PERSPECTIVE

Hormones and Cytokines in Childhood Obesity

NUR ARSLAN, BARIS ERDUR AND ADEM AYDIN*

*From the Department of Pediatric Gastroenterology, Metabolism and Nutrition and *Department of Social Pediatrics, Dokuz Eylul University School of Medicine, Izmir, Turkey.*

Correspondence to: Nur Arslan, Dokuz Eylul University School of Medicine, Department of Pediatric Gastroenterology, Metabolism and Nutrition, 35340 Izmir-Turkey. nur.arslan@deu.edu.tr

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Objective: Obesity is a growing worldwide health problem affecting both adults and children. Effective prevention and treatment modalities can be achieved by understanding the pathogenesis of obesity better. This review addresses some of the issues related to the hormones and cytokines taking part in the pathogenesis of obesity, energy balance and inflammation.

Design: We reviewed current literature on this broad subject especially concentrating on the functions of the hormones and cytokines taking part in the pathogenesis of the childhood obesity. Using the key words "obesity, children, hormones, cytokines" publications and cross references were evaluated from PubMed database between 1957 and 2009.

Results: In children, leptin and ghrelin are two hormones which have major influence on energy balance. Leptin is responsible from long term regulation of energy balance and ghrelin functions as an appetite stimulatory signal. In contrast to ghrelin, obestatin acts as an anorexigenic hormone by suppressing food intake. Adipokines secreted from adipose tissue are the key regulators of inflammation in obesity. Increased TNF-alpha and IL-6 levels but decreased levels of adiponectin and IL-10 are associated with increased inflammation, tissue injury and complications of obesity.

Conclusions: Development, pathogenesis and complications of childhood obesity consist of complex mechanisms including numerous cytokines and hormones. New treatment modalities depend on understanding these complex mechanisms.

Key words: *Childhood, Cytokines, Hormones, Obesity.*

In recent years, obesity is becoming an epidemic health problem. Worldwide, the prevalence of obesity in children has steadily increased since the 1980s. In 2007, it was estimated that globally 22 million children under 5 years were overweight, with more than 75% of overweight and obese children living in low and middle income countries(1). According to the American Obesity Association, 30% of children and adolescents between 6 and 19 years are overweight and about 15% are meeting criteria for obesity(2). In Ankara, which is the capital of Turkey, the prevalence of obesity in children and adolescents between the ages of 10 to 17 years was reported as 4.9%(3). The prevalence of childhood overweight and obesity was reported as 21-25% and 5-6% in Australia, 7.7% and 3.7% in China, and 20% and 7% in European Union countries, respectively(4-6). Childhood obesity has an increasing trend not only in the developed countries, but also in the developing countries. School based data in India demonstrates prevalence of obesity in the range of 5.6% to 24% among children and adolescents(7). In a study from Pakistan, among children and adolescent of affluent schools of Karachi, percentage of obese and overweight children were found 6% and 19% of the population studied(8). Although most of Africa has very low rate of obesity in children, the prevalence of

urban overweight/obesity increased by nearly 35% from 1992 to 2005 in African adults(9). The main drivers of the escalating trends of childhood obesity in the developing countries are cheap foods with high content of sugar and fat, sedentary lifestyle and rapid nutritional transitions consequent to increasing affluence, socioeconomic transitions, urbanization, mechanization and rural-to-urban migration(8).

The presence of obesity is associated with significant adverse effects on health including metabolic, endocrinologic, cardiovascular, gastrointestinal, pulmonary, neurologic, psychiatric, hematologic, and skeletal complications, and development of some types of malignancies. All of these unfavorable effects lead up to a shortened life span. Studies strongly suggest that vascular, histopathological and metabolic changes begin in the childhood period. Development of metabolic complications associated with obesity during childhood track into adulthood and increases the risk for type 2 diabetes, dyslipidemia and early cardiovascular disease. On this account, childhood obesity should be prevented at early ages.

