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Obesity, Diet, Exercise and Asthma in Children

Luis Garcia-Marcos and Manuel Sanchez-Solis
University of Murcia,
Spain

1. Introduction

During the past decades, an increase in several pediatric morbid conditions has been well documented. Two of the most important of these conditions are obesity and asthma. While the increase of asthma prevalence has been explained in part by the so-called hygiene hypothesis, which claims for a shift from a Th1 to a Th2 environment (if the immunological system does not have to deal with infections –Th1- due to a much more aseptic environment, it will turn to an allergic predisposition –Th2) (von Mutius, 2007). However, this hypothesis does not explain the high prevalences among inner city populations (Platts-Mills et al., 2005) or developing countries as found in the International Study of Asthma and Allergies in Childhood (ISAAC) (Asher et al., 2006). On the other hand, the increased prevalence of obesity is most probably due to an imbalance between the energy intake (both in quantity as well as quality) and the expenditure, in which the lack of exercise is a key point. In this chapter we will explore the complex relationship between asthma, obesity diet and exercise in children.

2. Obesity and asthma are linked together

2.1 The epidemiological link

In this section some of the epidemiological evidence regarding the link between asthma and obesity is reviewed.

2.1.1 Obesity/overweight is associated and precedes asthma

Numerous studies support the epidemiological association between asthma and obesity. Though many of them are cross-sectional, thus making it difficult to establish a casual relationship, some have been specifically aimed at disentangling the first question of which is first in those two apparently connected diseases. The meta-analysis by Sutherland and Beuther (Beuther & Sutherland, 2007) included seven studies which fulfilled their criteria of including adult individuals followed for at least one year in which the main outcome variable was incident asthma and whose obesity was measured using body mass index (BMI). The aforementioned studies included more than 300,000 individuals and the result clearly demonstrated that BMI was associated to incident asthma in a dose-response manner: the association was higher with obesity than it was with overweight.

There are also a number of epidemiological clues which suggest that obesity in childhood precedes asthma later in life. For instance, in a Tasmanian cohort study (Burgess et al., 2007)

of children recruited at the age of seven years, adiposity (defined as overweight at 7 years, or as highest quartile BMI) was associated with incident asthma between the ages of 21 and 32 years in girls, but not in boys. Although the number of subjects was low, the association was considerably high. Similarly, females who became overweight or obese between 6 and 11 years of age were seven times more likely to develop new asthma symptoms at ages 11 or 13, according to the Tucson Children Respiratory Study (Castro-Rodriguez et al., 2001). However, not all studies have found a higher association in girls. In fact, in the Children's Health Study (Southern California) the risk of new-onset asthma was higher in boys than in girls, although it was significant in both genders.

Not only do overweight or obesity seem to precede asthma but birth weight has also been shown to be related to later asthma. Although not all the reports coincide it does seem quite consistent that extreme high birth weights are strongly associated to asthma symptoms in school years (To et al., 2010). Furthermore, children with a predisposition for asthma may have a higher risk of developing asthma during childhood when their mothers are overweight before pregnancy, irrespective of the child's BMI (Scholtens et al., 2010). It is also of interest that infants breast fed for at least six moths have a better lung function, and this seems to be related to a lower weight gain. This was shown by Turner at al. (Turner et al., 2008) who followed 154 infants from birth. Maximal flow at functional residual capacity (V'maxFRC) was measured at 1 and 12 months of life: the change in V'maxFRC was inversely associated with change in weight. The group with lower V'maxFRC at 1 month and reduced change in V'maxFRC over infancy had the greatest weight gain and increased risk for asthma symptoms by the age of three years but not afterwards. Those authors concluded that postnatal weight gain may be indirectly associated with early transient asthma symptoms which might be the result of impaired lung growth during infancy, a situation which could be modifiable by breast feeding. A Danish cohort study in which lung function was measured at 6 weeks of age showed that infants in the upper quartile of BMI had lower $FEV_{0.5}$ (Bisgaard et al., 2009). To what extent this circumstance of the early years can be translated to older ages and established asthma is difficult to say, although a connection between obesity and architectural changes in the lung is suggestive, especially if the action of adipokines (which will be reviewed later in this chapter) is taken into account.

Taken together, epidemiological data indicate that body weight and asthma are related in some way, and that excess weight seems to precede asthma or asthma-related symptoms. This fact does not necessarily rule out that the two conditions develop in parallel with the former being apparent before. Furthermore, there are factors which modify the relationship between obesity and asthma. This has been shown in a cross-sectional study (Garcia-Marcos et al., 2008) including a very high number of children: although the association was highly significant for the whole group, it changed dramatically when the group was stratified between those asthmatics also suffering or not from rhinoconjunctivitis. Obesity was not a risk factor for those children with significant asthma who also suffered rhinoconjunctivitis. Although the study has limitations and rhinoconjunctivitis is not a perfect marker of atopy, it raises the question as to whether obesity may be related only to specific asthma phenotypes.

2.1.2 Obesity and asthma develop in parallel, especially in periods of fast growth and maturation

Rather than obesity being the cause of asthma, some findings support the hypothesis of parallel processes which may be related to a change of the environment in which children

develop. It is probably when development is more intense (immediately after birth and during puberty) when those processes may be more obvious. Some facts support this view:

- Perinatal events (Jaakkola et al., 2006; Sukalich et al., 2006) or mother food consumption during pregnancy have an influence on later obesity and asthma (Chatzi et al., 2008; Castro-Rodriguez et al., 2010).
- Breast feeding and dietary habits during infancy and later on, are related to obesity and asthma (Matheson et al., 2007); (Moreno & Rodriguez, 2007).
- It is among pre-puberal girls where the association between obesity and asthma is most apparent (Castro-Rodriguez et al., 2001); (Garcia-Marcos et al., 2007), and obesity favours early menarche.
- Epidemiological studies show that females who became overweight or obese between 6 and 11 years of age were seven times more likely to develop new asthma symptoms at age 11 or 13 (Castro-Rodriguez et al., 2001). Moreover, the early onset of puberty has been associated with the persistence of asthma after puberty (Guerra et al., 2004).
- Obesity and asthma are linked conditions during puberty. Although both obesity and asthma can start early in the child life, it is probably around puberty when the connections between those conditions may be better revealed, as some epidemiological studies have shown (Castro-Rodriguez et al., 2001); (Herrera-Trujillo et al., 2005). Some mechanisms might explain this process. For instance, leptin is a key permissive factor (Navarro et al., 2007) –probably through the activation of kisspeptin neurons (Kauffman et al., 2007)- for the onset of puberty. Furthermore, the increase in body weight which occurs during the pubertal spurt induces a corresponding increase of circulating leptin, but also of interleukin (IL)-6 and tumour necrosis factor alpha (TNF-α).
- Several areas in the genome are common to mediators related both to asthma and obesity.

