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Adiponectin in pulmonary disease and critically ill patients

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Abstract

Adiponectin is a predominantly anti-inflammatory protein produced by adipose tissue with possible signalling activity in the lung. It is increasingly associated with inflammatory pulmonary diseases, such as asthma and chronic obstructive pulmonary disease (COPD), and in critical illness. Although mouse studies indicate causative associations between adiponectin and asthma and COPD, the human literature in this regard is inconclusive. Some, but not all, studies demonstrate that serum adiponectin concentrations are inversely associated with asthma prevalence among premenopausal women and peripubertal girls. On the other hand, serum adiponectin concentrations are associated with lower asthma severity among boys but greater severity among men. Further, case-control studies demonstrate higher systemic and airway adiponectin concentrations in primarily male COPD patients than controls. Systemic adiponectin is positively associated with lung function in healthy adults but inversely associated in studies of male subjects with COPD. Murine and human studies further show contradictory associations of systemic adiponectin with critical illness. Higher premorbid systemic adiponectin concentrations are associated with improved survival from sepsis in mice. On the other hand, higher systemic adiponectin concentrations on day 1 of critical illness are associated with lower survival in critically ill patients with respiratory failure. In the absence of adequate longitudinal data, it is not possible to determine whether the adiponectin derangements are the consequence or the cause of the disease studied. Future research will determine whether modulation of adiponectin, independent of BMI, may be helpful in the prevention or treatment of asthma, COPD or critical illness.

Keywords

Asthma; COPD; Sepsis; Respiratory Failure; Adiponectin; Lung function

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Introduction

Adipose tissue produces over 50 proteins called adipokines that act as signalling molecules with effects on a wide array of bodily processes. Adiponectin, one such adipokine, plays an important role in the regulation of diabetes mellitus and atherosclerotic cardiovascular disease [1]. The possible role for adiponectin in inflammatory pulmonary diseases, such as asthma and chronic obstructive pulmonary disease (COPD), and in critical illness has been the subject of recent investigations.

Despite being produced by adipose tissue, systemic adiponectin concentrations are inversely correlated with body mass index (BMI) [2, 3]. One explanation for this surprising finding is that adipose tissue in the obese experiences localized hypoxia that inhibits its expression of adiponectin [4]. The hypoxia-induced necrosis of adipocytes attracts activated macrophages that collect to form functional syncytia surrounding the necrotizing adipocytes [5]. These syncytia produce tumor necrosis factor - alpha (TNF-α) and interleukin (IL)-6 which may inhibit the local production of adiponectin by the adipose tissue in a paracrine fashion [6].

Circulating adiponectin includes three distinct isoforms – low molecular weight (trimers); medium-molecular weight (hexamers) and high-molecular weight (HMW or higher order multimers), as shown in Figure 1. Three monomers of adiponectin form a trimer. Trimers linked by a disulfide bond form a hexamer. Several linked hexamers and trimers constitute the higher multimeric form. Systemic concentrations of the HMW isoform are disproportionately reduced in obesity. Thus, the proportion of HMW isoform to total adiponectin is lower among obese individuals than healthy controls. Interestingly, there is also a marked sexual dimorphism of the distribution of adiponectin isoforms in humans [7]. Compared to men, women have higher circulating concentrations of total adiponectin and higher proportions of its HMW isoform, despite greater levels of overall adiposity [8, 9]. It is believed that testosterone production during puberty in men lowers their systemic adiponectin concentrations, particularly the HMW isoform [8]. The testosterone role is supported by castration experiments in mice that result in an increase of total adiponectin, particularly of the HMW isoform [10]. On the other hand, postmenopausal women have higher circulating concentrations of total adiponectin and higher proportions of its HMW isoform than premenopausal women, with a negative association of circulating concentrations of total and HMW adiponectin with female sex steroids (estradiol and progesterone) among women [11]. *In vitro* experiments offer supporting evidence that estrogen decreases adiponectin expression in adipocytes [12]. Further, the various isoforms may vary in their potency of effect [13]. For instance, the HMW isoform is the most biologically active form of adiponectin in regulating insulin resistance [14]. It is unclear however whether the HMW isoform has a specific role in pulmonary diseases and critical illness.