It is well recognized that the causes of obesity are complex and multifactorial including metabolic, hormonal, genetic, and psychosocial factors. The main factor contributing to excessive weight gain in children is the impaired balance between energy intake and expenditure. Most of the known genetic causes of obesity primarily play role by augmenting energy intake. Increasing evidence suggests that numerous neuroendocrine peptides and cytokines, which are secreted mostly from adipose tissue, play a role in both short and long term energy balance, metabolism and inflammatory response in humans. Research about the pathophysiology and treatment of obesity has been directed to this area in the recent years.

In this review, the importance of adipose tissue in obesity, the hormones and cytokines, which seem to play major roles in adult and childhood obesity and its complications will be evaluated.

ADIPOSE TISSUE AND ADIPOKINES

Adipose tissue is not a passive site of energy storage. The major function of the adipocyte is to store and release energy in the form of triglyceride during excess food consumption and starved periods, respectively. Recent studies indicate that, in both children and adults, adipose tissue is an endocrine organ producing several proteins (adipokines) with broad biological activity(10). Although the liver participates in the systemic inflammation of obesity, the dominant controlling organ is the adipose tissue. Adipose tissue consists of adipocytes, fibroblasts, pre-adipocytes, macrophages and vascular tissue. After the maturation of the pre-adipocytes, they acquire the functions similar to those of the macrophage. These functions include the capacity responding to bacterial cell wall products, inducing cytokine cascades and secreting cytokines or acute phase reactants(10,11).

A number of cytokine mediators of inflammation are produced by adipose tissue. The most important of these mediators are interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-alpha), and adiponectin. C reactive protein (CRP) and interleukin-10 (IL-10) are not products of adipose tissue, but their circulating concentrations are under the control of adipokines. In obese patients, increase in IL-6, CRP, TNF-alpha and decrease in adiponectin and IL-10, induce pro-inflammatory stage, resulting in insulin resistance and endothelial dysfunction. Cytokines and molecules produced by adipose tissue are given in ***Table* I** (10).

GHRELIN

Ghrelin is a peptide of 28 amino acids with an n-octanoylated serine residue that is formed after post-translational processing from the 117-amino-acid peptid preproghrelin(12). This octanoyl structure is essential for its functions and transport across the blood-brain barrier. The gene that encodes human preproghrelin is located on chromosome 3p25-26. It is mainly synthesized from gastric fundus. It is also synthesized in small amounts in all human tissues studied, including hypothalamus, hippocampus, cerebral cortex, pituitary gland, small intestine, adrenal glands, pancreas, etc. The only receptor so far identified for ghrelin is growth hormone secretory receptor type 1a (GHS-R1a), which is expressed in mostly hypothalamus. Its gene is composed of 366 amino acids and is located on

TABLE I CYTOKINES AND MOLECULES PRODUCED BY ADIPOSE TISSUE

Acylation stimulating protein
Adiponectin
Angiotensin
Atrial natriuretic peptide
Cholesteryl ester transferase
Estrogens
Fatty acid binding protein ap2
FFA / Glycerol
IGF-binding protein 3 (IGFBP-3)
Insulin-like growth factor-I (IGF-1)
Interleukin-1 beta
Interleukin-6 (IL-6)
Interleukin-8 (IL-8)
Leptin
Lipoprotein lipase
Monobutyrin
PAI-1
Resistin
Retinol binding protein-4
Sterol regulatory element binding protein
Tumor necrosis factor-α (TNF-alpha)
Visfatin

Adapted from reference 11.

chromosome 3q26.2. The functions of the receptor GHS-R1b have not been clearly identified yet; however, it is considered to play a role in the activation of GHS-R1a(13). Ghrelin enters the brain through the bloodstream after being secreted by the stomach. In addition, ghrelin may reach the hypothalamus through the vagal nerve and nucleus tractus solitarius.

As suggested by its widespread distribution, ghrelin has a wide spectrum of biologic activities. Ghrelin plays a role in both short and long term regulation of energy balance, appetite, and weight gain. This hormone also increases gastric motility, gastric and pancreatic secretions, regulates glucose and lipid metabolism, stimulates cellular differentiation in adipose tissue, inhibits apoptosis in adipocytes, inhibits lypolysis and stimulates lipogenesis. As an orexigenic hormone, ghrelin stimulates food intake and body weight(14). Ghrelin contributes to preprandial hunger and meal initiation. Endogenous ghrelin rises immediately before eating and decreases again within the next hour(14). In long term energy balance, ghrelin increases food intake, decreases the use of fat as a metabolic fuel and promotes fat deposition.