2.1.3 The association between obesity/overweight and bronchial hyperresponsiveness is conflicting

A recent review by Shore (Shore, 2010) lists eight studies dealing with the association of obesity and bronchial hyperresponsiveness (BHR) in adults and a further eight in children. Except for one, all the studies in adults were carried out using metacholine in the challenge test. In children, there were studies using metacholine (n=3), histamine (n=1) and exercise (n=3). The results do not point in the same direction even in the two longitudinal studies (one in adults and one in children). The study in adults reported that high initial BMI was un-linearly associated to later BHR; and weight gain was also associated linearly with the risk of later BHR. On the contrary, the study performed in children (Hancox et al., 2005) did not find any association. Interestingly, however, a high BMI was associated to asthma only in women. This might indicate that the link between obesity and asthma might not necessarily be mediated through airway inflammation revealed by metacholine challenge testing. The cross-sectional studies in children which used metacholine in the challenge test showed all types of results: no association; association only in males; or association only in females. On the contrary, all three cross-sectional studies using exercise as the challenge test found a positive association. The cross-sectional studies in adults (none of them using exercise) also found mixed results, including one study which observed that BMI increased BHR in non-asthmatics but not in asthmatics.

Although a number of factors such as gender, type of challenge test, non-linear association between BMI and BHR (which might counteract the effect of BMI if both low and high BMI are associated to BHR), age groups, asthma control, lack of control for diet, etc. may explain the discrepancy between studies, it seems quite clear that the evidence of an association (if any) between BMI and BHR is not as strong as it is for asthma diagnosis or asthma symptoms. It is interesting that the results are concordant only for the exercise challenge test which does not produce smooth muscle reactivity (as metacholine does) but provokes mast cell activation. It might be hypothesized that obese individuals either create a different osmolality of the airways (the mechanism thought to be responsible for BHR with exercise) while exercising, which in turn causes a higher mast cell activation; or have more mast cells in their airways; or they are more sensitive to osmolality. Although findings in animal models are difficult to translate to humans, it is of great interest that obese mice sensitized and challenged with ovoalbumin have increased numbers of mast cells in their lungs as compared to lean controls (Mito et al., 2002).

2.2 The clinical link

Further evidence that obesity and asthma are related to each other is the fact that BMI predicts asthma control as an independent factor. For instance, in a very recent study, Farah et al. (Farah et al., 2011) reported on asthma control in 49 asthmatic subjects before and after three months of treatment with high doses of inhaled corticosteroids. The effects of treatment were stratified according to BMI (normal, overweight and obese) and the degree of control was assessed by means of the asthma control questionnaire (ACQ-5) although other variables, such as forced expiratory volume during the first second (FEV1), airways resistance (Rrs) and reactance (Xrs) as measured by the forced oscillation technique, BHR to metacholine, and exhaled nitric oxide (FeNO), were also measured before and after treatment. After the treatment period neither FeNO (as a surrogate of bronchial eosinophilic inflammation) nor FEV1 predicted asthma control according to ACQ-5. The two independent predictors of ACQ-5 were Rrs and BMI. The authors conclude that BMI is a factor which determines asthma control and is independent of airway inflammation, lung function and BHR. Furthermore, after ICS treatment, BMI again predicts ACQ-5, and this seems independent of obesity-related changes in lung mechanics.

From a different angle, but adding some evidence to the argument, one study (Maniscalco et al., 2008) has shown that weight loss helps to control asthma in asthmatic individuals. In a series of 12 consecutive asthmatic females who had laparoscopic adjustable gastric banding and consecutively a significant weight loss, asthma control was significantly improved as compared to a control group. Interestingly, no changes in FeNO were found before and after the surgical procedure. Previously, another study showed that a small group of asthmatics (mainly women) significantly improved their asthma control after a very-low-calorie-diet period of 8 weeks (Hakala et al., 2000). In this case, spirometric variables significantly improved leading the authors to think that improvement may be due to better lung mechanics. To the best of our knowledge there are no controlled studies evaluating the effect of weight loss in obese children.

2.3 A genetic link?

There are some regions of the genome that are linked with both asthma and obesity, as occurs with chromosome 5q, 6, 11q13 and 12q (Tantisira & Weiss, 2001). Chromosome 5q

contains genes coding the β_2-adrenergic receptor, which has been related to different asthma phenotypes, asthma severity and differential response to β_2-agonists (Hall et al., 1995). A change of Gln for Glu in this receptor has been also associated to obesity (Ishiyama-Shigemoto et al., 1999). Additionally, chromosome 5q contains the glucocorticoid receptor gene which has been involved in inflammatory responses associated to obesity and asthma. Chromosome 6 contains the gene for TNF-α, an interleukin which is important for both obesity and asthma. Another genome region which is linked with asthma and with obesity independently is that of chromosome 11q13 which contains genes for the uncoupling proteins UCP2-UCP3 (related to baseline metabolism) and for the low affinity receptor for IgE. To end, chromosome 12 contains the genes for inflammatory cytokines both related to asthma (such as IFN-γ, or nitric oxide synthase-1) and to obesity (such as signal transducer and activator of transcription protein 6 -STAT6-, or type 1 insulinoid growth factor) (Delgado et al., 2008). To what extent specific but very large areas of the genome are involved in the genesis of the parallel development of asthma and obesity is questionable. How epigenetic changes taking place under certain environments might influence genome areas related to both diseases is even more questionable.

