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Leptin and IL-6 as risk factors for metabolic cardiovascular syndrome in obese prepubertal children

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Background: *Potential risk factors for cardiovascular diseases (CVD) tend to cluster in childhood and are strongly associated with obesity.*
The prevalence of obesity in children has increased dramatically over the last 20 years, leading to higher health risk associated with complications such as type 2 diabetes, high blood pressure and cardiovascular disease.
Leptin is a hormone produced by the adipocytes to regulate food intake, its circulating levels directly correlate with the amount of body fat and body mass index (BMI).
Previous researchers had provided evidence suggesting that ob gene expression is up regulated by some inflammatory cytokines such as IL-6.
Aim: *The aim of this study is to explore the relationship between serum leptin, and interluikin-6 in order to detect the presence of any impairment of these parameters as risk factors for metabolic cardiovascular syndrome in obese prepubertal children, in an attempt to overcome the increased health risk associated with obesity in children.*
Subjects and methods: Eighty prepubertal children age range between (5-11) years old were enrolled in this study. Divided according to their weight into two groups: Obese group 50 subjects Lean group 30 aged matched subjects.
Circulating serum leptin and IL-6 were measured by ELISA technique.
Results: *both parameters studied showed a significantly higher values in obese children than in leans. No significant correlations were found to exist between these parameters in both groups. However correlations were much more prominent in obese group compared to lean groups.*
Conclusion: *Obese children exhibited a high prevalence of metabolic syndrome. The children with greater insulin resistance exhibited more risk factors. In the light of these findings intervention measures are necessary in order to prevent excessive weight gain during childhood.*

I. Introduction

Metabolic syndrome : is a cluster of metabolic abnormalities which may lead to CVD and other disease that all can be fatal . The five generally accepted features of metabolic syndrome are obesity, insulin resistance, dyslipidemia [including increased triglycerides and decreased HDL], impaired glucose tolerance, and hypertension(1). However, obesity has The central role in metabolic syndrome (2).
Recent studies suggest that this syndrome may also occur in children . (3)

Leptin is a peptide hormone encoded by the obesity gene. It is a 16-kDa protein produced primarily in adipose tissue. It plays an important role in regulating food intake, reproduction, and immune function (4) . Leptin is mainly secreted from adipose tissue in direct proportion to fat content, and it crosses the blood-brain barrier to interact with specific leptin receptors in the hypothalamus and brainstem.Leptin's actions in the hypothalamus and a variety of other peripheral organs are mediated by the long isoform of the leptin receptor(OB-R)(5). (Therefore, the major site of action of leptin is the hypothalamus, where the concentration of the functional isoform of Ob-R is maximal) (6) . Adipose tissue can also synthesize cytokines such as IL-6. In this way obesity itself promotes inflammation and potentiates atherogenesis independent of effects on insulin resistance or lipoproteins. (7) .

Interleukin-6 (IL-6) is produced by several cell types, such as immune cells, adipocytes, myocytes, and endothelial cells. Although IL-6 was initially identified as an immuno-modulatory cytokine secreted from macrophages, several previous studies revealed that IL-6 also has significant impacts on nonimmune events (8) including glucose metabolism.

Aim:The aim of this study is to explore the relationship between serum leptin, and interluikin-6 in order to detect the presence of any impairment of these parameters as risk factors for metabolic cardiovascular syndrome in obese prepubertal children, in an attempt to overcome the increased health risk associated with obesity in children.

II. Subjects and methods:

The study was performed during the period from January 2013 to march 2013. For this purpose 50 healthy obese children and 30 normal weight children were selected from people attended the hospital and students from primary schools .the age of children was between 5 to 11 years .

The study was done with the approval of the medical ethical committee in the ministry of health and ministry of education (Directorate General of education in diyala). the parents agreement for blood drawing from their children was also taken.

From each subject, five ml of venous blood were aspirated from a suitable vein. Sera were obtained after centrifugation at 4000 rpm for 15 minutes and were used assessing the levels of leptin and IL-6.

