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Review Article

Role of adipokines in obstructive airway disease and diabetes mellitus

Seema Singh [1], Sunita Singh [2], Santosh Kumar [1], S K Verma [1], and Surya Kant [1]

Department of Respiratory Medicine [1], Department of Microbiology [2], 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.

⇑ Corresponding author at:
Corresponding Author:
Dr. Sunita Singh, Research Officer, Department of Microbiology, King Georges Medical University, Lucknow, India
E-mail: drsunita95@gmail.com

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, Nakanishi *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.

REFERENCES

1. Masuzaki H, Ogawa Y, Sagawa N, Hosoda K, Matsumoto T, Mise H, Nishimura H, Yoshimasa Y, Tanaka I, Mori T, Nakao K. Nonadipose tissue production of leptin: leptin as a novel placenta-derived hormone in humans. Nat Med. 1997; 3:1029–1033. [PubMed: 9288733]
2. Bado A, Levasseur S, Attoub S, Kermorgant S, Laigneau JP, Bortoluzzi MN, Moizo L, Lehy T, Guerre-Millo M, Le Marchand-Brustel Y, Lewin MJ. The stomach is a source of leptin. Nature. 1998; 394:790–793. [PubMed: 9723619]
3. Larsson H, Ahren B. Short-term dexamethasone treatment increases plasma leptin independently of changes in insulin sensitivity in healthy women. J Clin Endocrinol Metab. 1996; 81:4428–4432. [PubMed: 8954054]
4. Messinis IE, Papageorgiou I, Milingos S, Asprodini E, Kollios G, Seferiadis K. Oestradiol plus progesterone treatment increases serum leptin concentrations in normal women. Hum Reprod. 2001; 16:1827–1832. [PubMed: 11527883]
5. Holness MJ, Munns MJ, Sugden MC. Current concepts concerning the role of leptin in reproductive function. Mol Cell Endocrinol. 1999; 157:11–20. [PubMed: 10619393]
6. Hsu A, Aronoff DM, Phipps J, Goel D, Mancuso P. Leptin improves pulmonary bacterial clearance and survival in ob/ob mice during pneumococcal pneumonia. Clin Exp Immunol. 2007; 150:332– 339. [PubMed: 17822444]
7. Mancuso, P. Leptin-Deficient Mice Exhibit Impaired Host Defense in Gram-Negative
8. Pneumonia.pdf. 2002. 8. WA, Mastronardi CA, Yu WH, Karanth S, Parlow AF, MSM. The possible role of prolactin in the circadian rhythm of leptin secretion in male rats. Proc Soc Exp Biol Med. 2000; 224:152–158. [PubMed: 10865230]
9. 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; 49:804–810. [PubMed: 18972601]
10. Matarese G, Moschos S, Mantzoros CS. Leptin in immunology. J Immunol. 2005; 174:3137–3142. [PubMed: 15749839]
11. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol. 2006; 6:772–783. [PubMed: 16998510]
12. La Cava A, Alviggi C, Matarese G. Unraveling the multiple roles of leptin in inflammation and autoimmunity. J Mol Med (Berl). 2004; 82:4–11. [PubMed: 14556053]
13. Otero M, Lago R, Gomez R, Dieguez C, Lago F, Gomez-Reino J, Gualillo O. Towards a proinflammatory and immunomodulatory emerging role of leptin. Rheumatology (Oxford). 2006; 45:944– 950. [PubMed: 16720637]
14. Adeghate, E. (2008). Visfatin: Structure, function and relation to diabetes mellitus and other dysfunctions. *Current Medicinal Chemistry*, *15*(18), 1851–1862.
15. Agusti, A. G., Noguera, A., Sauleda, J., Sala, E., Pons, J. and Busquets, X. (2003). Systemic effects of chronic obstructive pulmonary disease. *European Respiratory Journal*, *21*(2), 347–360.
16. Al Mutairi, S. S., Mojiminiyi, O. A., Shihab-Eldeen, A., Al Rammah, T. and Abdella, N. (2011).

