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Original article

Relation between obesity, lipid profile, leptin and atopic disorders in children

Background: *Obesity has become a disease of great importance affecting children and adolescents. Obesity can cause atopy or inflammation, where there are some common factors that predispose to both obesity and atopy.*
Objective: *To study the factors contributing to allergic disorders in obese children, the role of leptin in obesity related atopic disorders and the relation of birth weight and breast feeding to both obesity and atopy.*
Methods: *Forty seven obese children and adolescents and 45 healthy children (control group) were included in the study. The obese children were divided into 2 groups (based on the history of nasal allergy, bronchial asthma, skin, eye or food allergy), group I (n=21) atopic and group II (n=26) non atopic. All obese children were subjected to complete blood count, serum triglycerides and cholesterol, serum leptin (for control group also) and serum total immunoglobulin E (IgE) measurement.*
Results: *Body mass index (BMI) was significantly higher in group I than group II (33.35±9.93 vs. 23.70±9.7IU/L, p=0.000), also serum total IgE was significantly higher in group I than in group II (510.476±366.407 IU/L vs. 114.577±120.940 IU/L, p=0.000). Group II showed higher serum leptin level than group I (185.115±105.912 vs. 133.048±100.718 ng/ml), a difference not statistically significant (p = 0.092), yet, both were higher than the control group (7.24±5.98 ng/ml). Significant positive correlation was found between serum leptin level and age (p=0.000, r = 0.60) and BMI (p= 0.000, r = 0.720), while negative correlation was found between serum leptin and IgE (r= 0.289, P=0.049). Significant positive correlation was found between obesity (BMI) and family history of obesity (r = 4.672, p = 0.036).*
Conclusion: *There is a strong positive association between obesity and atopy: Serum leptin was higher in obese children when compared to control group more in non atopic than atopic group yet not statistically significant. Family history of obesity is an important predisposing factor for obesity in children. The frequency of atopy was higher in artificial than in breast fed obese children. Therefore efforts should focus on weight reduction as a part of treatment of asthma in obese children, also serum leptin assay is important in all obese children and further studies are needed to know more details about leptin hormone and its relation to both atopy and obesity.*

Keywords: Obesity, Leptin hormone, Atopy, Total IgE, Allergic disorders.

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INTRODUCTION

In the past two decades there has been a significant increase in the prevalence of asthma, atopy and obesity in children worldwide[1]. It is possible that these events are linked[2].

In Egypt the prevalence of overweight and obesity is 20.5%. Overweight and obesity was more prevalent among urban areas compared to rural ones. Females showed higher prevalence for overweight and obesity than males. Wasting was prevalent among 7.3% of the sample with higher prevalence in rural sites and males compared to urban sites and females[3].

An increase in the prevalence of obesity over recent decades has been reported in Britain and the United States. The simultaneous rise in the prevalence of asthma and atopy promoted investigators to speculate that obesity might be a causal factor in the inception of atopic diseases[4]. In fact, several studies (most of them cross sectional) have shown positive associations of obesity with respiratory symptoms, asthma, and airway hyper responsiveness[5].

The association between obesity and atopy has also rarely been explored. It is possible that obesity could cause atopy or inflammation and that there is some common factor that predispose to both obesity and atopy[6].

A strong inverse relation between breast-feeding and BMI has recently been found in children starting school, confirming previous reports based on smaller study samples, since breast-feeding is also a protective factor against asthma and atopy.

Leptin is an important regulator of the mass of adipose tissue and of body weight; it operates by inhibiting food intake and stimulating energy expenditure[7].

This study aimed to detect the relation between obesity and allergic disorders, relation of birth weight and breast feeding to obesity and allergic disorders, the role of leptin in obesity related atopic disorders, to plan for prevention and early detection of atopy in obese children.

METHODS

This study was conducted on 47 obese children and adolescents, attending the outpatient clinic of Children's Hospital, Ain Shams University. They were 23 males and 24 females with BMI > 95th percentile for age and sex using Egyptian charts. Their ages ranged from 4 – 18 years, with a mean age of 11.2 ± 3.9 years. In addition, 45 healthy children (BMI between 5th and 85th percentiles): 23 males and 22 females with a mean age 10.8 ± 4.2 years were included in the study as a control group. The obese children were divided into two groups:

Group I:

This group included 21 obese children with history of atopic diseases (bronchial asthma, allergic rhinitis, atopic dermatitis, and food or eye allergy) they were 10 males and 11 females, with a mean age of 11 ± 2.7 years.

