

Obesity and Allergic Diseases

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SUMMARY: In the last few decades, the prevalence of allergic diseases, asthma, allergic rhinoconjunctivitis and atopic dermatitis in particular, has been observed to increase in urban settings. In addition, epidemiological data show the proportion of overweight individuals to rise in the last two decades. Obesity and overweight are a major public health problem not only in industrialized countries but also in developing ones because the morbidity and mortality rates are greater in the obese. An increased body mass index is considered a risk factor for the occurrence of myocardial infarction, stroke, atherosclerosis, hypertension, insulin resistance, dyslipidemia and some types of carcinoma. An ever greater body of available data point to the possible association of allergic diseases with obesity and overweight. Impaired immune tolerance is considered to be a sequel of immune changes due to the activity of adipokines, bioactive molecules secreted in white adipose tissue. About 50 adipokines are currently known to be secreted in adipose tissue, some of them belonging to the group of cytokines such as tumor necrosis factor α and interleukin-6. The association between obesity and allergic diseases has not yet been fully clarified. While the observations recorded to date should not be neglected, additional studies are necessary to help understand the complex function of adipokines involved in allergic events.

KEY WORDS: allergic diseases, obesity, white adipose tissue, adipokines, TNF- α

INTRODUCTION

In the last few decades, the prevalence of allergic diseases such as allergic asthma (AA), allergic rhinoconjunctivitis (AR) and atopic dermatitis (AD) has been observed to increase, in urban settings in particular. The factors contributing to this rising pattern have not yet been fully elucidated, however, a number of potential causes have been implicated, including ever greater environmental pollution, exposure to "newly emerging" allergens for the human immune system, formation of so-called allergen conglomerates through allergen interaction with contaminated atmosphere, prolonged

stay indoors, sedentary work, inadequate physical activity, and stressful lifestyle (1). Recently, ever more data point to the possible association of allergic diseases with obesity and overweight.

ALLERGIC DISEASES ON AN INCREASE

Data from western countries show an increase in the prevalence of AD, e.g., of 7%-21% in schoolchildren from different areas of the USA (2,3) and 15.8% in New Zealand (4). In a Munich study, the cumulative prevalence of AD in children aged

≤2 years was 21.5% (5), whereas a study in pre-school children from two towns in Sweden yielded a cumulative AD incidence of 20.7% *versus* 15% recorded in the same area 5 years before (6). A study carried out in Denmark that included children aged 12-16 years showed a total AD prevalence of 21.3% and one-year prevalence of 6.7% (7). In Copenhagen, the cumulative incidence in two-year-old children was as high as 41% (8).

AR is also on an increase, with 20%-30% of the population suffering from this allergic disease worldwide (1). The same holds for the prevalence of AA, which shows a disturbing rise in children in particular. In the USA, the prevalence of AA in children increased from 3.6% in the 1980s to 8.9% in 2005 (9). In Denmark, 6.9% of children suffer from AA, and as many as 15.7% of children have some symptoms of AR (7).

Results of a study performed in 2003 in 18 Zagreb elementary schools as part of the International Study of Asthma and Allergies in Childhood (ISAAC) showed the City of Zagreb to have a relatively low prevalence of allergic diseases relative to other countries. The study included 1047 children aged 10 years. The 12-month prevalence of AA, AR and AD was 6.02%, 12.13% and 7.83%, respectively (10).

OBESITY AND OVERWEIGHT

In the last two decades, the increase in the prevalence of allergic diseases has been paralleled by a growing proportion of the obese and overweight in the general population. The World Health Organization (WHO) has issued a warning on obesity to becoming the leading challenge in the 21st century, as the proportion of obese persons shows a very disturbing increase. The morbidity and mortality rates are greater in the obese than in those with normal body weight. An elevated body mass index (BMI) poses a risk of myocardial infarction, stroke, atherosclerosis, insulin resistance (11), hypertension (12), Crohn's disease (13), and some types of carcinoma (14). Obesity and overweight pose a problem in both industrialized and developing countries. In Croatia, there are more than 20% (n=720,000) of obese individuals, along with 43% of male and 34% of female overweight persons. In 2003, the mean BMI in Croatia was 29.93 kg/m² (15). According to WHO data, one third of the world population are obese. In some European countries, the proportion of obese persons is lower than that recorded in Croatia, i.e. in Austria 10% of male and 14% of female, in France 11% of male and female, and in