Most research indicates that the primary effect of adiponectin on inflammatory processes is to inhibit pro-inflammatory mediators (TNF-α, IL-6, endothelial adhesion molecules ICAM-1 and VCAM-1, and nuclear factor-κB) [15–19] as well as promote anti-inflammatory mediators (IL-10 and IL-1 receptor antagonist) [19–21]. *In vitro* studies indicate that adiponectin can also bind bacterial lipopolysaccharides [22] providing additional down-regulation of inflammation in infectious states. Despite these observations across multiple studies, adiponectin has been found to paradoxically exhibit pro-inflammatory effects under certain conditions [23, 24].

Both adiponectin and its multiple receptors (AdipoR1, AdipoR2, T-cadherin, and calreticulin) are expressed on various cell types in the lung [25–28]. In addition, adiponectin is transported from blood into the alveolar lining fluid *via* the T-cadherin molecule on the

endothelium [25]. It is therefore possible that the lung is a target organ for adiponectin signaling and consequently, adiponectin derangements may be associated with diseases of the lung.

Adiponectin and Asthma

Although mouse studies show a causative association [29, 30], the human literature regarding the association between adiponectin and asthma is limited and contradictory.

Mouse studies

Allergen bronchoprovocation of sensitized BALB/cJ mice reduces both the adiponectin production from adipose tissue as well as the pulmonary expression of adiponectin receptor mRNA [29]. On the other hand, exogenous adiponectin infusion attenuates allergic airway inflammation and airway hyperresponsiveness in the same mouse model [29]. These findings are supported by a separate model of genetically adiponectin-deficient mice that demonstrates greater allergic airway inflammation in response to allergen bronchoprovocation than wild-type mice [30].

The adiponectin-asthma relationship in mice is *bidirectional* (Figure 2), whereby allergen inhalation affects serum adiponectin concentrations and exogenous adiponectin administration affects asthma. In humans with mild atopic asthma, bronchoprovocation from inhalational allergen challenge does not acutely affect serum adiponectin concentrations – thus suggesting that what is true in mice may not be entirely true in humans [31].

Human Studies

Current human data regarding the independent association between serum adiponectin and asthma prevalence or severity remain inconclusive, although there may be more consistency in the association observed among children as compared to adults. Furthermore, the obesity-asthma association does not appear to be explained by serum adiponectin alone [32], implying multiplicity of mechanistic pathways for the obesity asthma association.

Asthma prevalence—Some, but not all, studies demonstrate that serum adiponectin concentrations are inversely associated with asthma prevalence among premenopausal women and peripubertal girls. Studies suggesting such subgroup effects however have not confirmed them with statistically significant interactions. Nevertheless, the modification of physiological effect of adiponectin by female sex hormones is tantalizing. The studies are further complicated because of their use of varying definitions for the diagnosis of asthma and its severity.

One U.S.-based cross-sectional study showed a *protective* association between serum adiponectin concentrations and odds for clinically diagnosed asthma in premenopausal women, independent of BMI [32]. An unpublished longitudinal study involving the same cohort further showed that the inverse association between serum adiponectin and risk of *incident* asthma in women was stronger among current smokers [23]. In that study, low serum adiponectin was also found to be more important than BMI in predicting the risk of *incident* asthma among women [23]. These findings were however not confirmed for similarly defined asthma by either Sutherland *et al.* in a population-based birth cohort of approximately 1,000 young adult New Zealanders [33] or by Jartti *et al.* [34] in sequential cross-sectional studies of a Finnish cohort of children and adults. Surprisingly, men in the Sutherland study demonstrated a positive association with bronchodilator responsiveness, an asthma marker, while simultaneously showing an inverse association with exhaled nitric oxide, a different asthma marker associated with airway inflammation [33]. Several small

case-control studies have shown no difference after adjusting for obesity in either serum or bronchoalveolar lavage fluid adiponectin concentrations between adult asthmatics and controls [35–37]. On the other hand, among children, Nagel *et al.* demonstrated a protective association between serum adiponectin and odds for asthma in peripubertal girls, independent of BMI; this effect was stronger in nonatopic girls [38]. These results again could not be confirmed by a Korean study of similarly-aged children but mostly boys [39].

Asthma Severity—Although data are again limited and contradictory, the majority of evidence indicates that serum adiponectin concentrations are associated with lower asthma severity among boys and paradoxically with higher asthma severity among men.