Group II:

This group included 26 obese children without history of any atopic diseases; they were 13 males and 13 females with a mean age of 11.5± 3.1 years.

Exclusion criteria:

The main criteria for exclusion from the study were the presence of liver or kidney diseases, endocrinopathies, chromosomal abnormalities, chronic drug use (e.g. prolonged cortisone therapy) and the presence of infection.

Clinical evaluation:

An informed consent was signed by the parents before participating in the study. Our children and adolescents were subjected to the following: proper history taking with particular stress on birth weight, diet composition and food habits, family history of obesity and atopic diseases and history of chronic drug intake as corticosteroids.

A detailed clinical examination was performed, with particular stress on anthropometric measures, including calculation of BMI [Body Weight (Kg)/standing height (m^2)].

Laboratory investigations:-

Complete blood count (CBC) by Coulter Counter (Coulter Instruments, Model T660, Fullerton, California, USA) including lymphocytes and total eosinophils, stool examination, serum triglycerides and cholesterol, serum leptin by ELISA and serum total immunoglobulin E (IgE) by IgE ELISA immunoassay (Innovative Research Biologicals-21315 Hilltop Street, Southfield, Michigan 48033).

The control group was subjected to measurement of serum leptin only.

Sample collection:

Blood samples were taken after at least 12 hours fasting. Five cubic centimeters venous blood were withdrawn from each subject and divided into two portions. The first portion 3 cc was collected into plain tubes, left to clot, centrifuged and serum was separated under complete aseptic conditions into three aliquots for lipid profile (serum triglyceride and cholesterol), serum leptin and serum total IgE. The aliquots used for measurement of serum leptin and IgE were stored at –20^{o}C till the time of assay. The second portion was collected on EDTA for performing complete blood counts.

Principle of the test for assay of serum leptin level:

The DSL–10–23100 active Human Leptin ELISA was used. It is an enzymatically amplified 'two step' sandwich-type immunoassay (Diagnostic Systems Laboratories, Beckman Coulter Co, 445 Medical Center Blvd., Webster, Texas 77598 USA).

Statistical Analysis:

The results were analyzed by commercially available software package (Stat View, Abacus Concepts, Inc, Berkley, CA, USA). The data were presented as mean and standard deviation (SD). Student's "t" test was used to compare between two groups as regards parametric data, while Mann Whitney test was used for non-parametric data**.**

Pearson correlation coefficient "r" was used to determine the relationship between different quantitative variables. For all tests, a probability (p) of less than 0.05 was considered significant. Analysis of variance was used to compare mean values of more than 2 studied groups. P value less than 0.05 was considered significant while p value less than 0.01 was considered highly significant.

RESULTS

Comparing group I (atopic) and group II (non-atopic) obese subjects

As shown in table (1), highly significant statistical differences were found between group I and group II regarding BMI and serum IgE level (p = 0.000 for both). BMI was higher in atopic (group I) than non atopic (group II) subjects (33.53 ± 9.93 and 23.70 ± 9.7 respectively), and serum IgE level was much higher in group I than group II (510.476 ± 366.407 and 114.577± 120.940 IU/ml respectively). Regarding the serum leptin level, it was more in group II than group I (185.115±105.912 and 133.048±100.718 respectively), this difference was statistically insignificant (p=0.092). On the other hand, no significant statistical difference was found between the 2 groups regarding birth weight (p=0.930), serum triglyceride level (p=0.523), serum cholesterol level (p=0.243), type of milk feeding (p=0.408), sex difference (p=0.874) and age of starting weaning (p = 0.921).

Relation between serum leptin and different parameters in obese subjects

A significant negative correlation was found between serum leptin level and serum total IgE (r = 0.289, P=0.049) and positive correlation was found between serum leptin and age (r = 0.60, P = 0.000) and BMI (r = 0.720, P =0.000).

Meanwhile, the serum leptin level did not show any significant relation to gender, lymphocyte count, eosinophil count, serum cholesterol or family history of obesity. (Table 2)

Relation between BMI and different parameters in obese children

BMI was significantly higher in obese subjects with positive family history than those with negative family history of obesity (t = 4.672, p = 0.036). On the other hand, no correlations were found between BMI and birth weight (p = 0.492) or age at start of weaning (p =0.828). The type of milk feeding and the habit of eating while watching TV had no impact on BMI (p = 0.921 and 0.78 respectively). (Table 3).

Table 1. Comparison between atopic and non atopic obese children.