Spain 12% of male and 15% of female individuals. In Greece, however, obesity is found in as many as 28% of male and 38% of female population (15). In the USA, obesity and overweight also pose a major public health problem. Data on the 1999-2002 period show the prevalence of obese persons to exceed 30.5%, while the prevalence of overweight was 64.5%, with more than 4.7% of extremely overweight and BMI >40 kg/m² (16). Data on 10% of obese children worldwide and even 16% in the USA cause great concern, especially in conjunction with the fact that 30% of children in the USA are overweight and at risk of developing obesity (15,16).

BODY MASS INDEX

The main characteristic of obesity is excessive deposition of subcutaneous and visceral adipose tissue. Body mass index (BMI), also known as Quetelet index, is an alternative fatty tissue measure showing the body mass (kg) to body height (m²) ratio. BMI has been used since the 19th century, when it was defined by the mathematician Lambert Adolphe Jacques Quetelet, based on the assumption on BMI to be age, sex and race independent. However, anthropometric and hydrodensitometric measurements using the method of tritium dilution monitoring and dual-photon absorption have subsequently showed the percentage of adipose tissue to be greater in elderly and female individuals (17). Yet, BMI has continued to be used in epidemiological studies, since additional measurements cannot be implemented in large studies, while novel methods are rather expensive and occasionally require the use of radiologic techniques. Individuals with BMI of 25.0-29.9 kg/m² are considered to be overweight and those with BMI exceeding 30.0 kg/m² are obese.

ADIPOSE TISSUE AS AN ENDOCRINE ORGAN

Adipose tissue was considered as an energy reservoir until the discovery of leptin, a bioactive molecule structurally similar to cytokines, in 1994 (18). Nowadays, it is known that about 50 bioactive molecules are secreted in adipose tissue, which is therefore considered as an endocrine organ. Some of these molecules belong to cytokines, such as tumor necrosis factor α (TNF- α), interleukin-6 (IL-6) and interleukin-8 (IL-8); however, some molecules such as leptin and adiponectin do not have a cytokine structure. Thus, the previously used term "adipocytokines" has been substituted by the term "adipokines" (19). White adipose tis-

sue consists predominantly of adipocytes, and of connective tissue matrix, nervous tissue and stromal vascular cells (18). Analysis have shown that CD14+ and CD31+ macrophages account for some 10% of the stromal vascular fraction, their number being directly dependent on the amount of adipose tissue (20).

Besides the adipokines mentioned above, the following ones are also secreted in adipose tissue: growth factors such as transforming growth factor β (TGF- β); complement factors such as adipsin; blood pressure regulatory factors such as angiotensinogen; lipid metabolism factors; glucose homeostasis factors including adiponectin; angiogenesis factors; and probably an increasing number of adipokines in the future (18). Proinflammatory cytokines account for the major part of active molecules secreted in adipose tissue of obese persons. These cytokines are then released to the circulation maintaining the state of so-called mild inflammation. This subclinical proinflammatory state is responsible for all metabolic and cardiovascular alterations accompanying metabolic syndrome (21,22). Adiponectin is the only adipokine demonstrated to have an anti-inflammatory action; also, its secretion is known to decrease with fatty tissue accumulation (23). According to studies pointing to the possible association of obesity and allergic diseases, the reduced immune tolerance is considered to be consequential to the immune changes caused by the action of adipokines (24).