17. Arita, Y., Kihara, S., Ouchi, N., Takahashi, M., Maeda, K., Miyagawa, J., Hotta, K., Shimomura, I., Nakamura, T., Miyaoka, K., Kuriyama, H., Nishida, M., Yamashita, S., Okubo, K., Matsubara, K., Muraguchi, M., Ohmoto, Y., Funahashi, T. and Matsuzawa, Y. (1999).
18. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochemical & Biophysical Research Communications, 257*(1), 79–83.
19. Arshi, M., Cardinal, J., Hill, R. J., Davies, P. S. and Wainwright, C. (2010). Asthma and insulin resistance in children. *Respirology, 15*(5), 779–784.
20. Banks, A. S., Davis, S. M., Bates, S. H. and Myers, M. G.,Jr. (2000). Activation of downstream signals by the long form of the leptin receptor. *Journal of Biological Chemistry, 275*(19), 14563–14572.
21. Barnes, P. J. (2004). Small airways in COPD. *The New England Journal of Medicine, 350*(26),2635–2637.
22. Barnes, P. J. (2005). Molecular mechanisms and cellular effects of glucocorticosteroids. *Immunology & Allergy Clinics of North America, 25*(3), 451–468.
23. Parr, D. G. (2011). Patient phenotyping and early disease detection in chronic obstructive pulmonary disease. *Proceedings of the American Thoracic Society, 8*(4), 338–349.
24. Schols, A. M., Creutzberg, E. C., Buurman, W. A., Campfield, L. A., Saris, W. H. and Wouters, E. F. (1999). Plasma leptin is related to proinflammatory status and dietary intake in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 160*(4), 1220–1226.
25. Schwartz, D. R., & Lazar, M. A. (2011). Human resistin: Found in translation from mouse to man. *Trends in Endocrinology and Metabolism: TEM, 22*(7), 259–265.
26. Scotece, M., Conde, J., Abella, V., Lopez, V., Lago, F., Pino, J., Gomez-Reino, J. J. Gualillo, O. (2014). NUCB2/nesfatin-1: A new adipokine expressed in human and murine chondrocytes with pro-inflammatory properties, an in vitro study. *Journal of Orthopaedic Research: Official Publication of the Orthopaedic Research Society, 32*(5), 653–660.
27. Scotece, M., Conde, J., Vuolteenaho, K., Koskinen, A., Lopez, V., Gomez-Reino, J., Lago, F., Moilanen, E. and Gualillo, O. (2014). Adipokines as drug targets in joint and bone disease. *Drug Discovery Today, 19*(3), 241–258.
28. Setta, J. H., Neder, J. A., Bagatin, E., Terra-Filho, M., Napolis, L. M., Corso, S. D., Amorin, M., Rodrigues, R. T., Fernandes, A. L. and Nery, L. E. (2008). Relationship between induced sputum cytology and inflammatory status with lung structural and functional abnormalities in asbestosis. *American Journal of Industrial Medicine, 51*(3), 186–194.
29. Shin, J. H., Kim, J. H., Lee, W. Y. and Shim, J. Y. (2008). The expression of adiponectin receptors and the effects of adiponectin and leptin on airway smooth muscle cells. *Yonsei Medical Journal, 49*(5), 804–810.
30. Shore, S. A. (2008). Obesity and asthma: Possible mechanisms. *Journal of Allergy & Clinical Immunology, 121*(5), 1087–1093.
31. Shore, S. A., & Johnston, R. A. (2006). Obesity and asthma. *Pharmacology & Therapeutics, 110*(1), 83–102.
32. Sideleva, O., Suratt, B. T., Black, K. E., Tharp, W. G., Pratley, R. E., Forgione, P., Dienz, O.,Irvin, C. G. and Dixon, A. E. (2012). Obesity and asthma: An inflammatory disease of adipose tissue not the airway. *American Journal of Respiratory and Critical Care Medicine, 186*(7), 598–605.
33. Silswal, N., Singh, A. K., Aruna, B., Mukhopadhyay, S., Ghosh, S. and Ehtesham, N. Z. (2005).
34. Human resistin stimulates the pro-inflammatory cytokines TNF-alpha and IL-12 inmacrophages by NF-kappaB-dependent pathway. *Biochemical and Biophysical Research Communications, 334*(4), 1092–1101.
35. Sin, D. D., & Man, S. F. (2003). Impaired lung function and serum leptin in men and women with normal body weight: A population-based study. *Thorax, 58*(8), 695–698.
