

# Does leptin play a role in obesity–asthma relationship?

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The increase of asthma has paralleled the rising obesity during the past decades. Obesity is characterized by the increase of leptin in the circulation. Leptin is an obesity gene product, and it can stimulate the production of pro-inflammatory mediators, such as tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6 and interferon (IFN)- $\gamma$ . There is a link between leptin and asthma, especially in children. It remains unclear however, if leptin is in the pathway of obesity–asthma relationship and if it plays a distinctive role in asthma in obese vs. non-obese subjects. Since leptin is in a positive feedback loop with the pro-inflammatory cytokines such as TNF- $\alpha$ , there is a possibility that leptin is involved as a regulatory rather than an etiologic mechanism of asthma development. Weight loss is associated with decreased circulating leptin concentration in children. Weight control program may need to be considered in the treatment of asthma in obese children.

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The increase of asthma has paralleled the emerging obesity during the past decades (1). Several recent review articles have concluded that there is a positive association between obesity and asthma (2–4), but the underlying mechanisms have not yet been established. Several mechanisms have been postulated (3, 5). Firstly, obesity and asthma may share common genetic and environmental etiologies. Genetic and environmental factors may increase the risk of obesity concurrently with asthma (6, 7). Secondly, obesity may increase the risk of asthma through its effects on other disease process, e.g. obesity is a risk factor for sleeping-disordered breathing and gastro-esophageal reflux disease (8, 9), and these two diseases are associated with an increased risk for asthma (10, 11). Thirdly, *morbid* obesity can reduce lung volume and airway diameter and increase asthma via mechanical mechanisms (2, 12). Last but not the least appealing hypothesis, obesity is characterized by increases in the serum concentrations

of cytokines, chemokines, acute phase proteins and energy regulating hormones including leptin (13, 14). These mediators are produced by adipocytes and in general called adipokines. Although the precise mechanisms need to be determined, adipokines may alter *T helper 1 (Th1)–T helper 2 (Th2)* balance, immune tolerance, lung development, airway smooth muscle and airway responsiveness (2, 15), which are associated with asthma development.

Leptin is one of the adipose-derived energy regulating hormones and an obesity gene product (16). Circulating leptin is positively correlated with body fat percentage and body fat mass (17–19). In addition to its primary effects on energy regulation of inhibiting food intake and increasing energy expenditure, leptin has recently been identified to have pro-inflammatory properties via the stimulation of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6) from the adipose tissue (20, 21), and via the modulation of immunity to promote Th1 immune responses with increased production of interferon- $\gamma$  (IFN- $\gamma$ ) (16, 22) (Fig. 1). Leptin has been correlated with the production of pro-inflammatory mediators, such as TNF- $\alpha$ , IL-6

**Abbreviations:** BMI, body mass index; IFN- $\gamma$ , interferon-gamma; IL-6, interleukin-6; Th1, T helper 1; Th2, T helper 2; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

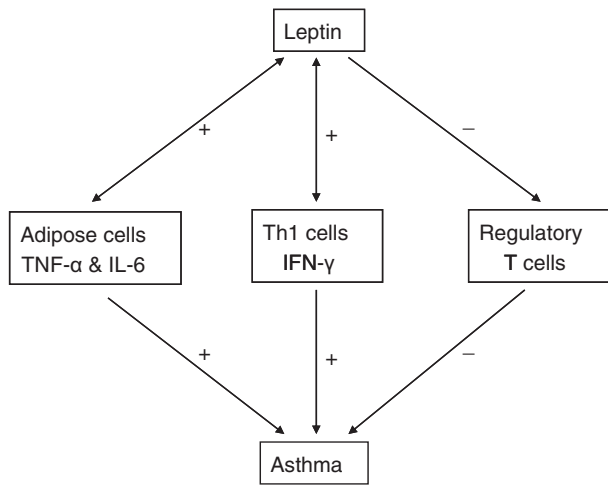


Fig. 1. Several possible effects of leptin on asthma. Leptin stimulates the production of TNF- $\alpha$  and IL-6 from the adipose tissue, promotes Th1 proliferation with increased production of IFN- $\gamma$ , and restrains regulatory T cells. Increased levels of TNF- $\alpha$ , IL-6 and IFN- $\gamma$ , and restricted function of regulatory T cells are associated with asthma.