In a large community-based cross-sectional study of American adults, Sood *et al.* showed that higher serum adiponectin concentrations were independently associated with adverse clinical outcomes of asthma (such as asthma-related symptoms, medications and disease activity) among men but not women. This is the only study in the literature that confirms the presence of statistically significant sex-specific interactions for adiponectin in asthma [23]. On the other hand, in a small clinic-based case-control study of American adults, Holguin *et al.* showed no association between concentrations of serum or bronchoalveolar lavage fluid adiponectin and of lung inflammatory biomarkers [37].

Studies of asthma severity among children demonstrate a clearer association with adiponectin than adults. Serum adiponectin concentrations were associated with less severe exercise-induced bronchoconstriction in a study of pre-pubertal asthmatic children, mostly boys, after adjusting for BMI [40]. Serum adiponectin concentrations were also associated with fewer maximum asthma symptom days, fewer exacerbations, and higher FEV_1/FVC ratio in a study including 14-year old boys with moderate to severe asthma [41]. Similarly, serum adiponectin concentrations were positively correlated with $FEF_{25–75\%}$ in another study of prepubertal and peripubertal children, mostly boys [39]. While it is possible that the conflicting findings between men and boys are due to significant methodological differences between the studies, testosterone-related changes in total adiponectin and adiponectin isoform distribution (towards a lower proportion of HMW isoform) in men compared to boys may also play a role [8, 42].

Longitudinal and interventional studies examining the effect of change in serum adiponectin on asthma severity are limited. A recent study found that a one-year weight reduction interdisciplinary intervention resulted in an increase in lung function and serum total adiponectin among post-pubertal obese adolescents with and without asthma as well as improved asthma severity in the asthma subgroup [43]. More importantly, the increase in serum adiponectin predicted improved lung function among both subgroups, independent of age and sex. One limitation of this multivariable analysis was that the predictive effect of change in serum adiponectin was not examined independent of the associated change in BMI.

To summarize, although adiponectin and its receptors are expressed in human airway cells, the adiponectin-asthma association in humans is currently controversial. Certain studies demonstrate that serum adiponectin concentrations are inversely associated with asthma prevalence among premenopausal women and peripubertal girls. On the other hand, serum adiponectin concentrations are associated with lower asthma severity among boys but greater asthma severity among men. It is possible that pro-inflammatory effects of adiponectin dominate under certain physiologic conditions and anti-inflammatory effects under others. It is also possible that the *balance* between pro-inflammatory systemic adipokines (primarily related to leptin [44–47]) and anti-inflammatory systemic adipokines (primarily related to adiponectin) is more important than the individual adipokines, in

relation to asthma. Given the nascent nature of the field of research, it is not known whether attempts towards systemic or local modulation of adiponectin, independent of BMI, may be effective in asthma prevention or treatment.

Adiponectin and COPD

There is evidence supporting a causative association between adiponectin and COPD in mice but the human literature in this area is limited and clear conclusions cannot be drawn.

Mouse studies

Genetically-induced adiponectin deficient mice (APN−/−) demonstrate greater expression of TNF-α and matrix metalloproteinases in their alveolar macrophages and abnormal alveolarization, resembling an emphysema-like phenotype [48, 49]. These changes are reversible following adiponectin supplementation, supporting an anti-inflammatory role for adiponectin [49]. The latter is further supported by the greater levels of extrapulmonary inflammation, vascular endothelial dysfunction, and comorbidities (such as cachexia and osteoporosis) in APN−/− mice than wild-type mice [49].

Intranasal elastase instillation among wild-type mice, while causing emphysema, has dramatically opposite effects on systemic and local adiponectin responses. While it reduces plasma adiponectin concentrations, it increases bronchoalveolar lavage fluid adiponectin and adiponectin receptor expression on lung macrophages and epithelial cells [49]. Chronic tobacco smoke exposure in wild-type mice has similar effects on bronchoalveolar lavage fluid adiponectin [28]. Thus, as lung tissue of wild-type mice is exposed to emphysema-promoting agents, the enhanced local levels of adiponectin and of adiponectin receptor expression likely lead to greatly magnified signaling of adiponectin-dependent pathways in the lung, ostensibly to fight inflammation. However, the picture appears to be more complex than that. For instance, when genetically-induced adiponectin deficient mice (APN−/−) mice are exposed to tobacco smoke, these mice do not demonstrate a further increase in lung inflammation and air space enlargement, as would be expected, but instead show a lesser degree of abnormality than similarly exposed wild-type mice [50]. Why adiponectin has pro-inflammatory effects under certain exposure situations and anti-inflammatory effects under others is uncertain and needs to be investigated.