Many factors influence the systemic concentrations of ghrelin and GHS-R1a. Fasting and chronic food restrictions are major factors that increase both serum ghrelin and GHS-R1a concentrations. Serum ghrelin levels are negatively correlated with body mass index. In a study it was demonstrated that in obese girls ghrelin concentrations were related to the body mass index independent from the feeding status(15). Lower levels of ghrelin in obese patients increase with weight loss. On the contrary, in anorexia nervosa high levels of ghrelin decrease significantly after weight gain occurs. It was demonstrated that obese children had lower ghrelin levels than the control group and ghrelin levels significantly increased after weight loss(16). In this study ghrelin levels in the control and obese groups were 67.26 ± 23.41 and 56.53 ± 15.97 pmol/L, respectively, with a significant difference (P=0.039). Moreover, ghrelin, obestatin and ghrelin/obestatin increased after weight reduction (P<0.05)(24).

Ghrelin may be used in a research setting as a marker of insulin resistance (IR) in children. Ghrelin levels were significantly correlated with insulin levels and HOMA-IR, independent of BMI in insulin resistant obese adolescents(17). A study in prepubertal insulin resistant obese children demonstrated that ghrelin was significantly suppressed shortly after glucose intake in an oral glucose tolerance test, and the fall in circulating ghrelin was negatively correlated with IR(18). Another study showed a significant correlation between insulin sensitivity and the maximum decrease of postprandial ghrelin concentrations (27.3 ± 2.7%) in overweight and obese children(19). A similar observation was reported in children with small-for-gestational age who did not achieve catch up growth in weight(20). However, increased ghrelin levels and improved insulin sensitivity were reported in obese

children after weight loss. These findings indicate that changes in ghrelin are independently associated with changes in glucose and insulin metabolism(21). Ghrelin levels may fluctuate with the pubertal stage and may have role in the regulation of reproductive physiology(22). In a study it was reported that ghrelin levels decreased with the advancing pubertal stage in obese children with insulin resistance. This study also showed that suppression of ghrelin secretion following oral glucose tolerance test was influenced by the pubertal stage(23). Another study demonstrated the ghrelin levels inversely correlated with luteinizing hormone and testosterone levels(24). These findings point out that ghrelin regulates reproductive physiology indirectly in humans. Recently, a study comparing the immuno-modularity effects of ghrelin among prepubertal overweight children and healthy controls was reported. The authors showed that serum IgA, IgG and IgE levels were elevated in the overweight group and significantly correlated with plasma ghrelin levels, suggesting that ghrelin might modulate humoral immunity in overweight and obese children(25).

Current research about ghrelin in the treatment or prevention of obesity aim the blockage of ghrelin receptors and the use of ghrelin agonists. Ghrelin receptor blockers may prevent recurrent weight gain after weight loss is achieved. Ghrelin agonists may also inhibit the effects of ghrelin by competition on the receptors. Although some animal studies support this hypothesis, there is no human study on this subject.

OBESTATIN

Obestatin is a 28-amino-acid amidated peptide derived from the ghrelin precursor by post-translational processing. It is encoded by the same gene that encodes ghrelin. Although obestatin is shown to be present in several tissues such as small and large intestine, pancreas, spleen and mammary gland; stomach seems to be main source of cells producing obestatin similar to ghrelin(26). Surgical removal of the stomach has been shown to reduce the levels of circulating obestatin and ghrelin by 50-80% in rats(27). To date, the receptor for obestatin remains unknown. Obestatin was suggested to interact with the receptors GPR39 and glucagon-like-peptide-1 (GLP-1); however, several studies did not support this suggestion. Further studies are needed to reveal the exact relation between obestatin and GPR39 or GLP-1R.