	Atopic n=21	Non atopic n=26	t/z	P
Birth weight	3.770 ± 1.130	3.730 ± 2.110	0.09	0.930
BMI	33.35 ± 9.93	23.70 ± 9.7	15.85	0.000*
S. leptin	133.048 ± 100.718	185.115 ± 105.912	- 1.722	0.092
Triglyceride	121.810 ± 68.020	109.385 ± 62.732	0.644	0.523
Cholesterol	183.238 ± 36.574	171.038 ± 33.272	1.183	0.243
IgE (IU / ml)	510.476 ± 366.407	114.577 ± 120.940	4.747	0.000*
Type of milk feeding B/A	40 / 60 (%)	66.7 / 33.3 (%)	- 0.181	0.408
Sex M / F	43.5 / 56.5 (%)	45.8 / 4.2 (%)	- 0.024	0.874
Age of starting weaning (mo)	4.33 ± 1.74	4.38 ± 1.76	0.100	0.921

A: artificial, B: breast, BMI: body mass index, F: female, M: male, S: serum.
***Highly significant**

Table 2. Serum leptin in relation to the studied parameters in obese children

Variable	Leptin level	t	r	p
Age			0.60	0.000**
Sex dist				
M = 23	155.13 ± 65.66	- 0.424		0.673
F = 24	168.29 ± 116.36			
Lymphocyte			- 0.293	0.060
Eosinophil			- 0.060	0.760
Serum total IgE			- 0.289	0.049*
Cholesterol			- 0.132	0.378
BMI			0.720	0.000**
Family history of obesity				
No (n = 15)	11.23 ± 3.95	0.002		0.998
Yes (n = 32)	161.85 ± 105.79			

BMI: Body mass index
***Significant, **Highly significant**

Table 3. Relation between BMI and studied parameters in obese children

Variable	BMI				
	Mean± SD	**f**	**t**	**r**	**p**
Birth weight				0.103	0.492
Type of milk feeding					
B (n = 37)	33.95 ± 8.922	0.08			0.921
A (n = 4)	35.97 ± 1.727				
B & A (n = 6)	34.63 ± 4.44				
Age at start of weaning (mo) 4.362 ± 1.737	34.187 ± 8.360			0.033	0.828
FH of Obesity					
No (n = 15)	32.568 ± 5.972		4.672		0.036*
Yes (n = 32)	37.640 ± 11.485				
Eating while watching TV					
Yes (n = 11)	34.80 ± 13.63		0.57		0.78
No (n = 36)	33.99 ± 6.21				

FH: Family history; B: Breast; A: Artificial
***Significant**

DISCUSSION

The present study was done to evaluate the relation between obesity and atopy in both sexes, the relation of birth weight and breast feeding to obesity and atopy and the role of leptin hormone in obesity related atopic disorders.

The results revealed that birth weight was not statistically related to obesity, (P = 0.492). This is in agreement with Overpeck et al[8], who found that prenatal influences (birth weight and length of gestation) do not contribute to the development of childhood and adolescent obesity in different ethnic groups, contradicting with, Whitaker and Dietz[9], whose study suggested that the risk for overweight is increased among persons with high birth weight (4000 gm or more), and with Parson et al.[10], who reported that the greater propensity to obesity in later life is seen in children heavier at birth.

Also birth weight in our study was not statistically related to atopy, (P=0.930). This is contradicting with Laerum et al[11], whose study, was done on a larger number of subjects, suggested that low birth weight is strongly associated with early childhood asthma.

Concerning breast feeding and its role in atopy the current study showed that the relation between both is statistically insignificant, (P=0.408) but a

history of breast feeding was encountered in 40% of atopic obese subjects compared to 66.7% of non atopic obese children. Breast feeding might delay the onset of asthma, or actively protect children less than 24 months of age against asthma. It might also reduce the prevalence of asthma in children exposed to environmental tobacco smoke[12].

Exclusive breast feeding for 4-6 months exerts some protective effect[12]. This protection may persist for at least the first decade of life. However the protective effects are relatively modest and have not been confirmed by all studies. Breast feeding might reduce atopic disease by favoring the development of gut flora populations of bifidobacteria and lactobacilli, which appear to be protective[13]. Also Karmer14, found that about 69% of asthmatic students were artificially fed.

The present study could not establish a relation between obesity and history of breast feeding. Karmer[14] found that around 65.4% of 404 obese students received breast feeding compared to 75.3% of the 202 controls ($P < 0.05$).

