

THE ROLE OF LEPTIN IN OBESE CHILDREN

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Introduction

Pediatric obesity is a major concern for clinicians. It represents a risk factor for several diseases later in life (1). The current increase in the prevalence of pediatric obesity has fostered a multidisciplinary discourse on the most appropriate strategy for reducing this epidemic. It is estimated that obesity currently affects 25% of children in the United States(2).

In our opinion, much more attention should be given to prevention and the development of preventive strategies at all ages. To attempt the prevention of childhood obesity, it would be clinically useful to have a predictive parameter or set of parameters with which to define an "at risk" state of obesity.



The obesity gene (*ob*) in mice encodes a protein produced by adipose tissue, leptin, which regulates body weight (3). Under experimental conditions, leptin affects the central nervous system and tends to reduce appetite and increase energy expenditure. Numerous studies have shown an increased expression of the *ob* gene (mRNA-leptin) in adipocytes or a marked increase in serum leptin concentration of obese subjects relative to lean subjects; a positive correlation with the body mass index has been reported (4,5). Leptin also exerts various effects on metabolism, glucose homeostasis and sexual development and activity. It has been reported that leptin serum levels do not merely reflect adipose tissue size but that they play in controlling of body weight homeostasis and fatness development. Some of these studies will be analyzed in this review, because the role for leptin to predict weight gain is still controversial.

The regulation of body weight, appetite and energy expenditure in children differs from that in adults, because of energy requirements for growth and maturation. The role of leptin in this dynamic phase of body weight regulation is incompletely understood (6,7).

In a research from Los Angeles, California high fasting leptin level at the start of the study was significantly associated with increasing fat mass in the cohort, indicating that children may be developing resistance to the effects of leptin (8).

On the other hand, some studies suggest that leptin may have a stimulating effect on fat oxidation in obese subjects (9) and it has been studied if leptin and total cholesterol are predictors of weight gain in pre-pubertal children (10). In addition to these roles, recent findings have shown that hyperleptinemia and insulin resistance are strongly related to the components of a metabolic syndrome of cardiovascular risk. Changes in the lipoprotein profile might contribute to later health outcomes. Leptin and other factors in addition to fat mass may mediate metabolic and fibrinolytic processes in obesity during late adolescence (11,12). Little is known about the effects of physical training on plasma leptin concentration in children. A study in this sense will be presented.

There is still much more to learn about leptin's physiology and clinical relevance. The study of the role of leptin in obese children represents one of the major challenges ahead.

The role of leptin to predict weight gain in obese children.

Studies of diverse populations, such as adult Mauritians (13), post obese women (14), have failed to find any associations between initial leptin concentrations and subsequent weight gain over differing periods (4 to 8 years). However, a positive relationship was found in a cohort of middle-aged Swedish women (15). There is a lack of studies in obese children. We can say that currently there is no clear position of the effect of leptin on weight gain in humans. Differences in race, age, sex, and follow-up time between studies mean that generalizations and comparisons are difficult. The variable weight gain differs widely among studies, from changes in body weight and body mass index to the percentage of fat and total fat mass. The studies here presented are important to know more about the role of leptin in weight gain or body fat in children with obesity.

Di Stefano Gi, *et. al.* (16) performed an extensive analysis in a large group of obese children and adolescents in order to establish in greater detail whether baseline leptin serum values were predictive of a subsequent response to an educational –based weight excess reduction program (WERP). They recruited 418 (241 males and 185 females) obese subjects, aged 9 – 15 years. The obese subjects were subdivided into responsive and non-responsive, according to reduction or not of their body mass index (BMI) Z-scores during the WERP. Leptin concentrations were assayed at baseline and were included together with other independent variables in statistical multiple regression analysis. Their results showed that at preliminary multiple regression analysis, a significant positive correlation between leptin values and BMI Z -score reduction at the second, third and fourth semester of follow-up was registered. These findings support a significant role for serum leptin concentration in predicting BMI changes as a response to an educational excess weight reduction program. In addition, the study demonstrated a significant influence of puberty as well as of age. However, they recognize that the role of leptin is influenced by mechanisms restricted to adipose tissue and the modulation of leptin expression. The importance to study this aspects is evident in this research.

Another important study from the University of Southern California (17) was carried out to determine whether initial basal levels or temporal changes in fasting leptin are associated with longitudinal changes in body fat mass in children.

The study group consisted of 85 children (42 white and 43 African American) with a mean initial age of 8.1 years. The children had between three and six annual visits for repeated measurements of body composition by DXA and fasting leptin level.

The major findings of this study was that high baseline leptin concentration was predictive of an increased rate of subsequent fat gain in boys and girls and in African Americans and whites, independent of the initial levels of fat mass. In contrast, the temporal changes in leptin and fat mass during this period of growth were significantly related in African Americans but not whites. They concluded that high initial levels of leptin were found to be predictive of increased fat gain in all children, regardless of race, sex, or degree of sexual maturation. They think that the children are becoming resistant to the effect of leptin during early puberal growth. I think could be interesting some studies with Mexican children.

A similar study, (in normal children) was conducted in Australia to identify specifically which biochemical indices predict excessive weight gain over time in a cohort of pre-pubertal children (18). Fifty nine healthy pre-pubertal children (age 6.3 – 9.8 years) were studied. The pre-pubertal state was defined by maternal report and self report by comparison with diagrammatic Tanner puberty stages. BMI was calculated for each subject and was expressed as a BMI Z-score and percentile using NCHS reference values. Body composition was determined using bioelectrical impedance

analysis (BIA). Glucose, total cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides were measured. No weight management intervention was provided to any family.

