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REVIEW ARTICLE

A Novel Hypothesis for Pathophysiology of Asthma in Obesity

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ABSTRACT

Both Obesity and asthma have been increased over recent decades. These multifarious characteristics cannot be studied as a whole in some other *in vitro* models by any alternative methods and therefore animal models are essential to decipher the mechanisms involved in such complex pathological process in order to find better therapeutic agents. Severity of asthma in obesity is due to higher level of leptin. Obesity has been suggested to be only single factor for the development of asthma or it makes existing asthma more severe. It also depends on factors such as age and sex. The complex interrelation between obesity and asthma is an example of the interaction between genes, plasma leptin level and the environment in the pathogenesis of both disorders. Obesity, by means of inflammatory mechanisms or changes in lifestyle, can trigger asthmatic symptoms in susceptible individuals. The combination of diet, serum leptin and adiponectin level may alter the normal pattern of airway muscle tone.

KEYWORDS

Leptin, Obesity, Asthma, Pro-inflammatory Mediators

INTRODUCTION

Asthma

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular masts cells, eosinophils, T lymphocytes, macrophages, neutrophils and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyper-responsiveness to a variety of stimul(1). As of 2009, 300 million people worldwide were affected by asthma leading to approximately 2,50,000 deaths per year(2).

Asthmatic patients experience intermittent attacks of wheezing, shortness of breath, and cough. The strongest risk factors for developing asthma are a combination of genetic predisposition with environmental exposure to inhaled substances and particles that may provoke allergic reactions or irritate the airways such as indoor allergens like house dust, mites, pollution and pet dander, Outside allergens such as pollens and moulds, Tobacco smoke, chemical irritants in the workplace, air pollution. Other triggers can include cold air, extreme emotional arousal such as anger or fear, and physical exercise. Even certain medications like

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aspirin, other non steroidal anti-inflammatory drugs, and beta-blockers can trigger asthma(1).

Obesity

Obesity is metabolic disorder and inflammatory condition(3), increased severely over the last two decades. Overweight and obesity are defined by the WHO as excess fat accumulation that presents a risk to health (4). Obesity has become an acute focal point of research, as it is a strong risk factor for various diseases. These include cardio vascular disease, diabetes, asthma, orthopedic diseases and some forms of cancers (5–9), not to mention the social stigma and low self-esteem that obese individuals may suffer (5). The rapid urbanization and Westernization of countries has led to consumption of larger amounts of energy with a decline in daily activity, which has resulted in rising epidemics of obesity (10, 11). According to the WHO, in 2008, over 1.4 billion adults older than 20 years of age were overweight; among them, approximately 200 million men and 300 million women were obese (4). The prevalence of obesity risen by 125 % when compared to period 1996-2000 with 2010-2011 which is alone risk factor for death (12). This sinario is not only limited to india and U.S. but also in the other developed and developing countries (13).

In obesity, five times higher leptin level was observed and it increases exponentially with increasing fat mass (14). Elevated Leptin level reflect states of energy imbalance (15) and leptin resistance (16). Mutation of mouse ob gene results in a syndrome that includes obesity, increased body fat deposition, hyperglycemia, hyperinsulinemia, hypothermia and impaired thyroid and reproductive function in both male and female homozygous ob/ob obese mice (17).

Obesity is often associated with cardiovascular risks, hypertension, dyslipidemia, and type 2 diabetes mellitus and has recognized as one of the most serious public health problems in the 21st century (18). Obesity and increasing weight gain might be risk factor for the development of asthma especially in women (19).

Is there any link between obesity and asthma?

Obesity and asthma are conditions that have been increasing in recent decades. This sudden increase is most probably caused by the shift towards the Westernized lifestyle and rapid urbanization. Strong association has been found between asthma and obesity and it has been shown that obesity increases the risk of asthma (20). The large and pathologically specific group of obese patients with asthma has attracted the attention of scientists and medical doctors worldwide. The present review explores the complex association between the two conditions, with focus on their epidemiology, but also involving the pathophysiology and clinical aspects, which can serve for the creation of the personalized, tailor-made intervention and prevention initiatives for severely affected patients.