and IFN- $\gamma$  in overweight and obese individuals (23–26). TNF- $\alpha$ , IL-6 and IFN- $\gamma$  are mediators associated with asthma (27, 28). In asthmatic children, IFN- $\gamma$ -producing CD4<sup>+</sup> T cells are inversely correlated with blood eosinophilia but positively correlated with airway hyperresponsiveness (29), suggesting a possible involvement of IFN- $\gamma$  in non-atopic asthma. Epidemiologic studies have demonstrated that obesity increases asthma but not atopy both in adults and in children (30, 31), although literature show inconsistent results (32, 33). In addition, obesity has been significantly associated with non-atopic asthma rather than atopic asthma in adult women and in children (34, 35). Thus, the obesity gene products such as leptin have been postulated to play a role in obesity–asthma relationship.

#### Is leptin associated with asthma?

The possible role of leptin in airway inflammation has been studied in animal models. Shore et al. have demonstrated that in leptin-deficient mice (models of genetic obesity), the exogenous administration of leptin augments pulmonary inflammation induced by acute ozone exposure (36), and increases allergen-induced airway responsiveness and the allergen-specific immunoglobulin E (IgE)-antibodies in serum (37). In a clinical study, Gurkan et al. demonstrated that serum levels of leptin were higher in children with newly diagnosed asthma before budesonide

treatment compared with non-asthmatic children despite similar body mass index (BMI) (38). Guler et al. reported that one unit increase of log leptin had a twofold increased odds for asthma after adjustment for BMI (39). However, results on the relationship of leptin and asthma are not entirely consistent in children (40, 41). The relationship between leptin and asthma may also differ in adults. In a large cross-sectional study of adults, Sood et al. reported that the highest quartile of serum leptin concentration was associated with 1.85 times increased odds for asthma in women in crude analysis (42). Leptin was no longer significantly associated with asthma in women when BMI was fixed, whereas the significant association between BMI and asthma remained when serum levels of leptin was adjusted for (42). This suggested that the relationship between leptin and asthma in adult women could to some extent be explained by the underlying relationship between BMI and asthma, but there was a possibility of over-adjustment. Sex related difference may be the explanation for the discrepancy of results in children and the adult women. Elevated levels of leptin have been reported to be associated with asthma in boys but not in girls (39), although serum levels of leptin are higher in girls than in boys (39, 43–46). Different mechanisms for asthma development may be applied in females with obese status. Evidence is emerging that female sex hormones influence the occurrence of wheeze and asthma among women (47–49), and female sex hormone is increased in obese females (50).

#### Is leptin in the pathway of obesity–asthma relationship?

Sood et al. reported that after adjustment for serum levels of leptin, the relationship between a BMI and asthma was attenuated but remained a borderline significance (42). This suggests that leptin may be involved in obesity–asthma relationship, but it only explains a small portion of the relationship. Alternatively, the effect of BMI on asthma is not mediated by the leptin pathway alone but involves other mechanistic and pathophysiologic pathways. In order to directly and adequately address the mediating effect of leptin on obesity–asthma relationship, further studies are needed in which the mediation tests are called for application (51). The mediation tests provide the ratio of mediating effect (obesity  $\rightarrow$  leptin  $\rightarrow$  asthma) vs. direct effect (obesity  $\rightarrow$  asthma) and the ratio of mediating effect vs. total effect, and a p value for significance.

### Does the role of leptin in asthma differ in obese and non-obese subjects?

Excessive amount of leptin is produced from the adipose tissue in obese subjects as compared with their non-obese counterparts (52, 53). Therefore, leptin is assumed to have a more vital effect on the asthma inflammation in obese than in non-obese individuals. The interactive effect of leptin and obesity in relation to asthma has been considered in a previous report. Mai et al. have studied the association between serum leptin concentration and asthma in normal weight vs. overweight children in Sweden (25). They found a tendency that the overweight asthmatic children had twofold serum levels of leptin as high as the overweight control children. In the normal weight children, however, serum levels of leptin were similar in children with asthma compared to children without asthma. However, because of the small sample size, the results are not conclusive for the study. Studies should further explore the possibility if leptin plays a distinguishing role in asthma between obese and non-obese subjects.