Our study showed that there is a weak association between gender and atopy where the percentage of allergy was slightly higher in females (56.5%) than in males (43.5%).This result was confirmed by Troisi et al[15], who suggested that following puberty, asthma incidence is greater in females. There is now evidence that estrogen use is a risk factor for asthma in adult individuals. Also Mandhane et al[16], reported that before puberty, the prevalence is 3 times higher in boys than girls, and is equal during adolescence, whereas adult-onset asthma is more common in women than in men.

Morgan et al[17], showed that pediatric asthma appears to affect more males (63%) than females (37%) with male to female ratio 1.8: 1. This agrees with most surveys of asthma in children18. Woolcock and peat[1], demonstrated that male to female ratio for the occurrence of asthma is about 1.5 in children. In Egypt, Abd El-Khalek et al[19], reported a male to female ratio of 2.3:1.

Khattab et al[20], reported a significant lower mean gonadotrophin level in pubertal male and female asthmatics compared to controls, also they reported low testosterone level in prepubertal male asthmatics and low estradiol level in pre-pubertal females.

Estrogen and progesterone have protean effects at the cellular level, consistent with potentially harmful effects in lung disease[21]. The menstrual cycle may be a trigger for asthma in few women or a cofactor, inciting, asthma along with other well described triggers[22-24].

Although there is evidence of a positive association between asthma and obesity in adults and children, very little is known about the role of leptin in asthmatic children. Guler et al[25], found a significant difference in serum leptin levels between asthmatic and healthy children, and that leptin was a predictive factor for having asthma. Also they found a significant but weak correlation between leptin levels and IgE in the overall group of asthmatic children. On the other hand, Doniec et al[26] found that asthma in children seems not to affect neurohormonal regulation of energy balance, where serum leptin and neuropeptide Y in asthmatic children did not differ from that of healthy children

In this study, the relation between atopy and leptin hormone level was insignificant, yet leptin hormone level was slightly increased in cases without allergic diseases compared to cases with allergy ($P=0.092$). Also the serum leptin hormone level was inversely proportionate with the serum total immunoglobulin-E and the relation between both was statistically significant ($P=0.049$).

This was in agreement with Rosenhaum et al[27], results. They reported that leptin concentration in both obese asthmatics and obese control revealed no significant difference between the two groups ($P>0.05$). Also they found that leptin concentration was not affected by the severity of asthma. The explanation of this contravention needs more researches on larger number of children with more spotlights on the type of atopy and the type of medications given for atopic children on leptin hormone levels.

The age at starting weaning was comparable among atopic and non atopic children ($P=0.921$) and this contradicted with the results of Kalliomaki et al[13], who found that introduction of all solids should be delayed until after the age of 6 months, and the more highly allergenic foods such as eggs, peanuts, tree nuts and fish can be delayed for 2-3 years to lessen eczema and food allergy.

It seems that food allergy is not the only factor coming into play in our atopic children. Other factors such as environmental pollutants and repeated infections are possible suspects.

Similarly the age at starting weaning had no relation to obesity or to BMI and this was contrary to earlier reports that indicated that the earlier the introduction of solid food to the infant, the higher the risk of being obese as a child[28].

Robbins et al.[29], explained the effect of breast feeding and onset of weaning on late adiposity by the fact that greater human milk intake was associated with lower leptin concentration relative to fatness in adolescence, who were formula fed,

this may be one mechanism that link early nutrition with later adiposity.

As regards relation between obesity and atopy, our study showed strong positive association between both where body mass index in children with atopy was 33.35 ± 9.93 whereas in non atopics it was 23.70 ± 9.70 (P=0.000).

Previous, cross sectional, studies have shown an association between obesity and both wheezing and diagnosed asthma[2,18]. However, the nature of the relationship has been established and, furthermore, if the association is causal, the direction of causation remains unknown. Obesity is associated with dyspnea on exercise, which could account for part of the cross sectional association between reported wheezes and obesity[30].

Chinn and Rona[4], suggested that obese individuals might have greater exposure to indoor allergens than subjects of normal weight because they spend more time indoors or that there might be dietary differences between the groups. They found no evidence that differences in nutrient intake could explain the association. However, both diet, especially micro-nutrient intake, and activity levels are difficult to measure.

Sin et al[31], demonstrated that while obesity is a risk for (objective) air flow obstruction, many more obese than non-obese participant were using bronchodilators despite a lack of objective evidence for airflow obstruction. These data suggest that mechanisms other than airflow obstruction are responsible for dyspnea development in obesity and that asthma might be over diagnosed in the obese population. Von Mutius et al[32], concluded that the effects of increased BMI on asthma could be mediated by mechanical properties of the respiratory system associated with obesity or by up-regulation of inflammatory mechanisms rather than by allergic eosinophilic inflammation of the airway epithelium.