The studies on animal models show innate enhancement of airway hyper-responsiveness which suggest that chronic airway hyper-responsiveness may be related to chronic low-grade systemic inflammation occurring in obesity. These results are confirmed by studies on asthmatic patients which show that levels of inflammation markers were higher in obese asthma patients and are related to the parameters of obesity. However, adipokines secreted by adipose tissue have also been involved in the regulation of inflammation and allergic responses, and suggested to affect the risk of asthma, especially in obese female patients. The studies on the association between adiposity and atopy have conflicting results and the issue needs to be investigated in the future. Obesity also decreases lung volume and increases airway resistance inducing symptoms that could mimic asthma. Clinical studies suggest that asthma in obese subjects may differ from the classical phenotype of the disease. Obese patients referred for asthma exacerbation present a reduced response to standard asthma medications (21).

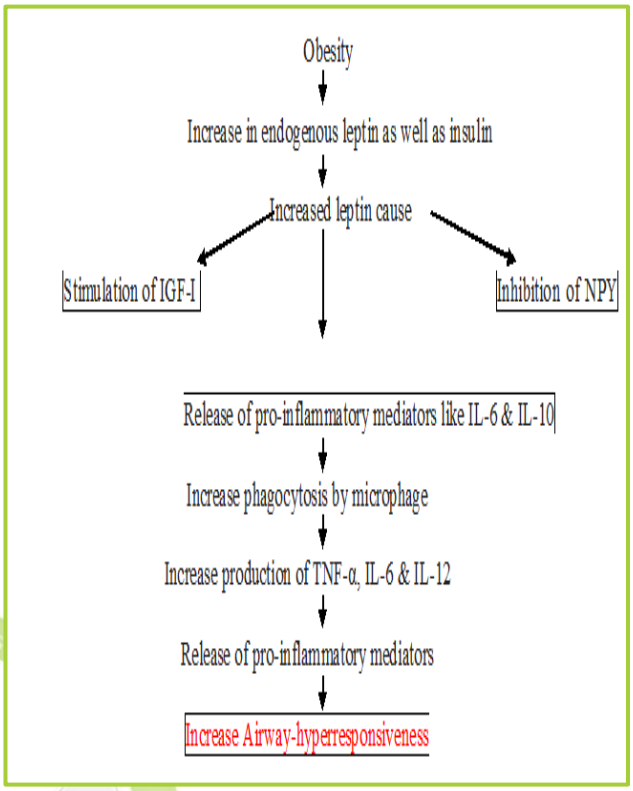
Not only is obesity a risk factor for asthma, but asthma in the obese has distinct features compared to disease in the non-obese. Obese asthmatics tend to have more severe disease (22-

23) respond less well to standard controller therapy, (24) and have evidence of cellular glucocorticoid resistance (25). This despite the fact they do not appear to have worsened airway inflammation as measured by either sputum eosinophils or neutrophils (26). It is also found that obese asthma patients have more severe disease with increased asthma exacerbations, decreased asthma control, and decreased steroid responsiveness (27). Accordingly, studies on the pathogenesis of asthma in the obese are critical to guide our understanding of this disease process; such studies will ultimately guide the development of new therapies to treat obese asthmatic population (28).

It is well aware that in obesity adipose tissue play major role as inflammatory state. Adipose tissue is not merely for storage of spare energy consumed but not used. Adipose tissue is a physiologically complex and highly active metabolic and endocrine organ that secretes various hormones like adipokines and adiponectin. These regulate the appetite in the central nervous system, as well as insulin, fatty acid levels and sex hormone precursors (29, 30).

