir Med 2010;104:40—6.
[56] Nair P, Radford K, Fanat A, Janssen LJ, Peters-Golden M, Cox PG. The effects of leptin on airway smooth muscle responses. Am J Respir Cell Mol Biol 2008;39:475—81.
[57] Sukumaran S, Jusko WJ, DuBois DC, Almon RR. Mechanistic modeling of the effects of glucocorticoids and circadian rhythms on adipokine expression. J Pharmacol Exp Ther 2011;337:734—46.
[58] Cimmino MA, Andraghetti G, Briatore L, Salani B, Parodi M, Cutolo M, et al. Changes in adiponectin and leptin concentrations during glucocorticoid treatment: a pilot study in patients with polymyalgia rheumatica. Ann N Y Acad Sci 2010;1193:160—3.
[59] Gong DW, Bi S, Pratley RE, Weintraub BD. Genomic structure and promoter analysis of the human obese gene. J Biol Chem 1996;271:3971—4.