Principle of assessment of Leptin by quantitative sandwich enzyme immunoassay technique (ELISA). This technique include antibody specific for leptin pre-coated onto a microplate. Standards and samples are pipetted into the wells and any leptin present is bound by the immobilized antibody. After removing any unbound substances, a biotin-conjugated antibody specific for leptin is added to the wells. After washing, avidin conjugated Horseradish Peroxidase (HRP) is added to the wells. Following a wash to remove any unbound avidin-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of leptin bound in the initial step. The color development is stopped and the intensity of the color is measured.

Principle of assessment of IL-6 also by ELISA teqnique. The microtiter plate provided in the kit is pre-coated with an antibody specific to IL-6. Standards or samples are then added to the appropriate microtiter plate wells with a biotin-conjugated polyclonal antibody preparation specific for IL-6 and Avidin conjugated to Horseradish Peroxidase (HRP) is added to each microplate well and incubated. Then a TMB (3,3',5,5' tetramethyl-benzidine) substrate solution is added to each well. Only those wells that contain IL-6, biotin-conjugated antibody and enzyme-conjugated Avidin will exhibit a change in color. The enzyme-substrate reaction is terminated by the addition of a sulphuric acid solution and the color change is measured spectrophotometrically at a wavelength of 450 nm ± 2 nm. The concentration of IL-6 in the samples is then determined by comparing the O.D. of the samples to the standard curve.

Anthropometrical Measurements: Body mass index (BMI) is a measure used to determine children's obesity. It is calculated using a child's weight and height. BMI does not measure body fat directly, but it is a reasonable indicator of body fatness for most children and teens.

A child's weight status is determined using an age- and sex-specific percentile for BMI rather than the BMI categories used for adults because children's body composition varies as they age and varies between boys and girls.

Centers for Disease Control and Prevention (CDC) Growth Charts are used to determine the corresponding BMI-for-age and sex percentile. For children and adolescents (aged 2—19 years):

A- Obesity is defined as a BMI at or above the 95th percentile for children of the same age and sex.

B- Normal is defined as a BMI at or above the 5 th to 85 th percentile for children of the same age and sex .