In contrast to ghrelin, obestatin has been reported to act as an anorexigenic hormone, suppressing food intake, inhibiting gastrointestinal motility and decreasing body weight. Studies in humans have demonstrated that plasma obestatin levels do not vary significantly with a fixed energy meal, but are significantly lower in obese subjects as compared to lean controls(28). This data indicates a role for obestatin in long-term body regulation. There are controversial results for ghrelin/obestatin ratio in obese people. Circulating pre-prandial ghrelin to obestatin ratios were found elevated in human obesity and the ratios were positively correlated with body mass index(29). A study demonstrated increased ghrelin, obestatin and ghrelin/obestatin ratio in obese children after weight reduction(16). Higher obestatin concentrations and lower ghrelin concentrations were found in obese children compared to nonobese ones(30). Imbalance and pre-prandial changes in ghrelin/obestatin ratio may have a role in etiology or pathophysiology of obesity. Additional studies enrolling children are required to get a better understanding of its biological function.

LEPTIN

Leptin is a protein containing 166 amino acids and is the product of human obese (OB) gene located on chromosome 7q31.3. Leptin is produced mainly by adipose tissue. It is also synthesized in small amounts in other human tissues such as the stomach, heart, mammary epithelium and placenta. Leptin acts through the leptin receptor (LEPR or OBR). It is the product of OBR gene located on chromosome 1p31 and is highly expressed in hypothalamus and cerebellum. Vascular tissues, stomach and placenta are other tissues where OBR are synthesized in addition. After leptin is secreted by the adipose tissue, it enters the brain through the bloodstream, similar to ghrelin. Gastric leptin may also reach hypothalamus through the vagal nerve and nucleus solitarius.

Effects of leptin on various systems have been reported, including reproduction, immune system, hematopoesis, angiogenesis, bone formation and wound healing. It plays an important role in energy balance by inhibiting energy intake contrary to ghrelin, and by regulating body weight and energy homeostasis. Serum leptin levels are elevated in obese children; besides, leptin levels decrease during the weight loss period(31-32). A recent study conducted in overweight children and adolescents showed that being female and having greater BMI were significantly and independently associated with increased serum leptin levels(31). In a study conducted in 115 obese children, a steep decline in leptin concentrations during the first 10-11 days was encountered, which was followed by a less steep decline until day 82 during the weight loss stage. Leptin levels declined to 39% of the baseline levels in boys and 51% in girls in this study(32). Leptin regulates the expression of orexigenic and anorexigenic neuropeptides after it crosses blood brain barrier and binds to its receptor. Ghrelin and leptin, which are secreted independently from each other, stimulate and suppress hypothalamic neurons containing various neuropeptides, resulting in anorexic or orexic effects on energy balance(13). Studies about the effect of leptin on circulating ghrelin levels displayed controversial results(33). In one of these studies, any correlation between circulating fasting ghrelin and leptin levels could not be found in obese children and adolescents. Another study disclosed that serum ghrelin levels correlated inversely with age, insulin levels, and BMI, but not with leptin in 51 children(33). It has been suggested that ghrelin blocks the activity of leptin through the hypothalamic receptor pathways; however, the influence of ghrelin on circulating leptin levels has not been demonstrated yet. Factors affecting the circulating leptin and ghrelin levels are given in ***Table* II**(13).

Leptin may play role in the complications of obesity. In 321 elementary school children (109 normal, 212 obese), leptin was determined as the most sensitive adipokine marker for predicting the accumulation of cardiovascular risk factors and the presence of metabolic syndrome(34). In a recent study, leptin was evaluated as a biomarker of adiposity in adolescents to investigate whether leptin levels in adolescence were indicative of adiposity related cardiovascular disease. This study showed that fat mass index and percentage of body fat were associated with leptin levels in both males and females(35). Elevated serum leptin may also be an indicator of fatty liver disease. A 2-fold increase in serum leptin levels in normal weight children with fatty liver when compared to those without fatty liver was demonstrated. In the same study, elevated serum leptin levels were also observed in overweight children with fatty liver(36).