2.4 The inflammation link

The hypothesis that the increase in the prevalence of asthma and obesity, being parallel, could be related to one another (Chinn & Rona, 2001) seems quite plausible. However, a definite link between the two conditions has yet to be definitely established, as it seems to be related to the age and gender of the studied population (Castro-Rodriguez et al., 2001; Chen et al., 2002; Garcia-Marcos et al., 2007), and also to the asthma phenotype (Garcia-Marcos et al., 2008; Gilliland et al., 2003). However, some of the epidemiological and experimental information reviewed in former sections seems to indicate that obesity may precede asthma. To explain this, several inflammatory mechanisms have been evoked:

2.4.1 Adipokines

Adipokines are cytokines produced by the adipose tissue. Some of them are associated both to obesity and to asthma.

2.4.1.1 Leptin

Leptin is mainly produced by white adipose tissue proportionally to the amount of such tissue. Leptin production is regulated by food intake: food consumption up regulates the *ob* gene, thus increasing leptin synthesis; conversely, fasting reduces leptin levels. Infection and sepsis and various pro-inflammatory cytokines including TNF-α and IL-1 increase leptin. Conversely to this acute response, chronic inflammation causes a reduction in leptin levels. Leptin is also moderated by sex hormones: while testosterone inhibits leptin production, ovarian sex steroids increase it, a fact which keeps up with gender-related dimorphism of this adipokine: leptin levels are higher in females than BMI and age-matched males. The main target organ for leptin is the hypothalamus in which it triggers efector pathways to suppress appetite and increase energy expenditure. Apart from the metabolic processes, leptin is also involved in other functions, including the immune response both innate and adaptative: it increases several pro-inflammatory cytokines, such as TNF-α, IL-6 and IL-12, and increases chemotaxis and the functioning of natural killer cells. Overall, leptin increases Th1 and suppresses Th2 response by acting on T regulatory cells (Treg). The leptin receptor gene (*db* gene) is expressed in the lung tissue

of several animals and also in humans (Tsuchiya et al., 1999). Although the role of those receptors is not yet clear their presence indicates that the lung is a target organ for leptin. There is also some evidence that leptin can stimulate surfactant protein synthesis (Malli et al., 2010). However, the evidence that leptin influences lung growth and maturation comes from animal models, thus extrapolation to humans remains a major limitation. There also appears to be some role of leptin in respiratory function control, at least in mice (Groeben et al., 2004; Tankersley et al., 1996).

Asthmatic 12-year-old children who are overweight have higher levels of leptin than overweight children who are not asthmatics, despite there being no difference of BMI between the two groups (Mai et al., 2004). This has been also shown in preschool children with normal weight, although reduced to male gender (Guler et al., 2004). Very interestingly, however, is that leptin and BMI are both associated to asthma in adults in an independent way, so when adjusting for leptin levels there is still an association of BMI with asthma (Sood et al., 2006). Furthermore, in asthmatic children leptin and IgE serum levels are highly correlated to each other (Guler et al., 2004). Atopic asthmatic boys have higher leptin levels than non-atopic asthmatic boys. The extent to which leptin has the ability to recruit eosinophils into the lungs and to augment leukotriene synthesis by macrophages may actually be the explanation of its association with atopy still remains controversial (Mancuso et al., 2004; Wong et al., 2007). Further than allergic inflammation as a possible pathway to asthma mediated by leptin, this hormone seems to also have some up-regulatory effect on the sympathetic nervous system, although it does not seem to be important in regulating airway smooth muscle tone (Nair et al., 2008), a fact which might be in connection to the non-consistent findings related to the association between obesity and BHR. However, its is interesting that leptin and leptin receptor are significantly reduced in bronchial epithelial cells in patients with mild asthma which is uncontrolled and in severe treated asthmatics as compared to mild asthmatics under good control, and healthy controls. Additionally, leptin and leptin receptor expression correlated inversely with the thickness of the basement membrane, which is a salient feature of lung remodeling (Bruno et al., 2009).

2.4.1.2 Adiponectin

Adiponectin has an anti-inflammatory role, and decreases with increasing obesity. Contrary to this apparent anti-inflammatory role favoured by obesity, adiponectin is increased in other chronic inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus or inflammatory bowel disease. Moreover, elevated levels of adiponectin in cord blood have been associated with an increased risk of asthma in children born from atopic mothers (Rothenbacher et al., 2007). More importantly, adiponectin decreases during puberty only in boys, and remains unchanged in girls (Andersen et al., 2007), a situation that would make gender a modifying factor in the association between obesity and asthma during puberty. Adiponectin and all its currently known receptors are expressed in multiple cell types in the lung (Hug et al., 2004; Miller et al., 2009; Takemura et al., 2007) which makes it a suitable candidate for an additional link between obesity and asthma. In ovoalbumin sensitized mice, administration of exogenous adiponectin protects against cell infiltration and cytokine levels. Serum adiponectin reduces allergic airway inflammation and BHR in mice (Shore et al., 2006). On the other hand and also in mice, adiponectin inhibits the proliferation of vessels associated to smooth muscles although it does not affect muscle itself (Medoff et al., 2009). These findings suggest that adiponectin is involved in allergic inflammation and pulmonary vascular remodeling in a mouse model of chronic asthma.

The number of studies in humans is scarce and the study by Rothenbacher et al. (Rothenbacher et al., 2007) seems to be contradictory to the animal model. Among children with a maternal history of atopy, lower level of adiponectin was associated to lower incidence of asthma or obstructive bronchitis during the first two years of life. Conversely, higher levels of cord serum adiponectin were associated to higher incidence of those respiratory conditions. Among those children without a maternal history of atopy, there was no association of the adipokine and the incidence of asthma or obstructive bronchitis. Other epidemiological studies in humans have rendered inconclusive results. In two cross-sectional studies with a relatively low number of school children, serum adiponectin was not associated to an ever diagnosis of asthma (Nagel et al., 2009) or to current asthma confirmed by metacholine challenge test (Kim et al., 2008). In two very large epidemiological studies in adults, although a clear association between higher BMI and asthma was found in both of them, adiponectin was only inversely associated with current asthma in premenopausal women in one. In a more recent study, 368 adolescent asthmatics were followed for one year: adiponectin was inversely associated to asthma symptoms and exacerbations and positively to FEV1/FVC but only in male subjects (Kattan et al., 2010). FeNO was not associated to serum adiponectin. Conversely, a study in adults did find that adiponectin was associated to lower values of FeNO in men but not in women. No further association of the adipokine and different asthma markers was found in any gender. (Sutherland et al., 2009).