36. Sinden, N. J., & Stockley, R. A. (2010). Systemic inflammation and comorbidity in COPD: A result of 'overspill' of inflammatory mediators from the lungs? review of the evidence. *Thorax, 65*(10), 930–936.
37. Smith, S. G., Watson, B., Clark, G. and Gauvreau, G. M. (2012). Eculizumab for treatment of asthma. Expert Opinion on Biological Therapy, 12(4), 529-537.
38. Sood, A. (2010). Obesity, adipokines, and lung disease. *Journal of Applied Physiology, 108*(3), 744–753.
39. Sood, A., Cui, X., Qualls, C., Beckett, W. S., Gross, M. D., Steffes, M. W., Smith, L. J. and Jacobs, D. R.,Jr. (2008). Association between asthma and serum adiponectin concentration in women. *Thorax, 63*(10), 877–882.
40. Sood, A., Dominic, E., Qualls, C., Steffes, M. W., Thyagarajan, B., Smith, L. J., Lewis, C. E. and Jacobs, D. R. Jr. (2011). Serum adiponectin is associated with adverse outcomes of asthma in men but not in women. *Frontiers in Pharmacology, 2*, 55.
41. Sood, A., Ford, E. S. and Camargo, C. A.,Jr. (2006). Association between leptin and asthma in adults. *Thorax, 61*(4), 300–305.
42. Sood, A., Qualls, C., Seagrave, J., Stidley, C., Archibeque, T., Berwick, M. and Schuyler, M. (2009). Effect of specific allergen inhalation on serum adiponectin in human asthma.*Chest, 135*(2), 287–294.
43. L., Cook, K. S. and Flier, J. S. (1989). Adrenal glucocorticoids regulate adipsin gene expression in genetically obese mice. T*he Journal of Biological Chemistry, 264*(3), 1811–1815.
44. Steppan, C. M., Bailey, S. T., Bhat, S., Brown, E. J., Banerjee, R. R., Wright, C. M., Patel, H. R.,Ahima, R. S. and Lazar, M. A. (2001). The hormone resistin links obesity to diabetes.*Nature, 409*(6818), 307–312.
45. Steppan, C. M., & Lazar, M. A. (2004). The current biology of resistin. *Journal of Internal Medicine, 255*(4), 439–447.
46. Sukumaran, S., Jusko, W. J., DuBois, D. C. and Almon, R. R. (2011). Mechanistic modeling of the effects of glucocorticoids and circadian rhythms on adipokine expression. *Journal of Pharmacology & Experimental Therapeutics, 337*(3), 734–746.
47. Summer, R., Little, F. F., Ouchi, N., Takemura, Y., Aprahamian, T., Dwyer, D., Fitzsimmons, K., Suki, B., Parameswaran, H., Fine, A. and Walsh, K. (2008). Alveolar macrophage activation and an emphysema-like phenotype in adiponectin-deficient mice. *American Journal of Physiology – Lung Cellular & Molecular Physiology, 294*(6), 1035–1042.
48. Sutherland, T. J., Sears, M. R., McLachlan, C. R., Poulton, R. and Hancox, R. J. (2009). Leptin,adiponectin, and asthma: Findings from a population-based cohort study. *Annals of Allergy, Asthma, & Immunology, 103*(2), 101–107.
49. Takabatake, N., Nakamura, H., Abe, S., Hino, T., Saito, H., Yuki, H., Kato, S. and Tomoike, H. (1999). Circulating leptin in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine, 159*(4 Pt 1), 1215–1219.
50. Takefuji, S., Yatsuya, H., Tamakoshi, K., Otsuka, R., Wada, K., Matsushita, K., Sugiura, K., Hotta, Y., Mitsuhashi, H., Oiso, Y. and Toyoshima, H. (2007). Smoking status and adiponectin in healthy Japanese men and women. *Preventive Medicine, 45*(6), 471–475.
51. Tang, C. H., Fu, X. J., Xu, X. L., Wei, X. J. and Pan, H. S. (2012). The anti-inflammatory and anti-apoptotic effects of nesfatin-1 in the traumatic rat brain. *Peptides, 36*(1), 39–45.
52. Tarkowski, A., Bjersing, J., Shestakov, A. and Bokarewa, M. I. (2010). Resistin competes with lipopolysaccharide for binding to toll-like receptor 4. *Journal of Cellular & Molecular Medicine, 14*(6B), 1419–1431.
53. Tartaglia, L. A., Dembski, M., Weng, X., Deng, N., Culpepper, J., Devos, R., Richards, G. J., Campfield, L. A., Clark, F. T., Deeds, J., Muir, C., Sanker, S., Moriarty, A., Moore, K. J.,