Although the association between asthma and BMI is a matter of controversy, the results of Garn et al[33], showed that the severity of asthma increases with increasing BMI. Luder et al[5], concluded that the prevalence of overweight was significantly higher in children with moderate to severe asthma than their peers, and being overweight was associated with significantly more severe symptoms. They found a decrease in FEV_1, and $FEF_{25-75\%}$ in obese children.

Strong positive association between obesity and leptin hormone levels was found in the studied children (P=0.000). Other authors also demonstrated raised serum levels of leptin in obese children. Hassin et al[34], studied serum levels of leptin in seventy-seven children (44 girls and 33 boys) whose mean age was 11.3 years, with body mass index (BMI) greater than 95% for age. They found higher level of serum leptin among obese children when compared to control group (38.6 ± 21 ng/ml versus 7.8 ± 6.5 ng/ml respectively). It was hypothesized that children manifest relative leptin resistance to support increased growth and development of reproductive capacity.

Nolan et al[35], showed that leptin concentration is significantly higher in their obese subjects (22.89 ± 6.4 ng/ml) than non-obese ones (11.13 ± 7.48 ug/ml) (P<0.05). This might be due to adipocytes from obese subjects which produce several folds leptin than those from lean patients.

The family history of obesity, in our study was playing an important role as a predisposing factor of obesity (P=0.036) and this was confirmed by other authors[36,37,38]. They reported that genes predisposing to extreme obesity may be detected within the family structure and affected sib pair.

Overweight parents are more likely to have overweight children. These individuals with genetic propensity for overweight are likely to select environment for themselves and their children, including low levels of activity and high fat intake that promote the development of overweight[33].

As regards the relation between leptin hormone level and gender our study showed non-significant relation between both (P=0.673) and this result was contradicted with Garn et al[33], who demonstrated that leptin concentration is significantly higher in females (14.30 ± 10.95 ng/ml) than males (8.76 ± 5.66 ng/ml) (P<0.05). Serum leptin was reported by many authors to be higher in women than men[35,39,40].

Two explanations have been proposed for the sexual dimorphism of serum leptin. First, females have a higher ratio of subcutaneous to omental fat mass, in addition, a significant higher subcutaneous to omental fat ratio of leptin expression has been demonstrated in females by Montague et al[41]. Consequently higher serum leptin levels in females may reflect those gender variations in regional body fat distribution and leptin expression.

Second, it has been suggested that reproductive hormone status may account in part for this dimorphism[41].

Regarding age and leptin hormone level our study showed significant positive relation between both (P=0.000) and this may be due to the possibility that higher leptin levels in older subjects may be due to a higher percentage of adiposity.

The relation between serum leptin and cholesterol levels was non-significant. This

disagrees with the results of Lob-Corzilius[42], which showed a negative significant correlation between them. Cholesterol levels are usually higher in the older age group and the mean age in our study was 11.2 ± 3.9 while in the aforementioned study it was 15.3 ± 8.2 years. Also the number of patients studied was less in our work (47 versus 240).

The results of the present work showed that there was no significant relation between obesity and taking food during watching TV (P=0.78). However the percent of obese children taking food during watching television was more where BMI was 34.80 ± 13.63 in cases taking food during watching TV and 33.99 ± 6.21 in cases who were not. There are reports that regarded TV viewing as a risk factor for the development of overweight and obesity and a vicious circle is established.

Three potential mechanisms have been suggested to link television viewing and obesity. The first mechanism is reduced energy expenditure from television viewing displacing physical activity[43]. The second mechanism is increasing dietary energy intake from eating during viewing or from the effect of food advertising. Exposure to food advertisements may produce incorrect nutritional beliefs. Experimental studies with children have demonstrated direct effect of exposure to high-calorie food advertising on actual snack choice and consumption[44]. A third potential mechanism is that television viewing decreases resting metabolic rate. The children seem to fidget, more when sitting quietly than when reading or watching TV[44].

In conclusion, family history of obesity plays an important role as predisposing factor of obesity in children. Atopy was more prevalent in artificial than in breast fed obese children. Efforts should focus on making weight reduction as a part of treatment of asthma in obese children. Although serum leptin is highly related to obesity yet it does not play a significant role in atopy in obese children.

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