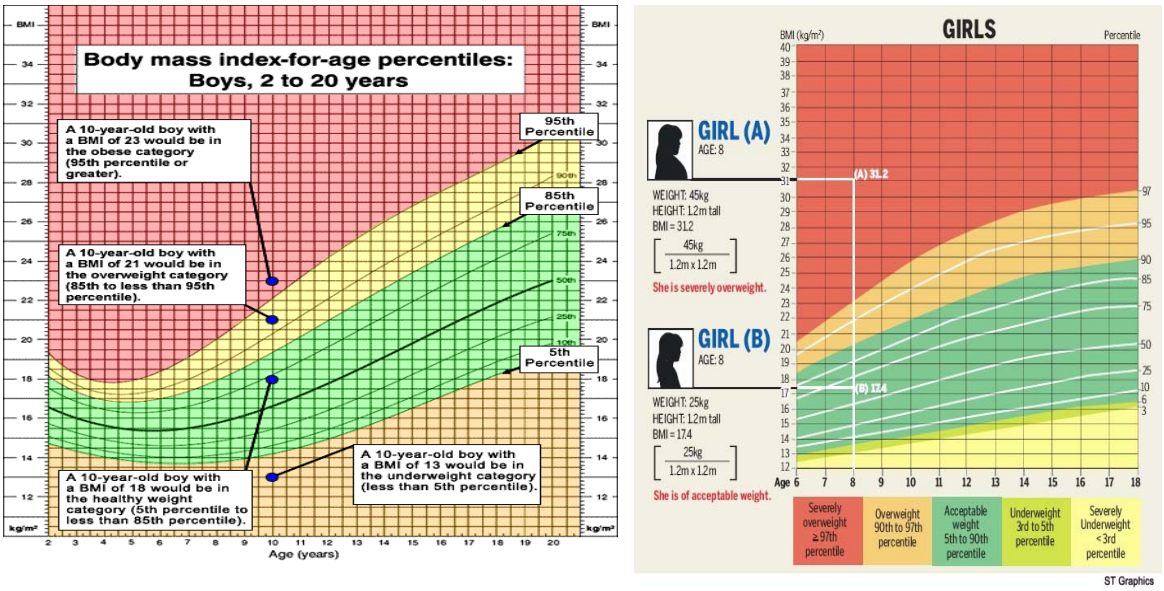


Figure (1): Centers for Disease Control and Prevention (CDC) Growth Charts for male and female children (www.cdc.gov/growthcharts/)

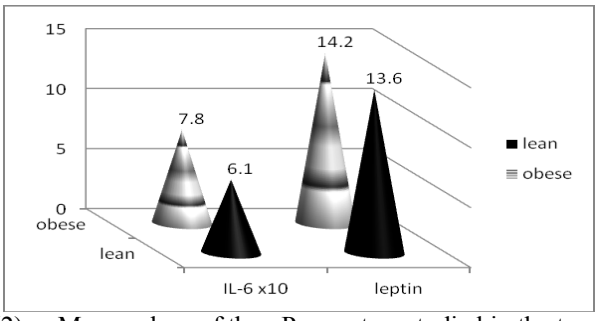
Data were entered and analyzed using SPSS version 16 (SPSS Inc , USA) for windows (Microsoft corporation , USA). Continuous variable were expressed as mean ± SD , while categorical variable were expressed as a percentage and 95 % CI . T – test, Anova . The level of significance for all statistical test was set at 0.05 .

III. Results and discussion:

Table 1 and figure (2) summarizes the results obtained in both obese and lean weight children. As shown in mean , standard Error of the mean and significance.

Table 1: Mean , standard Error mean , sig (2-tailed) of the Parameters studied in the two groups

	Obese (Mean ± SEM)	lean (Mean ± SEM)	*P*
Leptin	14.2 ± 0.42	13.6 ± 0.75	0.463
IL-6	0.78 ± 0.07	0.61 ± 0.44	0.103



Figure(2) : Mean values of the Parameters studied in the two groups

Both leptin and IL-6 were elevated in obese subjects when compared to lean one although non-significant.

Leptin in general inhibits NPY/AgRP neurons and activates POMC/CART neurons (9), resulting in reduced food intake (10) and increased energy expenditure (11) . The effects of gut satiation signals such as CCK can be amplified by leptin which acts in the CNS, including the ARC in particular (12). There are three types of leptin receptors identified: among those, Ob-Rb receptor, which is highly expressed in the hypothalamus (6) and is thought to act as the main receptor involved in appetite control. Subcutaneous administration of recombinant leptin reduces fat mass. (13) However, obese individuals often have high leptin levels, which result in a failure to respond to exogenous leptin. This leptin resistance severely limits the therapeutic utility of leptin, and it is likely to result from reduced leptin receptor signal transduction (14).

Adipose tissue and skeletal muscles are the major organs of lipid metabolism regulated by adipokines. Several reports have described the function of IL-6 in lipid metabolism in adipose tissue, skeletal muscle and liver. Interstitial IL-6 concentrations in adipose tissue are ~100-fold higher than in plasma, implying an important auto- and paracrine regulatory function in this tissue (15). IL-6 has lipolytic properties and increases lypolysis of adipose tissue and adipocytes in vitro (16) . The main contributor to IL-6 elevation is skeletal muscle. It has been reported that IL-6 directly promotes skeletal-muscle differentiation of primary human skeletal-muscle cells and promotes lipid degradation (17).

IV. In conclusion:

Obesity in children increases the risk of metabolic syndrome with increased leptin and IL-6. Interleukin -6 and leptin may have a role in increasing the risk of cardiovascular disease

In the light of these results one should take intervention measures which are necessary to prevent excessive increase in weight during childhood.

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