Human Studies

Currently, the human data on the association between adiponectin and COPD prevalence or severity remain inconclusive and suggest both pro-inflammatory and anti-inflammatory effects of adiponectin in different population subgroups.

COPD prevalence—Systemic adiponectin is positively associated with lung function in healthy adults but inversely associated in subjects with COPD. Further, men with COPD have higher systemic and local adiponectin concentrations than controls.

Thyagarajan *et al.* showed a positive longitudinal association between serum adiponectin and spirometric lung function in a large community-based study of young healthy adults, independent of sex, obesity and smoking [51]. Interestingly, the authors hypothesized that systemic adiponectin may affect lung growth during early adulthood rather than lung function decline in later life. The attenuation of this association after adjustment for insulin resistance and systemic inflammation suggests that these covariates are on a causal pathway linking adiponectin and lung function. The longitudinal findings by Thyagarajan *et al.* are opposed by a small case-control study that showed high plasma adiponectin concentrations to be associated with worse lung function in COPD [52], as discussed in the next section.

There is limited data, primarily clinic or hospital-based case-control or cross-sectional studies, that examine the predictive effect of serum adiponectin on risk for COPD, independent of BMI. It must be cautioned that in the absence of longitudinal or interventional studies, the direction of the adiponectin-COPD association cannot be conclusively established. Nevertheless, unlike the Nakanishi's mouse model that associated hypoadiponectinemia with emphysema-like changes [49], three small human studies have demonstrated that serum adiponectin concentrations in male COPD patients were *higher* than those in controls [52–54]. Another study showed that levels of bronchoalveolar lavage adiponectin and adiponectin expression in airway epithelial cells in subjects with emphysema were *greater* than healthy (disproportionately female) non-smoking controls [28]. Interestingly, in contrast to subjects with emphysema who had increased levels of bronchoalveolar lavage adiponectin, current smokers without COPD had reduced levels of bronchoalveolar lavage adiponectin [55]. The molecular mechanism by which tobacco smoke exposure may down-regulate adiponectin expression and the development of COPD may up-regulate adiponectin expression is unknown.

COPD severity—Systemic adiponectin is associated with greater disease severity among men with COPD and has not been studied among women with COPD.

One small case-control study showed plasma adiponectin to be associated with worse spirometric parameters in a BMI-adjusted analysis [52] while two others showed no correlation [53, 54]. In a subgroup of COPD patients with elevated serum TNF-α concentrations, serum adiponectin concentrations were positively associated with serum TNF-α concentrations and inversely associated with lung volume parameters in an unadjusted analyses [54].

Acute COPD exacerbation—Systemic adiponectin concentrations rise during acute COPD exacerbations and return to baseline several days to weeks later [56]. This profile may reflect the body's compensatory mechanisms to fight the early exuberant pro-inflammatory stimuli in acute COPD exacerbations but is opposite in direction to the profile observed in mechanically ventilated critically ill patients with acute respiratory failure [57–59], as discussed below.

To summarize, case-control studies demonstrate higher systemic and airway adiponectin concentrations among primarily male COPD patients than controls. However, in the absence of longitudinal studies, it is unclear whether the elevated concentrations are the cause or the consequence of COPD. Systemic adiponectin is positively associated with lung function in healthy adults but inversely associated in subjects with COPD. Systemic adiponectin is associated with greater COPD severity in men and has not been studied among women with COPD. The state of the literature is such that it is not even possible to hypothesize whether modulation of adiponectin, independent of BMI, may be helpful or harmful in COPD prevention and treatment in future studies.

Adiponectin and Non-small Cell Lung Cancer

The role of hypoadiponectinemia as a poor prognostic factor in non-small cell lung cancer is not well established. While one study showed lower serum adiponectin concentrations in advanced cancer, as compared to limited stage disease [60], another study did not show any association in multivariable analyses [61].