TNF- α is the most extensively investigated cytokine which is known to steer the functions of some other cytokines. TNF- α is secreted by adipocytes and stromal vascular cells, mostly in subcutaneous and to a minor extent in visceral adipose tissue. The mRNA for its TNF-R1 and TNF-R2 receptors is known to be secreted in adipose tissue. TNF- α is characterized by marked pleiotropic action, as there are more than 20 TNF- α receptors. It directly influences the secretion of IL-6 (25). According to some reports, TNF- α increases the T helper type 2 lymphocyte (Th-2) production of cytokines such as IL-4 and IL-5, thus being directly involved in the mechanisms of early hypersensitivity (24,26).

IL-6 secretion in the circulation correlates positively with fatty tissue deposits. It is considered that 30% of IL-6 is secreted exclusively in adipose tissue. IL-6 modifies glucose tolerance, aggravates insulin resistance (18), and stimulates hepatic production of C-reactive protein (CRP) (19). As part of its immune activity, IL-6 is known to stimulate B lymphocytes for the production of antibodies (27).

DISCUSSION

A number of recent epidemiological studies indicate the incidence of atopic diseases to be higher in obese than in normal weight individuals. In a prospective study conducted in the USA in the population of nurses aged 26-46, increased BMI after age 18 was associated with a greater incidence of allergic asthma (28). As this study included exclusively female population, there are no data on the possible sex differences. In a Canadian study that included both male and female subjects aged 20-64, obesity was associated with the development of asthma in women but not in men (29). One of the reasonable explanations for such a pattern may be found in the greater percentage of adipose tissue in women as compared with men with the same BMI. In addition, female sex hormones, progesterone and estrogen in particular, may have a role in the etiology of asthma. Progesterone and estrogen are secreted in adipose tissue (21). The 17 β -estradiol, which is considered to act as a strong modulator of IL-4 secretion, was found to be elevated in a group of healthy but obese women. Adipose tissue is considered to contain an array of steroidogenic enzymes involved in the synthesis of estrogen. Testosterone aromatization to estradiol was also observed to be greater in obese than in normal weight women (30). In postmenopausal women receiving hormone replacement therapy (HRT), the incidence of asthma was found to be twofold that in their non-HRT counterparts, thus clearly pointing to estrogen involvement in the etiology of asthma (31). A similar study including subjects of both sexes and relatively younger age groups (age 18-30) also showed an association between increased body weight and asthma in women but not in men (32). In contrast to these reports, results of a study carried out in Atlanta, USA, indicated an association of BMI and asthma, with the incidence of asthma being comparable in the two sexes (33). The more so, a study from California, USA, which included children of both sexes aged 7-18, showed the risk of asthma to be greater in male than in female children (34).

The association of BMI and atopy has also been investigated. In a study from Munich in children aged 4-17, the rate of positive prick tests to nutritive and inhalation allergens was considerably higher in children with higher BMI. There was no sex difference (35). On the contrary, a study performed in Arizona, USA, an association of BMI and hypersensitivity was demonstrated in female but not in male children. Positive prick test to at least

one allergen was recorded in 54.2% of female children having put on weight *versus* 35.9% of female children without weight gain (36). Similar results have also been reported from a Taiwan study (37). A study of atopy in healthy but obese women revealed threefold levels of specific IgE to particular allergens while the levels of total IgE were not increased in comparison with control group subjects, thus demonstrating direct association between obesity and Th-2 immune response (30).

Some studies failed to demonstrate an association between obesity and asthma. One of these was a study from England that included children aged 8 and 9 (38). In a study from New Zealand, no such association was found in childhood but it did emerge in late adolescence to rise considerably by the age 26 (39). It should be noted that the above mentioned study in England (38) was launched in the early 1970s, when the association of obesity and allergic diseases had not yet been so pronounced; thus, it is rather considered a phenomenon characteristic of the last 2-3 decades (40).

CONCLUSION

The association of obesity and allergic diseases has not yet been fully clarified. The observations and findings reported to date should by no means be neglected, while additional research is necessary to improve the understanding of the complex function of adipokines involved in allergic events.

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