2.4.1.3 Resistin

Resistin is also known as adipocyte-secreted factor or "found in inflammatory zone 3" (FIZZ3). It has recently been discovered and has been proposed as a link between obesity and diabetes. In contrast to mice, resistin is expressed in human adipocytes in low amounts; in fact it is in bone marrow where this adipokine is most expressed in humans (Filkova et al., 2009). Resistin has recently been shown to initiate a pro-inflammmatory state "in vitro" and "in vivo". Pro-inflammatory mediators such as TNF-α, IL-1β or IL-6 can strongly increase the expression of resistin in peripheral mononuclear cells. As stated above, resistin is minimally expressed in human adipose tissue, but adipocytes may be targets for it. Nagaev et al. have demonstrated that resistin, similarly to its action on peripheral blood mononuclear cells, can induce adipocytes to express IL-6 and TNF-α (Nagaev et al., 2006).
Resistin has been shown to be increased in the murine models of genetic as well as in diet-induced obesity. This has also been shown in humans. In an asthma cohort study on adult asthma, levels of resistin were higher in asthmatic patients as compared to controls, and resistin levels increased with increased severity of the disease (Larochelle et al., 2007). Conversely, atopic asthmatic children have lower resistin levels as compared to the non-atopic asthma and control groups (Kim et al., 2008). However, in a recent study (Arshi et al., 2010) in children of a similar age to those in the previous study (11 years) resistin levels were not different between a group of atopic asthmatics and a control group. In fact, its levels in the former study were about double than in the latter both in the control and in the atopic asthmatic groups. More recently, a study has shown that in a group of non-obese corticosteroid naïve adult female recently diagnosed asthmatics resistin predicted favourable anti-inflammatory effects of inhaled corticosteroids as assessed by levels of eosinophil cationic protein, eosinophil protein X and myeloperoxidase. Furthermore, an "in vitro" assay found that fluticasone significantly reduced resistin-induced IL-6 and TNF-α production in cultured monocytes/macrophages (Leivo-Korpela et al., 2011).

2.4.1.4 Adipsin

This adipokine is the rate-limiting enzyme in the alternate pathway of complement activation and is primarily expressed by adipocytes and monocytes/macrophages in humans. Adipsin has however been barely studied in asthma or allergic diseases. In a group of non-obese corticosteroid naïve adult female recently diagnosed asthmatics and with a positive bronchodilator tests, levels of adipsin were similar to the control group (Leivo-Korpela et al., 2011); however this adipokine has been reported to be significantly increased in individuals with seasonal allergic rhinitis, but only in males. Sublingual immunotherapy did not seem to affect adipsin levels (Ciprandi et al., 2009). Information regarding whether adipsin might have a role in asthma (if any) is still very scarce and we will have to wait until new studies publish their results.

2.4.1.5 Visfatin

Visfatin is identical to pre-B cell colony enhancing factor, a cytokine which is increased in the bronchoalveolar lavage fluid in animal models of acute lung injury and in neutrophils of septic patients. Exercise training with weight loss induced a significant reduction of plasma visfatin in non-diabetic women (Choi et al., 2007). Although this protein represents an additional link between obesity and inflammation, its role in asthma (if any) is still to be elucidated.

2.4.2 Immunologic properties of adipose tissue

The view of adipose tissue as a sole storage system has radically changed in the last decade. Further than being able to synthesize adipokines, adipocytes share some similarities with macrophages. In fact, preadipocytes can differentiate into macrophages, but the two cell types are distinct. On the other hand, about 10% of cells in the adipose tissue are macrophages. The number of macrophages in the adipose tissue is directly related to adiposity and to the size of adipocytes both in humans and in mice (Curat et al., 2004). Apart from secreting adipokines, adipocytes also secrete chemokines and cytokines, such as TNF-α, IL-6, Il-10, IL-1β and other factors such as monocyte chemoattractant protein-1 (MCP-1). It is thought that those mediators are secreted by the adipocyte itself since when adipose tissue is increased there is an up-regulation of genes related to inflammation. Indeed macrophages of the adipose tissue are an additional source of inflammatory mediators.

- TNF-α is the most important of cytokines produced by adipose tissue. It increases formation of Th2 cytokines such as IL-4 and Il-5, IL-6 and Il-1β by the bronchial epithelial cells. On the other hand, TNF-α increases the expression of leptin and adiponectin in cultured adipocytes (Kirchgessner et al., 1997). TNF-α is an important cytokine in the innate immune response and has been involved in the pathophysiology of several chronic inflammation diseases, including asthma (Thomas et al., 1995; Thomas & Heywood, 2002). This cytokine has an array of effects on the immunological system which have direct implications for the asthmatic response, such as recruitment of neutrophils, macrophages and mast cells; recruitment and activation of eosinophils; up-regulation of adhesion molecules both in the respiratory epithelium and on the vascular endothelium, which in turn can further increase inflammatory cell recruitment; proliferation and differentiation of fibroblasts (related to asthma remodeling and potentially to a more severe type of asthma); activation and increased release of cytokines by T cells of the Th2 arm; and induction of corticoisteroid resistance (Brightling et al., 2008).

- IL-6 is a proinflammatory cytokine which has a central role in host defence against infection and tissue injury. This interleukin derived from antigen presenting cells can induce production of IL-4 in naïve CD4+ cells, thus polarizing them into Th2 cells; i.e. to the allergic type of inflammation. This interleukin also modulates the intensity of the immune response by inhibiting Treg cell development. Additionally IL-6 promotes generation of Th17 cells (cells involved in autoimmune diseases) in mice, though its ability to do so in humans is subject to debate (Wilson et al., 2007). It has been recently shown that IL-6 levels are elevated in sputum of asthmatic patients as compared to healthy volunteers (Neveu et al., 2010).
- IL-10 is a cytokine with important regulatory function, having multiple biological effects in different cell-types. IL-10 modulates allergic disease in humans: the expression of IL-10 by antigen presenting cells in the airway of healthy subjects is important for inducing and maintaining tolerance to allergens (Commins et al., 2008).
- IL-1β is a potent mediator in response to infection and injury, and is increased in asthmatic airways as it is in other chronic inflammatory diseases. Apart from its pro-inflammatory effects, IL-1β has been shown to induce migration of vascular smooth muscle cells in culture and to provoke migration of endothelial cells. Its potential effects on the airway epithelial cell have been recently shown in cell cultures (White et al., 2008).