Weight change after six months demonstrated no correlation with fasting plasma levels of leptin, insulin, insulin:glucose (IG) ratio, cholesterol, triglyceride or high density lipoprotein (HDL) cholesterol. However, after 12 months there was a significant negative correlation between BMI Z-score change and initial plasma leptin and this relationship strengthened when adjusted for body fat. No relationship was observed between weight change after 12 months and plasma levels of insulin, IG ratio, HDL cholesterol or triglyceride. In this study, plasma leptin and total cholesterol were found to be predictive of weight gain over 12 months in a cohort of pre-pubertal children. They think that these two variables are potential predictors and can be readily measured in clinical practice.

Plasma leptin concentrations in relation to insulin, growth hormone, exercise, and lipoproteins.

Little is known about the interrelationship between leptin and all of these factors. Some studies developed during the last years are presented here.

First, a possible effect of insulin on leptin production is still a matter of debate. Although acute effects have been considered unlikely, a prolonged exposure to insulin might influence leptin. Insulin and leptin concentrations seem to be associated, but plasma insulin does not acutely regulate leptin production. A putative clinical relevance of this leptin-insulin relationship, could be in accordance with the suggestion by Zimmet and colleagues (19) that hyperleptinemia could be the missing link in the metabolic syndrome. A study was developed to evaluate the association of plasma leptin concentration with obesity and the components of insulin resistance syndrome (IRS) among school children in Taiwan (20). They randomly selected 1264 children aged 12-16 years. Obesity measurements included body mass index (BMI) and waist-to-hip circumference ratio (WHR). Also, they calculated an IRS summary score for each individual by adding the quartile ranks from the distribution of systolic blood pressure (BP), serum triglyceride (TG), HDL-cholesterol (inverse), and insulin levels.

The results showed that boys had higher BMI and WHR, BP and IRS score and lower leptin, insulin, TG, and HDL-C levels than girls. BMI, WHR and plasma leptin levels were significantly associated with the IRS summary score and each of its components in both genders. Children with higher leptin levels (> 75th percentiles) have significantly higher BP, TG, insulin levels and IRS scores than children with low leptin levels. The associations between plasma leptin level and the IRS components and score were still significant after adjusting for BMI in boys, but less so in girls. In both genders, after adjusting for WHR, plasma leptin levels were still significantly associated with the IRS components and summary score. The final model that included the standard covariates, BMI and leptin, but not WHR, was the most predictive of the IRS summary score among school children. They concluded that insulin resistance syndrome in childhood, characterized by high blood pressure, dyslipidemia, and hyperinsulinemia, may be an early marker of cardiovascular risk. From the present, at least in this study, BMI and leptin in combination are the most predictive markers of insulin resistance syndrome among school children in Taiwan.

On the other hand, the interrelationship between insulin, leptin and growth hormone in growth hormone –treated children has been studied. In a research conducted by Zadik Z. *et al*, they examined insulin homeostasis during growth hormone therapy, and investigated the effect of GH treatment on insulin and leptin concentration in obese children. In these patients (obese children with Prader-Willi Syndrome and treated with growth hormone; non-obese short children and treated

with growth hormone) increased insulin dosage did not induce an increase in leptin concentration as had been hypothesized (21).

About plasma leptin concentrations in obese children and physical training, a study was published in the American Journal of Clinical Nutrition on 1999 (22). Little is known in this relationship. The objective of this study was to determine the effects of 4-month periods with and without physical training on leptin in obese children and to explore the determinants of leptin at baseline and in response to physical training. They studied 34 obese, 7-11 years old children randomly assigned to engage physical training during either the first or second 4 months of the 8 months study. The results demonstrated that in obese children, leptin concentration decreased during 4 months of physical training and increased during a subsequent 4 months period without physical training, fat mass was highly correlated with baseline leptin, and greater reductions in leptin during 4 months of physical training were seen in children with higher pretraining leptin and in those whose total mass increased least.

An important study about the role of leptin and lipoproteins during weight reduction in overweight children was conducted in Vienna (23). They studied the possible association of leptin with plasma lipoproteins. They measured leptin, lipoprotein cholesterol and apolipoproteins (apo) A-I and B in 34 obese children (age 12.5 years and relative BMI 28%) before and after three weeks of weight reduction in a dietary camp. Lipoprotein binding of endogenous and exogenously radiolabelled leptin was studied by preparative ultracentrifugation. The conclusions in this study were that plasma leptin decreases in overweight children undergoing short term weight reduction. In obese children, plasma apo A-I and HDL cholesterol are independent predictors of leptin concentrations during weight loss, respectively. In addition, HDLs transport a variable portion of leptin in the circulation; therefore it is important to consider this interaction for leptin physiology.

Conclusions

Leptin is an adipocyte -secreted hormone that seems to play an important role in the body weight regulation in obese children. Despite a clear bodyweight function in obese children, its physiological role is not yet fully understood. The studies here presented showed the role of leptin to predict weight gain in obese children and its interrelationship with other parameters, such as insulin, lipoproteins, exercise, and growth hormone. However, further studies are necessary to clarify this relationship. Leptin is significantly broadening our understanding of the mechanisms underlying neuro-endocrine function. We know about the implications of leptin as a lipostatic factor and central satiety agent. However, the distribution of leptin receptors in peripheral tissues provided a fertile area for investigation and a more dynamic view of leptin started to unfold. Considerable evidence for systemic effects of leptin on specific tissues and metabolic pathways indicates that leptin operates both directly and indirectly to initiate complex pathophysiological processes. To us, studying the biochemical and molecular mechanisms in which leptin of obese children is involved represent one of the major challenges ahead. Dietitians should participate more not only in the nutritional services to obese children, but in metabolic, molecular, and physiological research in this field.

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