In obese patients, excessive food intake enhances

TABLE II FACTORS AFFECTING CIRCULATING LEPTIN AND GHRELIN LEVELS

Factor	Effect on circulating leptin	Effect on circulating ghrelin
Age	↓ with increasing age	↓ with increasing age
Gender	↑ in females	↑ in females
Body mass index	↑ with increasing BMI	↓ with increasing BMI
Fasting	↓	↓
Food intake	↑	↓
High serum glucose	↑	↓
Insulin	↑	↓
Carbohydrate rich diet	↑	↓
Fat rich diet	↓	↑
Exercise	↓	No change
Growth hormone	No change	↓

Adapted From Reference 13.

leptin levels resulting in decreased hypothalamic sensitivity and leptin resistance. In leptin deficient patients, leptin treatment was demonstrated to decrease appetite and increase weight loss(37). These effects were very limited in obese patients without leptin deficiency(38). In the light of these data, the therapeutic approaches were directed to overcome leptin resistance. A new molecule called Fc-leptin immunfusins, which had an extended circulating half life and enhanced pharmacological properties, led to a significant weight loss in non-leptin deficient mice. In healthy humans, Fc-leptin was demonstrated to contribute to weight loss after 12 weeks of dietary fat restriction(39). Moreover, daily administration of Fc-leptin in addition to a diet was found to prevent adaptations occurring during weight loss(40).

ADIPONECTIN

Adiponectin is a protein of 30 kDA, which is highly expressed in adipose tissue. The expression of adiponectin mRNA is dependent on the adipose tissue localization. There are 2 recently cloned adiponectin receptors, adipoR1 and adipoR2, located on chromosomes 1q32 and 12p13, which are expressed in skeletal muscle and liver, respectively. Signal transduction pathways in these receptors have not been clarified yet.

Circulating adiponectin levels are decreased in obese patients, particularly in patients with abdominal obesity. Serum adiponectin levels increase in conjunction with weight loss. A 245% increase in adiponectin levels after one year of weight loss period in 48 obese children was observed in a study(41). The factors contributing to lower the levels of adiponectin in obese cases are not clear. Low insulin-stimulated adiponectin secretion from adipocytes owing to insulin resistance in the adipocyte tissue, increased suppression of its secretion by TNF-alpha and IL-6 may be the possible mechanisms(42). Clinical importance of adiponectin comes from its insulin-sensitizing, anti-inflammatory and anti-atherogenic properties. High adiponectin levels are inversely correlated with obesity, insulin resistance, risk for development of type 2 diabetes, dyslipidemia, and cardiovascular disease(43,44). In a study evaluating 46 obese prepubertal children and 34 obese adolescents, the authors showed that lower adiponectin concentrations significantly correlated with several indices of insulin resistance such as the areas under the curves for glucose and insulin, whole-body insulin sensitivity index, glucose 120', and insulin 30'(43). Recently, in obese children and adolescents, the clear link between low adiponectin levels and the metabolic syndrome was demonstrated(44). Moreover, another study detected a rise in insulin sensitivity associated with decreased adiponectin levels in 307 children between ages of 5 and 8 years(45). Adiponectin decreases circulating free fatty acids by increasing their oxidation by skeletal muscle. The decreased hepatic triglyceride content, secondary to decreased circulating free fatty acid levels, is thought to increase hepatic insulin sensitivity(46). Adiponectin regulates liver glucose production by lowering mRNA expression of key enzymes of gluconeogenesis(47). Adiponectin may also stimulate glucose uptake in adipocytes and muscle by directly activating adenosine monophosphate–activated protein kinase. In addition to its insulin sensitizing effects, it was reported that adiponectin acts as a protector of atherosclerosis by modulation of endothelial adhesion molecules, transformation of macrophages into foam cells, modulation of vascular smooth muscle cell proliferation, and inhibition of TNF-alpha secretion(48). It was also demonstrated that serum adiponectin levels were significantly associated with HDL cholesterol levels as a biochemical marker decreasing the risk of atherosclerosis(48). A study in children demonstrated that adiponectin levels were inversely correlated with obesity and insulin resistance and directly correlated with HDL levels(49).