It should not be forgotten that apart from adipocytes, adipose tissue contains a considerable number of macrophages. Those cells are located in the white adipose tissue, which –as compared to brown adipose tissue which has as main role non-shivering thermogenesis- is the majority of adipose tissue and serves as energy storage. The number of macrophages in this tissue is proportional to adiposity and adipocyte size, both in mice and humans, and no difference exists between visceral and subcutaneous white fat (Weisberg et al., 2003).

2.4.3 Other endogenous molecules relating obesity with asthma

There are other hormones which may be related to obesity and asthma since they can be associated with processes related to food intake/body weight and inflammation.

2.4.3.1 Alpha-melanocyte stimulating hormone

Alpha-melanocyte stimulating hormone (α-MSH) belongs to a group of hormones called melanocortins, which include ACTH among others, with a common precursor (proopiomelanocortin). This hormone produces a significant down-regulation of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α, as well as chemokines such as IL-8 and interferon gamma (IFN-γ). Furthermore, chemotaxis induced by IL-8 in human neutrophils and monocytes is blunted by α-MSH. Additionally, this hormone has been shown to induce IL-10 production (Brzoska et al., 2010). In a murine model, α-MSH was able to inhibit airway inflammation induced by aerosol sensitization and subsequent challenges with OVA. Additionally, the levels of two important interleukins related to the allergic response, IL-4 and IL-13, were highly decreased in the broncho-alveolar lavage fluid of mice treated with α-MSH. In agreement with the important role of IL-10 as an anti-inflammatory mediator, the action of α-MSH was dependent on the presence of IL-10, as IL-10 knock-out mice were resistant to treatment with α-MSH (Raap et al., 2003). In the context of an association between asthma and obesity, what is on interest of α-MSH is the fact that the hormone is included in one of the main mechanisms of energy balance. There are melanocortin receptors in the CNS and effects on food intake and on energy expenditure

have been observed with treatments containing ligands of those receptors (Williams et al., 2000). Those receptors are hypothesized to be downstream mediators of the effects of leptin signaling: leptin increases the expression of the proopiomelanocortin gene in neurons of the nucleus tractus solitarius (Schwartz et al., 1997). Thus, α-MSH may play a role both in allergic inflammation and in food-intake control. In fact, the melanocortin system appears to be a common pathway for mediation of both leptin and ghrelin (Lebrethon et al., 2007).

2.4.3.2 Ghrelin

Ghrelin is not only a mere growth-hormone releasing factor but also an important appetite regulator, energy conservator and suppressor of the sympathetic nervous system. Ghrelin, secreted from the peripheral organ, has its regulatory region in the hypothalamic arcuate nucleus, where the regulatory region of appetite is located. Circulating ghrelin excites this region and stimulates food intake after passing through the blood-brain barrier. Additionally, this hormone can exert its action through receptors in the vagus nerve (Kojima & Kangawa, 2010). Apart from being an orexigenic hormone, ghrelin has an interesting association with IgE in humans. In a case-control study of obese school children, Matsuda et al. (Matsuda et al., 2006) found that ghrelin was inversely and significantly correlated with BMI but also with IgE both in allergic and non-allergic subjects as defined from a combination of asthma and skin symptoms. This correlation with IgE is higher among overweight patients as compared to normal weight ones, in which the correlation is still significant (Okamatsu et al., 2009). The strong inverse correlation between plasma ghrelin and serum IgE levels suggests that ghrelin may inhibit IgE production in some manner. In this context, it is of interest that in splenic murine T lymphocytes, mRNA levels of IL-4 and IL-10, which both increase IgE synthesis, are suppressed by ghrelin (Xia et al., 2004).

2.4.3.3 Eotaxin

Eotaxin is a key chemotactic agent responsible for the eosinophil-mediated bronchial inflammation. In their pivotal study, Vasudevan et al. (Vasudevan et al., 2006) showed that eotaxin circulating levels are increased in diet-induced obese mice. They also showed that after weight loss in humans eotaxin was significantly reduced. In a group of obese and non-obese Korean women it was shown that circulating eotaxin was similar in both groups, although women with central obesity had significantly higher levels of eotaxin than those without it. This study also showed that weight reduction after following an exercise program for 12 weeks was associated to a significant decrease in circulating eotaxin levels in the whole group (Choi et al., 2007).

Not only has eotaxin been studied in relation to obesity but also as to how this chemokine interacts with allergy inflammation in the context of obesity. In a murine allergy model (Calixto et al., 2010), diet-induced obesity enhanced eosinophil trafficking from bone marrow to lung tissues, and delayed their transit through the airway epithelium into the airway lumen. Consequently, eosinophils remain longer in lung peribronchiolar segments. Furthermore, Kim et al. (Kim et al., 2011) cultivated and differentiated pre-adypocites and investigated eotaxin expression during differentiation and found that levels of this chemokine increased as adipocytes differentiated. Eotaxin was further expressed when cultured cells were challenged with TNF-α and IL-4.

2.4.3.4 Plasminogen activator inhibitor 1

Remodeling of the airway is a key feature of asthma and is associated to a more severe type of disease. Plasminogen activator inhibitor 1 (PAI-1) is a potent inhibitor of both tissue-type

plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA). Both t-PA and u-PA are involved in the dissolution of fibrin and in the degradation of the extracellular matrix. Activated mast cells are a major source of PAI-1, and mast cell-derived PAI-1 is highly expressed in patients with fatal asthma (Cho et al., 2000). Furthermore, a gene polymorphism associated with PAI-1 levels is preferably transmitted to asthmatic patients; and deletion of PAI-1 prevents extracellular matrix deposition in a murine model of asthma (Cho et al., 2001); (Oh et al., 2002). In a very recent study (Cho et al., 2011), it was found that plasma levels of PAI-1 were significantly higher in obese subjects as compared to controls after adjusting for race and smoking status; furthermore, PAI-1 plasma levels were significantly and inversely correlated to forced vital capacity. Thus, it could be hypothesized that the reduction of FVC in obese patients may be in part mediated by PAI-1. Although research on the association of PAI-1 as a link between obesity and asthma is still very scarce, this is a field which warrants further investigation.