Adiponectin and Critical Illness

There are limited studies examining the role for adiponectin in critical illness with often contradictory results between murine and human studies. Adiponectin has largely anti-inflammatory effects in both the mouse model of polymicrobial sepsis [62, 63] and critically ill humans with respiratory failure [57, 64]. Walkey *et al.* observed that systemic adiponectin was positively correlated with systemic IL-10 (another anti-inflammatory cytokine) but not correlated with systemic pro-inflammatory cytokines in critically ill patients with respiratory failure [59].

Mouse studies

Adiponectin has anti-inflammatory effects in a mouse model of polymicrobial sepsis. Thus, APN −/− mice produced increased pro-inflammatory cytokines in response to sepsis, as compared to wild-type mice [63]. Further, higher premorbid systemic adiponectin concentrations were associated with improved survival from sepsis in mice [63]. This conclusion was observed with two sets of experiments. First, wild-type mice showed improved survival from sepsis than APN −/− mice. Next, wild-type mice treated with rosiglitazone (to increase their premorbid systemic adiponectin concentrations) showed improved survival from subsequent sepsis than untreated wild-type controls or treated APN −/− controls (that were unable to raise their premorbid systemic adiponectin concentrations with rosiglitazone). It is possible that the pharmacologic elevation of premorbid systemic adiponectin concentrations in wild-type mice may help downregulate or ‘fine-tune’ the subsequent exuberant pro-inflammatory response of early sepsis, improving their survival. If this hypothesis was tested to be true in humans, it may become possible to prevent sepsis-related mortality with premorbid use of thiazolidinedione drugs.

Human Studies

Systemic adiponectin concentrations in humans fall during the acute phase of various critical illnesses and rise again with convalescence [57–59]. Interestingly, this profile is different from that of COPD exacerbations [56], as discussed previously. The early phase of critical illness is a net pro-inflammatory state with high systemic TNF-α and IL-6 concentrations inhibiting adiponectin production. On the other hand, anti-inflammatory mechanisms are salient during the recovery phase with reduced systemic concentrations of TNF-α and IL-6 resulting in a corresponding bounce-back in systemic adiponectin concentrations. Consistent with this paradigm, serum adiponectin is associated with lower C-reactive protein levels on day 7 but not day 3 of critical illness [57].

Walkey *et al.*’s observational cross-sectional study of a large heterogeneous group of mechanically ventilated critically ill patients (29% with either pneumonia or sepsis) showed results opposite to those of Uji *et al.*’s murine sepsis study [64]. Walkey *et al.* found that higher systemic adiponectin concentrations on day 1 of critical illness were associated with *lower*, not higher, survival after adjustment for confounders such as BMI and APACHE II score [64]. In fact, the area under the receiver operating curve for day 1 adiponectin in predicting 28-day survival was higher *i.e.* more predictive than that for all other predictors studied, including APACHE II score. Of course, premorbid concentrations of adiponectin were not available in this observational study and thus, one does not know whether an initial expected drop in adiponectin occurred during the early phase of critical illness. The authors speculate that the higher day 1 adiponectin concentrations of non-survivors may in fact represent a dysfunctional response to the stress of early critical illness – suggesting that an early drop in adiponectin and subsequent return to baseline may in fact be beneficial for survival in the critically ill. Consistent with this hypothesis, nonsurvivors in this study

showed an attenuated increase in adiponectin between Day 1 and Day 6 (when adiponectin may be expected to return close to its premorbid concentrations).

To summarize, murine and human studies show differing associations of systemic adiponectin with critical illness. We do not know whether this represents the obvious differences in mouse *vs.* human species; sepsis *vs.* respiratory failure as the inciting condition; or incomplete data from human studies. In the absence of longitudinal data from critically ill patients that includes premorbid concentrations, it is not possible to determine whether the association between higher adiponectin concentrations on day 1 and lower survival is causal or simply a biomarker for that outcome.

Adiponectin and Novel Therapeutic Agents

Although it is still currently unclear whether modulation of systemic adiponectin or its signaling pathways has any therapeutic benefit in pulmonary or critical illnesses, it may serve as a novel therapeutic or preventative tool for these illnesses in the future. One obvious pharmaceutical treatment would be the exogenous administration of adiponectin by inhalational or intravenous route. Although this has been tried in mouse models [29], problems to be overcome prior to human administration include establishing what the biologically active molecule is, what role post-translational modifications have upon the function and associated difficulties in generating biologically active molecules on a large scale.