Smutko, J. S., Mays, G. G., Wool, E. A., Monroe, C. A. and Tepper, R. I. (1995).
54. Identification and expression cloning of a leptin receptor, OB-R. *Cell, 83*(7), 1263– 1271.
55. Tian, Z., Sun, R., Wei, H. and Gao, B. (2002). Impaired natural killer (NK) cell activity in leptin receptor deficient mice: Leptin as a critical regulator in NK cell development and activation. *Biochemical & Biophysical Research Communications, 298*(3), 297–302.
56. Tilg, H., & Moschen, A. R. (2006). Adipocytokines: Mediators linking adipose tissue, inflammation and immunity. Nature Reviews. Immunology, 6(10), 772-783.
57. Tomoda, K., Yoshikawa, M., Itoh, T., Tamaki, S., Fukuoka, A., Komeda, K. and Kimura, H. (2007). Elevated circulating plasma adiponectin in underweight patients with COPD. *Chest, 132*(1), 135–140.
58. Tsoukias, N. M., & George, S. C. (1998). A two-compartment model of pulmonary nitric oxide exchange dynamics. *Journal of Applied Physiology, 85*(2), 653–666.
59. Uibu, T., Oksa, P., Auvinen, A., Honkanen, E., Metsarinne, K., Saha, H., Uitti, J. and Roto, P.(2004). Asbestos exposure as a risk factor for retroperitoneal fibrosis. *Lancet, 363*(9419), 1422–1426.
60. Verbraecken, J. & McNicholas, W. T. (2013). Respiratory mechanics and ventilatory control in overlap syndrome and obesity hypoventilation. *Respiratory Research, 14*, 132-9921-14-132.
61. Vondracek, S. F., Voelkel, N. F., McDermott, M. T. and Valdez, C. (2009). The relationship between adipokines, body composition, and bone density in men with chronic obstructive pulmonary disease. *International Journal of Copd, 4*, 267–277.
62. Vuolteenaho, K., Koskinen, A., Kukkonen, M., Nieminen, R., Paivarinta, U., Moilanen, T.and Moilanen, E. (2009). Leptin enhances synthesis of proinflammatory mediators inhuman osteoarthritic cartilage--mediator role of NO in leptin-induced PGE2, IL-6, and IL-8 production. *Mediators of Inflammation, 2009*, 345838.
63. Vuolteenaho, K., Koskinen, A., Moilanen, T. and Moilanen, E. (2012). Leptin levels areincreased and its negative regulators, SOCS-3 and sOb-R are decreased in obese patients with osteoarthritis: A link between obesity and osteoarthritis. *Annals of the Rheumatic Diseases, 71*(11), 1912–1913.
64. Waki, H., Yamauchi, T., Kamon, J., Ito, Y., Uchida, S., Kita, S., Hara, K., Hada, Y., Vasseur, F., Froguel, P., Kimura, S., Nagai, R. and Kadowaki, T. (2003). Impaired multimerization of human adiponectin mutants associated with diabetes. Molecular structure and multimer formation of adiponectin. *Journal of Biological Chemistry, 278*(41), 40352– 40363.
65. Walkey, A. J., Rice, T. W., Konter, J., Ouchi, N., Shibata, R., Walsh, K., deBoisblanc, B. P. and Summer, R. (2010). Plasma adiponectin and mortality in critically ill subjects withacute respiratory failure. *Critical Care Medicine, 38*(12), 2329–2334.
66. Waschki, B., Kirsten, A., Holz, O., Muller, K. C., Meyer, T., Watz, H. and Magnussen, H. (2011). Physical activity is the strongest predictor of all-cause mortality in patients with COPD: A prospective cohort study. *Chest, 140*(2), 331–342.
67. Weisberg, S. P., McCann, D., Desai, M., Rosenbaum, M., Leibel, R. L. and Ferrante, A. W.,Jr. (2003). Obesity is associated with macrophage accumulation in adipose tissue. *The Journal of Clinical Investigation, 112*(12), 1796–1808.
68. Wellen, K. E., & Hotamisligil, G. S. (2005). Inflammation, stress, and diabetes. *Journal of Clinical Investigation, 115*(5), 1111–1119.

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