2.5 The mechanical link

The mechanical load of obesity might affect lung growth, leading to reduced pulmonary function. For instance, leptin-deficient mice which are obese very early in their development have substantially smaller lungs than normal ones (Shore et al., 2003). Maternal obesity in pregnancy increases the risk of pregnancy complications, caesarean sections and adverse birth outcomes, which have in turn been associated with respiratory illness in children. However, little is known of the effect of obesity in the mother during pregnancy with regard to respiratory diseases in the offspring. A recent Norwegian study (Haberg et al., 2009) (Norwegian and Child Study) which includes 100,000 pregnant mothers was able to analyse data from more than 33,000 mother-children pairs up to the age of 18 months of the infants and demonstrated that after adjustment for many factors including birth weight, preterm birth and pregnancy complications, infants born from obese mothers had a modest but significant increased risk (3.3%) of suffering from at least one episode of wheezing during the follow-up period. To what extent this finding is related to the low-grade inflammation status of mothers during pregnancy or to mechanical factors "in utero" and how they might affect lung development in the foetus is still to be determined. Furthermore, it is not known if this effect is maintained in later years.

Independently of its effects on lung development either in the fetal period or later on, obese subjects have a low functional residual capacity due to changes in the elastic properties of the chest wall (Shore & Johnston, 2006). At low volumes, the retractile forces of the lung parenchyma are reduced, thus airway smooth muscle has a lower load when functional residual capacity is reduced. Consequently it might shorten still further when activated (either by parasympathetic tone or broncho-constricting agents such as metacholine) (Naimark & Cherniack, 1960). However, some studies have noted that there is bronchial constriction in obese subjects after correcting for lung volume, which suggests that other mechanisms are involved. Apparently low tidal volume (which is common in obese individuals) may be one such mechanism: stretching of the airways smooth muscles causes cross-bridging of actin-myosin to detach, and the bigger the tidal volume (stretch) the easier it is for bronchodilation to occur. Low tidal volume facilitates more cross-bridging between actin and myosin, thus making airway smooth muscle stiffer and harder to stretch. Hence reduction of tidal volume in obese subjects could lead to a vicious circle in which small airway muscle strain leads to greater stiffness, and this leads to even less muscle strain in

every breath (Shore, 2008). This paradigm is supported by the fact that both obese and asthmatic subjects have lower bronchodilation after deep breaths (Hakala et al., 1995; Skloot & Togias, 2003).

There could be additional mechanical explanations as to the reasons why airways in obese subjects are more easily constricted than in normal ones. Closure of small peripheral airways is common in obese individuals, especially in the supine posture (Hakala et al., 1995). Some authors have postulated that the frequent opening and closure of those airways may lead to the rupture of alveolar attachment to bronchioles, thus disconnecting airways from the attached parenchyma and exacerbating constriction (Milic-Emili et al., 2007). To what extent those less oxygenated areas could lead to higher artery pressures and pulmonary edema, further complicating the situation, is still very speculative although there is some evidence of edema in obese subjects and pulmonary hypertension in obese women (Bergeron et al., 2005); (Taraseviciute & Voelkel, 2006). Hypoxemia might exacerbate local hypoxia occurring in obese adipose tissue, a situation which contributes to the general inflammation of obesity (Hosogai et al., 2007; Ye et al., 2007). Situations related to obesity such as obesity hypoventilation syndrome or sleep disordered breathing could further aggravate this situation and although extreme and far from asthma, could add some clues to the mechanical associations between asthma and obesity.

2.6 The experimental link (animal models)

Three are several models in which the lung features of obese mice have been characterized. According to Shore (Shore, 2007), those are:

- *ob/ob* Mice: This is a type of mice which is not capable of synthesizing leptin, which is a satiety hormone formed in the adipose tissue. These mice eat in excess and are already obese at four weeks of age. These mice have smaller lungs than the wild type.
- *db/db* Mice: In this type of mice there is an altered leptin receptor in the hypothalamus (Ob-R_b) so the effect of leptin on satiety is lost. Thus, *db/db* mice are similar to *ob/ob* mice. As in the case of *ob/ob* mice, *db/db* mice have smaller lungs than the wild type.
- Cpe^{fat} Mice: These mice have a missense mutation of the enzyme carboxipeptidase E (Cpe) which makes it inactive. Cpe cleaves neuropeptides such as corticotrophin-releasing factor and neuropeptide Y which control eating behaviours and energy consumption. In the absence of Cpe mice become obese but not as fast as *ob/ob* or *db/db* mice. These mice have lung size comparable to that of the wild type.
- Diet-induced obese mice: feeding recently weaned mice with a diet in which 45-60% of calories are derived from fat produces obesity. Obesity is milder than in the three prior models and lung size is again similar to that of the wild type.

Taken together, the results from the studies from animal models in obese mice suggest that obesity might be related to asthma in several ways. In the first place very early obese mice have smaller lungs and this might have implications both at the mechanical and at the ultra-structural level, in particular in the way lungs are alveolarized. Secondly, obesity either acquired very early or later on in the mice's lives increases BHR and this neither seems to be directly mediated by leptin nor is secondary to a prior inflammation. Lastly, obesity might have some effect on asthma through allergic sensitization as that hormone seems to increase sensitization, and thus BHR to allergen challenge (Shore et al., 2005), this being dependent on when obesity and sensitization develop.