Several existing drug classes that affect systemic adiponectin concentrations may be easier to administer than adiponectin itself. The most important drug class in this regard is the thiazolidinediones or TZDs such as pioglitazone and troglitazone. TZDs are synthetic ligands of the peroxisome proliferator-activated receptors, specifically of the gamma type (PPAR-γ), that increase adiponectin mRNA in adipocytes, resulting in increased production and secretion of adiponectin [65]. Sulfonylureas such as glimepiride, glibenclamide, and gliclazide stimulate the adiponectin production *albeit* through a different mechanism than the TZDs, namely an antagonistic interaction with protein kinase A activity [66]. Fibrates, such as fenofibrate, increase systemic adiponectin concentrations by enhanced PPAR-γ activity [67–69]. Angiotensin converting enzyme inhibitors such as ramipiril and angiotensin receptor blockers such as telmisartan, valsartan and candesartan have also been shown to increase systemic adiponectin concentrations [70–72]. The proposed mechanisms include adipocyte differentiation [73] and PPAR activation [74]. Calcium channel blockers such as amlodipine and efonidipine [75] and a central-acting anti-hypertensive agent rilmenidine [76] also increase systemic adiponectin concentrations whereas statins such as simvastatin have variable effects [77]. On the other hand, the opposite effect has been noted with valproic acid. A study examining valproic acid in mice found that this medication inhibits adiponectin gene expression in a dose-dependent manner [78].

In addition to pharmaceutical agents, nutritional interventions may help regulate systemic adiponectin concentrations. Results in animal models demonstrate that the consumption of diets rich in polyunsaturated fatty acids and supplementation with omega-3 and eicosapentaenoic acid increase adiponectin gene expression and plasma concentrations [79]. In humans, the consumption of a healthy and Mediterranean diet is positively associated with adiponectin concentrations, although the mechanisms are not fully understood [79]. As the literature on adiponectin's role in a variety of disease states expands and matures, these interventions may become useful tools in modulating adiponectin concentrations for future therapeutic benefit.

Limitations of the Literature

Being a nascent field of research, the associations between adiponectin and lung diseases/critical illness currently suffer from many critical gaps in the literature. There is generally a lack of adequately powered longitudinal and weight-intervention studies; inadequate adjustment for confounding effect of obesity; limited studies of sputum or bronchoalveolar lavage fluid adiponectin; and no examination of adiponectin isoforms. Further, women with COPD have not been adequately studied – a subgroup of COPD that may indeed show the most interesting findings. Adiponectin is both positively and inversely associated with lung function, depending upon the population subgroup studied. It is therefore possible that adiponectin has both anti-inflammatory effects in the lungs of some subjects and pro-inflammatory in others.

Human studies of adiponectin and critical illness are similarly limited by small-sized single-center studies; enrollment of heterogeneous groups of critically ill patients; and inadequate control of potential covariates, such as glycemic control, BMI, and other inflammatory mediators. More importantly, adiponectin may exert varying degrees of influence at various time points in critical illness. Thus, future longitudinal studies will need to measure concentrations of adiponectin at multiple time points in the disease course and ideally, starting from the premorbid state. Both upstream regulators of adiponectin expression and downstream targets of adiponectin will need to be better studied to determine the mechanistic bases for these associations.

To summarize, there is developing literature to suggest a potential role for adiponectin in inflammatory pulmonary conditions such as asthma and COPD as well as critical illnesses such as respiratory failure with and without sepsis. Future research will determine whether pharmacological modulation of adiponectin, independent of BMI, may be helpful in the prevention or treatment of these conditions in targeted populations.