TNF-ALPHA

TNF-alpha is a proinflammatory cytokine, which is mainly produced by macrophages and lymphocytes, to a less extend by adipose tissue. The reason for increased circulating TNF-alpha levels observed in obese people is not thought to be associated with over-production in the adipose tissue. It is hypothesized that systemic effects of leptin or other adipokines may induce TNF-alpha secretion from macrophages and lymphocytes(50).

The two clinically important effects of TNF-alpha in obese children and adults are insulin resistance and endothelial inflammatory changes. In rats, TNF-alpha is thought to play a major role in the pathophysiology of insulin resistance through the phosphorylation of the insulin receptor substrate-1 (IRS-1) protein on serine residues(51). Improvement in insulin sensitivity has been demonstrated after the neutralization of endogenous TNF-alpha in obese rats(52). Increased plasma levels of the soluble fraction of tumor necrosis factor receptor 2 have been found to be associated with insulin resistance in healthy volunteers(53). In a study including 47 obese children, HOMA index, TNF-alpha and C-reactive protein levels were found to be significantly higher in obese children compared with the control group(54). TNF-alpha activates the transcription factor nuclear factor-κB, which leads to a series of inflammatory changes in vascular tissue. These inflammatory changes of the vascular tissue have been shown to result in endothelial dysfunction and hypertension(55). In a study including 64 children and adolescents (11 children with obesity, 11 with hypertension, 28 with diabetes and 14 with obesity accompanying hypertension), obesity and obesity accompanying hypertension have been found in association with elevated TNF-alpha and IL-6 levels(56). The elevated levels of IL-6 and TNF-alpha in children with atherosclerosis risk factors, particu-larly obesity, may confirm the presence of inflammatory process in early phases of atherosclerosis.

IL-6

IL-6 is a circulating multifunctional cytokine with various functions such as inflammation, host defense, and tissue injury. It is produced by many cell types and tissues, including immune cells, fibroblasts, endothelial cells, skeletal muscle, and adipose tissue. Adipose cells contribute 15 to 30% of circulating IL-6 levels in the absence of acute inflammation(57).

It is well known that IL-6 production is significantly enhanced by adipose tissue in obesity(58). The two major adverse effects of increased IL-6 in obesity are insulin resistance and increased risk for cardiovascular complications. Circulating IL-6 was found associated with insulin resistance in healthy men, in obese women, and in cancer patients(59,60). There is a positive correlation between plasma IL-6 levels and insulin resistance in human obesity both in adults and children(61). In 105 obese children and adolescents (14 glucose-intolerant, 91 with normal glucose tolerance tests) and the control group of 27 healthy children, circulating plasma levels of IL-6 in glucose-intolerant obese patients were significantly higher compared with normotolerant obese patients and control subjects(61). High plasma levels of IL-6 is a predictor of type 2 diabetes and future myocardial infarction (62,63). Administration of IL-6 in healthy volunteers induces dose dependent increases in blood glucose(64). This effect is thought to come from resistance to insulin action. IL-6 inhibits insulin receptor signal transduction in hepatocytes, increases circulating free fatty acids from adipose tissue and reduces adiponectin secretions, all of which have adverse effects on insulin sensitivity (65,66). IL-6 induces hepatic CRP production, which is demonstrated as an independent major risk factor for cardiovascular complications(67). In 20 obese adolescents with fatty liver, significantly increased levels of C-reactive protein and IL-6 levels were found, compared with the control group(54). Large quantities of IL-6 are found in human atherosclerotic plaques. Moreover, IL-6 impairs endothelium-dependent dilatation in human veins, so IL-6 seems to be an important aggravating factor of coronary artery disease(68).

IL-10

IL-10 is a cytokine secreted by activated macrophages and lymphocytes. Low production capacity of IL-10 has been demonstrated in obesity, metabolic syndrome, and type 2 diabetes(95). IL-10 has insulin-sensitizing, anti-inflammatory and endothelial protective properties by antagonizing TNF-alpha and IL-6(69,70). In a study including 184 children with obesity and obstructive sleep apnea, levels of IL-10 were found negatively related to BMI(71). Reduced IL-10 level in obese patients is an important risk factor for insulin resistance, atherosclerotic plaque instability and acute coronary ischemia.