2.7 A distinct asthma phenotype in the obese?

There seems to be enough epidemiological, clinical and mechanistic evidence that obesity and asthma "live" together in some individuals. Whether this comorbidity is a distinct phenotype as suggested by some authors; or obesity is a risk factor for asthma incidence and worse control, is difficult to say (Castro-Rodriguez & Garcia-Marcos, 2008; Lessard et al., 2008; Lugogo et al., 2010). However, both the mechanical, hormonal and immunological links between the two conditions suggest that obesity probably leads to asthma in many cases and could be in part responsible for the "asthma epidemic". Moreover, there are two other important factors –diet and exercise- which can favour both asthma and obesity in parallel. An official American Thoracic Society workshop report recently published concludes that obesity is a risk factor for asthma in all age groups and that asthma in the obese might represent a distinct phenotype with a more severe disease with a worse response to treatment (Dixon et al., 2010). The report states the urgent need to further investigate the mechanisms of asthma in this risk group and to develop new therapies directed to this specific population.

3. Diet as an independent factor in the development of asthma and obesity

Diet and exercise are probable common pathways for asthma and obesity irrespective of which of the two conditions starts first. This is quite well documented during the first months after birth. Infants who are breastfed have a different bacterial colonization of their intestine than those who are fed with artificial formulas (Harmsen et al., 2000). Similarly, children fed with the latter formulas gain weight more rapidly, although this does not seem to be translated into later obesity (Burdette et al., 2006). Although the information is still sparse, it is quite probable that the so-called microflora fingerprinting –which remains very stable throughout the years- is related to diet. Either by this mechanism which might be included into de hygiene hypothesis or by others, such as the antioxidant or pro-oxidant properties of some foods (Roberts et al., 2006), or the modulating properties of prebiotics -like fibers- to adjust intestinal microflora (Schley & Field, 2002), may have an effect on asthma and obesity.

There are currently enough studies to conclude that there is an association between consumption of some types of nutrients or foods and asthma. An ecological analysis of the European Community Respiratory Health Survey (ECRHS) showed a trend towards decreasing sensitization (specific IgE) prevalence with higher intakes of fruit and vitamins A and C (Farchi et al., 2003). Furthermore, other studies have found an association between consuming citrus/kiwi fruit and a lower last year prevalence of several asthma symptoms (Forastiere et al., 2000; Wickens et al., 2005); and also of rhinitis. The frequent intake of vegetables showed an inverse relationship with prevalence rates of asthma, allergic rhinoconjunctivitis and atopic eczema (Weiland et al., 1999). The intake of cereals has also been shown to be associated to a lower prevalence of asthma (Garcia-Marcos et al., 2007; To et al., 2004). A recent meta-analysis on food intake and asthma arrived at interesting conclusions (Nurmatov et al., 2011) in spite of the limitations of applying the meta-analysis technique to epidemiological studies which cannot be –by definition- perfectly controlled. With respect to individual nutrients, vitamins A, D, E and zinc seem to be protective, while vitamin C and selenium do seem to be neither a protective nor a risk factor. Higher consumption of fruit and vegetables are associated to a lower prevalence of asthma, with

fruit having a higher impact. However the associations were not adjusted for obesity or exercise.

Two different groups, including ours, have very recently associated Mediterranean diet to a lower prevalence of asthma at different ages (Castro-Rodriguez et al., 2008; Chatzi et al., 2007; Garcia-Marcos et al., 2007) independently of exercise. Furthermore, Mediterranean diet also showed this protective effect in the offspring when the mother consumed it during pregnancy (Chatzi et al., 2008), although the effect might be restricted just to olive oil intake (Castro-Rodriguez et al., 2010). The reasons why this type of diet is associated with a lower prevalence of asthma could be explained in several ways. Considering that Mediterranean diet is rich in both antioxidants and *cis* monounsaturated fatty acids this is not an unexpected finding. Individually, a more frequent intake of seafood and also of cereals is associated with a lower prevalence of significant asthma. At 8-10 years of age atopy is a risk factor for a more severe asthma (Ponsonby et al., 2002), so it could be speculated that at least in part the protection offered by this diet is mediated through allergy modulation. The protection from asthma that Mediterranean diet seems to offer is probably due to a mixed effect of taking "protective" foods and avoiding "risky" foods. Protective foods may be those with antioxidant properties and rich in prebiotics, such as fibers (as in the Mediterranean diet); and risky foods may be those rich in *trans* fatty acids and unsaturated fat (as in fast foods) (Garcia-Marcos et al., 2007; Innis & King, 1999; von Kries et al., 2001). In fact, Mediterranean diet has been shown to increase the total antioxidant capacity in healthy adults (Pitsavos et al., 2005). Mediterranean diet has additionally been associated to a reduced prevalence of obesity. Due to its content in fibre and unsaturated fat (olive oil, fish) this diet is associated to better weight control (Schroder, 2007). On the contrary, fast food is related to an increase of calorie intake (Schmidt et al., 2005) and is greatly related to the school and family environment, especially during the transition to adulthood (Nelson et al., 2006)

3.1 Oxidant-antioxidant imbalance in asthma

Reactive oxygen species (ROS), formed in every cell during metabolic processes, are increased in asthma and can mediate pathophysiologic changes which are characteristic of this condition, such as initiating lipid peroxidation and favouring the release of arachidonic acid from cell membranes; contracting smooth muscle; increasing airway reactivity and vascular permeability; augmenting the synthesis and release of cytokines and chemokines; impairing the response to β_2 adrenergic drugs; and decreasing cholinesterase and neutral endopeptidase activities (Nadeem et al., 2008). Lungs have several antioxidant mechanisms including enzymatic (catalase, glutathione peroxidase ans superoxide dismutase) and non-enzymatic ones (vitamin C, E, albumin, uric acid, cerulopasmin and glutathione). Increased ROS generation is found when the activity of neutrophils, eosinophils, monocytes and macrophages is increased, as occurs in asthma (Kelly et al., 1988). Oxidative stress (a situation of imbalance between the production of ROS and the ability to detoxify the reactive intermediates or to repair the resulting damage) is an important consequence of asthma inflammation; is associated with an altered activity in anti-oxidation in lungs and blood; and also with airway reactivity (Katsumata et al., 1990; Nadeem et al., 2005; Sackesen et al., 2008).