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ABBREVIATIONS

COPD	Chronic obstructive pulmonary disease
IL	Interleukin
TNF	Tumor Necrosis Factor
BMI	Body mass index
APN −/−	Genetically-induced adiponectin deficient mice
FEV_1/FVC	Ratio of forced expiratory volume in one second to forced vital capacity
$FEF_{25–75\%}$	Maximum mid-expiratory flow
HMW	High-molecular weight
APACHE	Acute Physiology and Chronic Health Evaluation
mRNA	Messenger ribonucleic acid

PPAR	Peroxisome proliferator-activated receptor
TZD	thiazolidinedione

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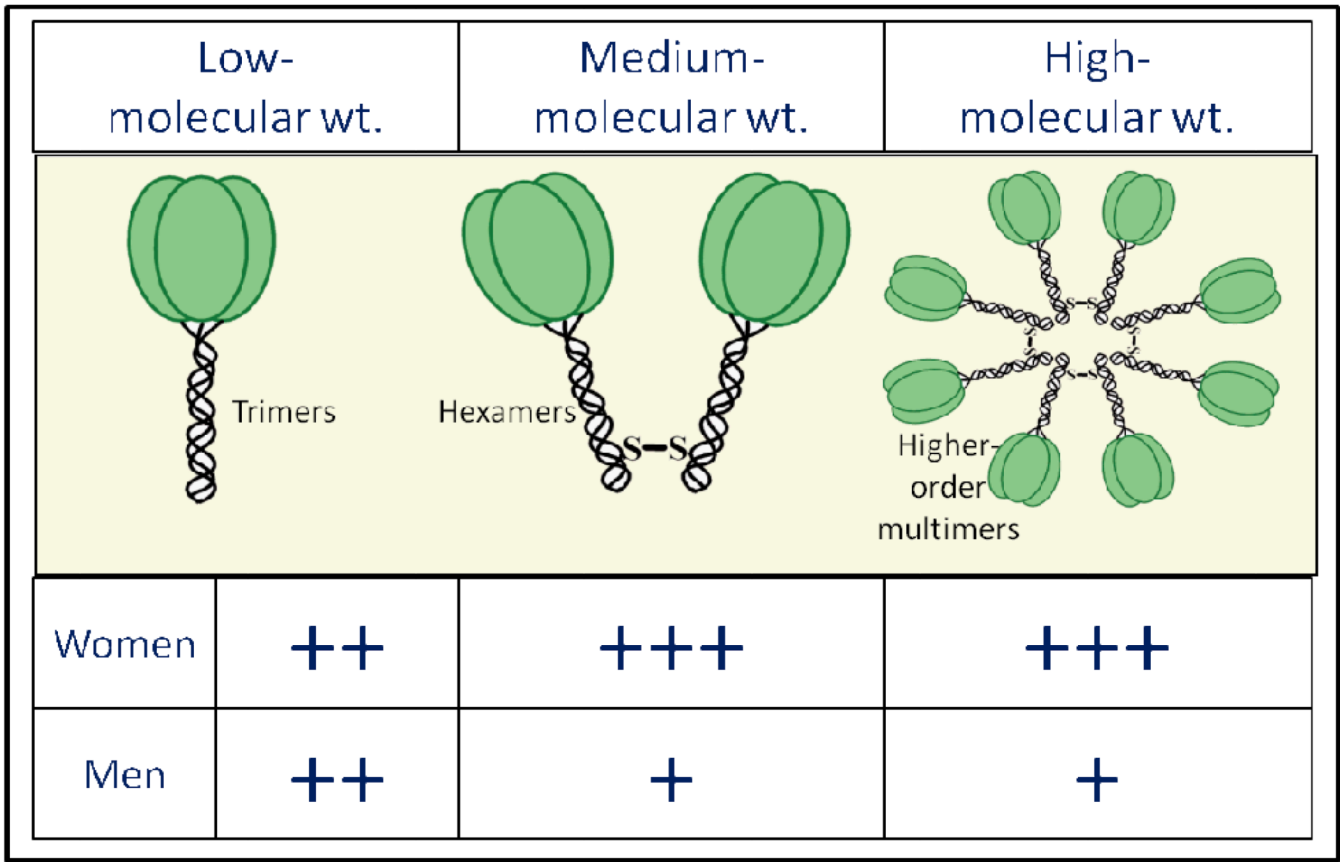

Figure 1.
Schematic representation of the sexual dimorphism of the absolute concentrations of the circulating adiponectin isoforms. Compared to men, women have higher absolute concentrations of circulating total adiponectin and all its isoforms. When the isoforms are expressed as a proportion of the total, women have higher proportions of high and medium molecular-weight isoforms but a lower proportion of the low molecular-weight isoform than men. The figure summarizes the data published previously by Peake et al. [9]