### Leptin as a regulatory mechanism vs. being etiologic

Leptin stimulates the production of TNF- $\alpha$  and IL-6 from the adipose tissue (20, 21). Previous studies report that serum leptin is a potent inflammatory promoter to exacerbate the existing inflammation in individuals with various lung diseases (54, 55). Inflammatory mediators such as TNF- $\alpha$  also promotes the expression and release of leptin from the adipose tissue (56, 57), formulating a positive feedback mechanism. In addition, leptin in cord blood was not predictive for wheeze within the first 2 yr of life (58). Thus, leptin may be more in a regulatory mechanism of asthma than being etiologic (38). This raises another important question whether leptin contributes to poor asthma outcomes in obese individuals. Leptin may also exert regulatory mechanism through its effect on regulatory T cells (Fig. 1). Leptin has recently been found capable to restrain proliferation of regulatory T cells (59), and regulatory T cells protect against both Th1-mediated autoimmune disease and Th2-mediated immune disease such as asthma (15, 59).

### Factors affecting leptin

Many factors have been suggested to affect the serum levels of leptin, such as sex, age, puberty, BMI, breastfeeding, and utilization of steroids (25, 38, 39, 46). Circulating leptin levels are

relatively low in childhood. There is evidence that boys have lower levels of leptin than girls in cord blood and in circulation during the first years of life despite an absence of difference in body weight (44, 46). During childhood, leptin levels increase gradually with age in both sexes. However, it is unclear if age has an independent effect on serum levels of leptin (39, 60). The weak correlation between the leptin levels and age during this period may be explained by the concurrent increase in body fat mass. The gender difference in leptin levels tends to fade away right before the onset of puberty (61). With the onset of puberty, leptin levels increase in girls but decrease in boys following the increase of pubertal stage (61). This can be explained by the effect of sex hormones on leptin expression, as testosterone can inhibit and ovarian sex steroids can increase the expression of leptin (62). Incontrovertibly, leptin is positively associated with body fat mass, body fat percentage and BMI (17, 19). Exercise and weight loss reduce circulating leptin concentration both in children (63, 64) and in adults (65, 66). Higher levels of serum leptin have been detected in breastfed than in bottle-fed infants during the first years of life (46, 67). This difference may be due to an endocrine response to different milk, or may be due to a direct consequence of this hormone being absorbed by breastfed infants, as low levels of leptin are present in breast milk (68). Studies have also shown contradictory results of higher leptin levels in formula-fed infants (43, 45), and the question remains if breastfeeding has a long-lasting effect on the circulating leptin levels in offspring. The administration of systemic steroids may increase the levels of leptin in circulation (69), but inhaled steroids have been reported to have no impact on serum levels of leptin (38, 69). When the role of leptin in obesity–asthma relationship is evaluated, these factors need to be taken into consideration.

### Other aspects

There is a significant diurnal variation in leptin levels. A study have demonstrated relatively constant levels from 10 AM to 6 PM, followed by increased levels during the night with peak levels between 10 PM and 2 AM (70). Feeding has also an impact on circulating levels of leptin. Thus, blood samples for the analysis of leptin have usually been collected in the morning after overnight fasting in the previous studies in order to minimize bias caused by its circadian variation.

## Conclusion

It is likely that there is a link between leptin and asthma, in particular in children. However, there is still a lack of sufficient evidence for leptin being in the pathway of obesity–asthma relationship or playing a distinctive role in obese subjects vs. non-obese subjects. Weight loss is associated with decreased circulating leptin concentration in children. Weight control program is beneficial for a variety of health outcomes in obese children, and it may also need to be considered in the treatment of asthma.

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