There are numerous reports showing deficiencies of antioxidants in asthma: low levels of vitamin C in airway lining fluid, serum, plasma, whole blood and brochoalveolar lavage

fluid; vitamin E in brochio-alveolar lavage fluid, red cells and plasma; or beta-carotene in serum (Kalayci et al., 2000; Kelly et al., 1999; Sackesen et al., 2008; Shanmugasundaram et al., 2001; Vural & Uzun, 2000; Wood et al., 2008). The cooperation of several antioxidants provides a better defense against ROS, so the total antioxidant capacity of serum is probably a better index than the measurement of a specific antioxidant. Again, antioxidant capacity in serum is reduced in asthmatics during exacerbations as compared with healthy individuals and is less reduced in subjects with stable asthma (Katsoulis et al., 2003). Very recently, oxidative stress has been shown to be increased in children with previous bronchilitis obliterans (Mallol et al., 2011) and although in this study the authors did not find correlation with lung function tests, several studies have indeed shown an inverse relationship between oxidative stress and lung function in asthmatics (Nadeem et al., 2005; Ochs-Balcom et al., 2006; Picado et al., 2001; Wood et al., 2000).

Taken together these results indicate that an oxidant-antioxidant imbalance could play a crucial role in the development of asthma symptoms and in the severity of the disease. Accordingly, certain diets may favor or protect from asthma depending upon their ability to maintain a better oxidant-antioxidant balance.

4. Exercise is an independent protective factor for asthma and obesity

Although it would be expected that asthmatics perform less exercise and severe asthmatic perform even less, it is not so straightforward that the lack of exercise favours obesity, which in turn favours asthma. Although this causal pathway may be present in some asthmatics, more exercise –independently of BMI- has been associated to a lower prevalence of mild asthma, although it does not influence severe asthma. If the association of asthma with exercise was a reverse causation effect it should be expected that at least in severe asthmatics, there was an inverse association, which does not seem the case when diet and BMI are controlled: in their study Garcia-Marcos et al. showed that after adjusting for BMI and Mediterranean diet exercise was not associated with severe asthma; and mild asthma was less prevalent among children who exercise more (Garcia-Marcos et al., 2007). Therefore, it might be hypothesized that at least in mild cases, the lack of exercise is associated to asthma. In this context, a very interesting and challenging hypothesis was proposed by Alexander in 2005 who maintains that the increase of asthma prevalence might be due in part to a "disuse contracture" which reminds of the mechanical link between obesity and asthma (Alexander, 2005). The following paragraphs are a brief explanation of that hypothesis.

Bronchial constriction and BHR are crucial features of asthma and are both driven by bronchial smooth muscle. When lumen is narrower than normal in a permanent way, there is also a reduction in the length of the annular components of the bronchii, namely smooth muscle fibres and collagen. Under-extension causes contracture: elastic components (smooth muscle and collagen) need a certain tension to operate correctly and when this is not provided by intermittent stretching they either fail to extend during growth (infants and schoolchildren) or reduce in length (adults) to a point in which habitual usage is enough to provoke a peak tension needed for effective functioning. This situation maybe reversible in its first stages but becomes permanent with time due to fixed cross-linking (Akeson et al., 1977). While this is typical of the joint tissues, it is most probably applicable to muscles and elastic tissues of the airways, which in continued growing (as in infancy and childhood) without stretching to their potential length the result would result in an increased thickness

of the wall and narrowing of the lumen, which, in turn, will start a vicious cycle: thicker wall, less ability to stretch and more difficult distension to inspiration, less distension, less lumen and thicker wall again. If lumen is reduced to a critical point and according to Laplace's law, the product of atmospheric pressure times radius will not be able to counteract wall tension and bronchii would collapse. In this situation a very small increase of muscle tone will be enough to cause bronchial closure. Moreover, exercise increases respiratory rate and speed of airflow, thus reducing transmural pressure and further favouring collapse.

In summary, this hypothesis contemplates asthma as a lack of lung expansion by exercise during growth. While just a hypothesis, the idea of a lack of "sufficient" inspiration has been contemplated as a feasible explanation for the influence in asthma prevalence of TV watching. The ALSPAC study, after following a large sample of more than 5,000 children, found that new asthma cases, as diagnosed by a doctor, between the ages of 3.5 and 11.5 years were associated to the number of hours of TV watching after controlling for other risk factors including BMI: those watching more than 2h/day had double odds of having new onset asthma a compared to those watching 1-2h/day, while those watching less than 1h/day had just half the odds (Sherriff et al., 2009). While previous studies showed that new cases of asthma during adolescence are associated to lower fitness (Rasmussen et al., 2000; Vogelberg et al., 2007), sometimes confused by smoking, children in the ALSPAC study were too young to consider smoking-related TV watching as a plausible explanation. Sedentary lifestyle ("disuse contracture") is a more plausible explanation. Additionally, the ALSPAC group suggested as an additional explanation of their results that respiratory patterns associated to TV watching may also play a role: prolonged periods of watching a videotape are associated with lower sigh rates than while reading (Hark et al., 2005). Thus, "modern" as opposed to "classical" sedentary lifestyle maybe and additional factor favouring the "disuse contracture".

5. Conclusion

Obesity and asthma are linked together, a link which has been shown at different levels and has plausible pathways. However, it is still to be established if obesity causes asthma (or a specific asthma phenotype) or if the two conditions are part of a parallel development in the context of the western lifestyle in which sedentary habits and unhealthy diets (together with lower contact with germs and/or with "non-traditional" germs) may interact to favour an internal environment in which not only obesity and asthma, but other diseases such as type II diabetes or rheumatoid arthritis develop more easily.

The epidemiological and animal studies carried out to date have probably rendered all possible information and it is the time of more controlled trials. New pregnancy/birth cohort studies specifically designed to disentangle the interrelationship between asthma, obesity, exercise and diet are needed. Creative clinical trials will also have an important role here, although designing and performing them is a great challenge. The implications of the results of such studies on public health policies are crucial.

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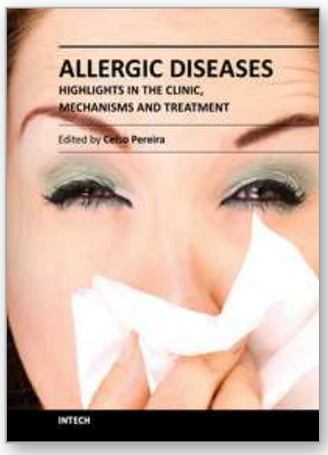
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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
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