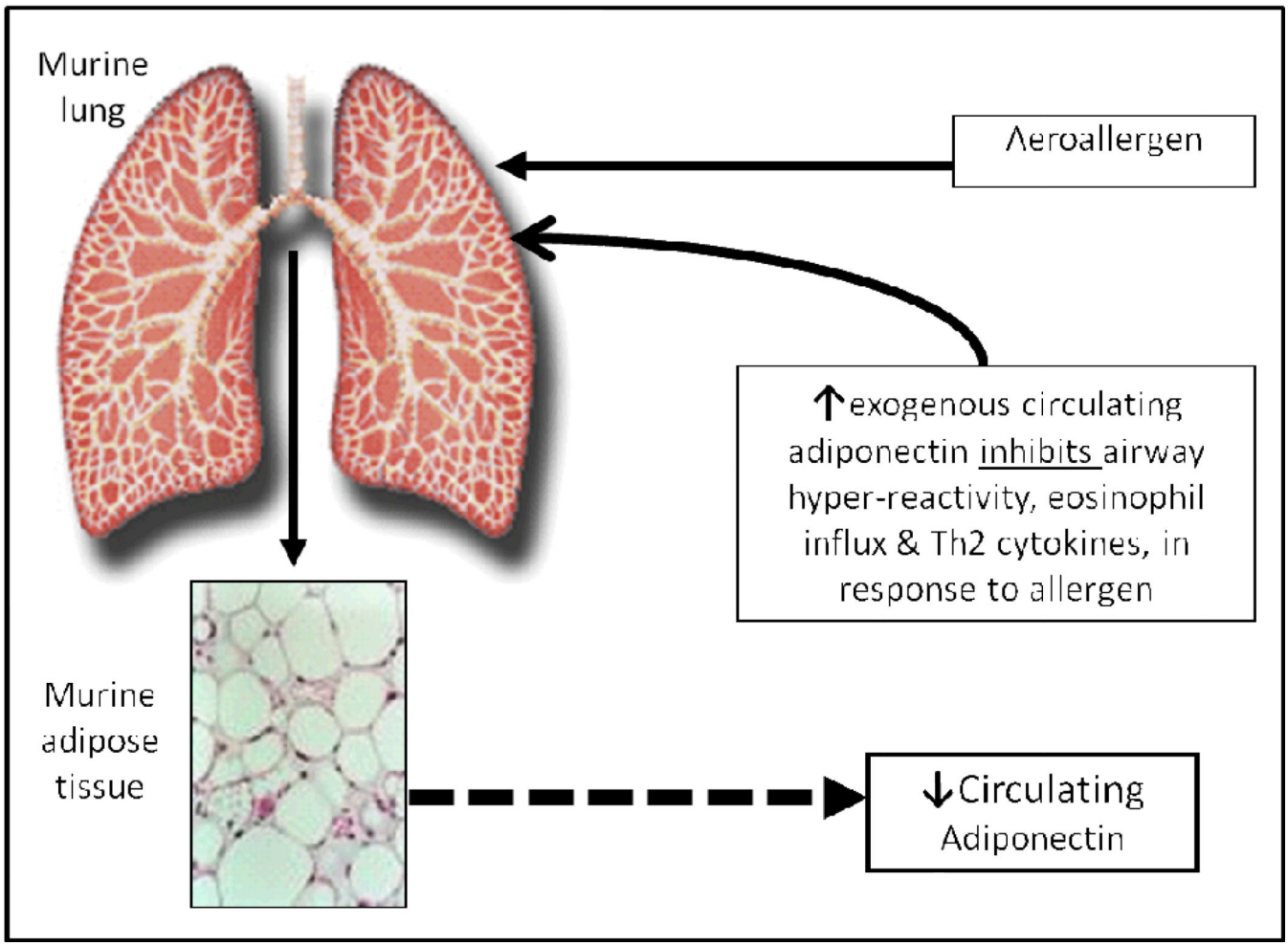

Figure 2.
A schematic representation of the bidirectional association between adiponectin and asthma, based upon the murine research by Shore *et al.* [29]. Figure as originally published in Sood et al. (2011) Serum Adiponectin is Associated with Adverse Outcomes of Asthma in Men but Not in Women *Front Pharmacol* 2:55. doi: 10.3389/fphar.2011.00055 [23].