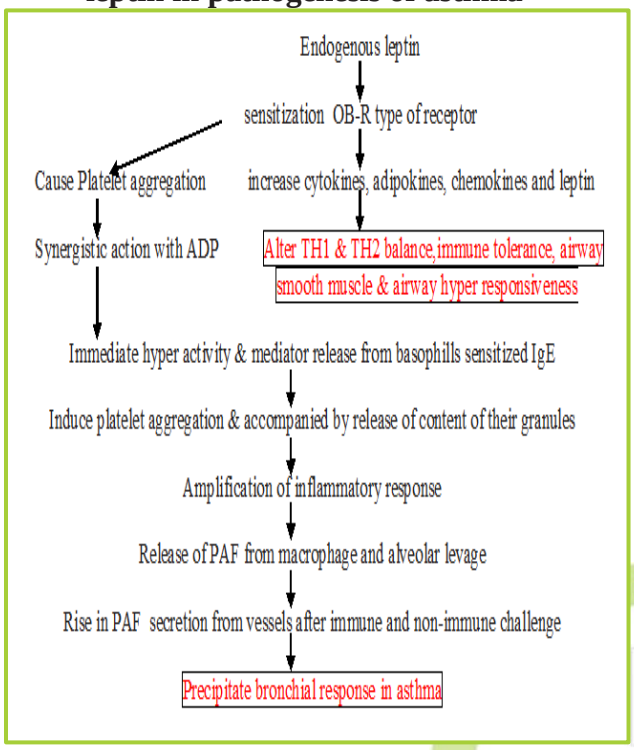
Leptin is from adipokine family which is realeaed from adipose tissue that functions as the afferent signal in negative feedback loop regulating body weight. Leptin circulates as a 16-kD protein in mouse and human plasma(11). Five of the known leptin receptor isoforms, OB-Ra, OB-Rb, OB-Rc, OB-Rd, OB-Rf contain transmembrane domains (29-30). OB-Rb is most prominent and it is single transmembrane-spanning receptor that belongs to the class I family of cytokine receptors (31). Leptin binding to OB-R receptors activate Janus kinase (JAK)-STAT- signaling transduction cascade (20). Increase in the normal functioning of adipose tissue in obese subjects reflects a systemic pro-inflammatory state which leads to elevated serum concentrations of various cytokines, and soluble fractions of their receptors and chemokines (21) which are common factor for Airway hyper responsiveness (AHR) (Figure 1).

Figure-1: Presenting Obesity in pathogenesis of asthma



Many of these mediators are synthesized and secreted by cells from adipose tissue which includes IL-6, IL-10, eotaxin, tumor necrosis factor (TNF)-α, TGF-ß1, C-reactive protein, leptin, and adiponectin (22-24). Leptin impairs immune function in both ob/ob (25) and db/db mice (26). These impairment have been observed principally in cell-mediated immune response, in resistance to viral and bacterial infections and in macrophage function (27). Leptin has been shown to act directly on CD4+ helper T cells including their proliferation and increasing cytokine production (23). Impairment of cell-mediated immune reaction & imbalance the TH1 & TH2 (Figure 2) which are causative factor for asthma. Platelet aggregation due to activation of cytokine releases platelet activating factor (PAF) and complement system. PAF is one factor for Hypersensitivity reaction at bronchial level. Leptin stimulates proliferation of T-lymphocytes and promotes helper type 1 immune response. Serum leptin increases as BMI increases (32).

Figure-2: Presenting role of endogenous leptin in pathogenesis of asthma



When leptin deficient mice are injected with BSA or myelin they develop a greatly attenuated form of these disorders (33-35). These studies suggest that leptin may play a role in organ specific inflammatory disorders. Asthmatic patient however have been found to have elevated leptin levels.

CONCLUSION

From this review we proposed hypothesis that in obesity as leptin and other adipokines level increases, pro-inflammatory mediators like IL-6, IL-12, TNF-α etc can exaggerate the asthma. Leptin also found to be releasing PAF by leptin receptor in respiratory tract and causing hyper-responsiveness which make existing asthma more severe.

In conclusion, this new outlook illustrating the pathophysiology of asthma in obesity and considering and with evi¬dences, one can provide novel therapeutic measures putting into consideration the advantages of this natural morphological defensive mechanism. The review also indicates that mechanical and inflammatory effects of obesity may explain the influence on asthma. Further studies on the association between adiposity and atopy on airway inflammation may confirm the active role of fat tissue, not only simple mechanical impairment of the thorax movement. Longitudinal studies are needed to understand the association between asthma, and obesity, which may open new therapeutic options for asthma treatment in obese patients.

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