In conclusion, numerous hormones and cytokines have a key role in the pathogenesis and complications of obesity in both children and adults. Leptin is responsible for the long term energy balance. Ghrelin, on the other hand, is a fast acting orexigenic hormone playing a role in the short term energy intake. In contrast with ghrelin, obestatin is an anorexigenic hormone which suppresses food intake. Adipose tissue is an endocrine organ producing several adipokines that are the key regulators of inflammation and tissue injury involved in obesity associated complications in children and adults. Increased levels of TNF-alpha and IL-6 and decreased levels of adiponectin and IL-10 lead to inflammation and injury in several tissues and organs.

REFERENCES

1. World Health Organisation. Childhood overweight and obesity. 2008. www.who.int/dietphysicalactivity/childhood/en/index.html. Accessed on August 15, 2010.
2. Devi S. Progress on childhood obesity patchy in the USA. Lancet 2008; 371: 105-106.
3. Agirbasli M, Cakir S, Ozme S, Ciliv G. Metabolic syndrome in Turkish children and adolescents. Metabolism 2006; 55: 1002-1006.
4. Olds TS, Tomkinson GR, Ferrar KE, Maher CA. Trends in the prevalence of childhood overweight and obesity in Australia between 1985 and 2008. Int J Obes (Lond) 2009; Oct 13: [Epub ahead of print].
5. Ji CY, Cheng TO. Epidemic increase in overweight and obesity in Chinese children from 1985 to 2005. Int J Cardiol 2009; 132: 1-10.
6. Branca F, Nikogosian H, Lobstein T (eds). The Challenge of Obesity in the WHO European Region and the Strategies for Response. Copenhagen, WHO Regional Office for Europe 2007.
7. Greydanus DE, Bhave S. Obesity and adolescents; time for increased physical activity. Indian Pediatr 2004; 41: 545-550.
8. Aziz S, Noorulain W, Zaidi UE, Hossain K, Siddiqui IA. Prevalence of overweight and obesity among children and adolescents of affluent schools in Karachi. J Pak Med Assoc 2009; 59: 35-38.
9. Ziraba AK, Fotso JC, Ochako R. Overweight and obesity in urban Africa: A problem of the rich or the poor? BMC Public Health 2009 ; 9: 465-473.
10. Gregor MF, Hotamisligil GS. Adipocyte stress: the endoplasmic reticulum and metabolic disease. J Lipid Res 2007; 48: 1905-1914.
11. Trayhurn P. Adipocyte biology. Obes Rev 2007; 8: 41-44.
12. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 1999; 402: 656-660.
13. Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. Obes Rev 2007; 8: 21-34.
14. Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes 2001; 50: 1714-1719.
15. Foster CM, Barkan A, Kasa-Vubu JZ, Jaffe C. Ghrelin concentrations reflect body mass index rather than feeding status in obese girls. Pediatr Res 2007; 6: 731-733.
16. Zou CC, Liang L, Wang CL, Fu JF, Zhao ZY. The change in ghrelin and obestatin levels in obese children after weight reduction. Acta Paediatr 2009; 98: 159-165.
17. Stylianou C, Galli-Tsinopoulou A, Farmakiotis D, Rousso I, Karamouzis M, Koliakos G, *et al.* Ghrelin and leptin levels in obese adolescents. Relationship with body fat and insulin resistance. Hormones (Athens) 2007; 6: 295-303.
18. Galli-Tsinopoulou A, Stylianou C, Farmakiotis D, Rousso I, Karamouzis M, Nousia-Arvanitakis S. Ghrelin serum levels during oral glucose tolerance test in prepubertal obese children with insulin resistance. J Pediatr Endocrinol Metab 2007; 20: 1085-1092.
19. Maffeis C, Bonadonna C, Consolaro A, Vettor R, Banzato C, Silvagni D, *et al*. Ghrelin, insulin sensitivity and postprandial glucose disposal in overweight and obese children. Eur J Endocrinol 2006; 154: 61-68.
20. Iñiguez G, Ong K, Peña V, Avila A, Dunger D, Mericq V. Fasting and post-glucose ghrelin levels in SGA infants: relationships with size and weight gain at one year of age. J Clin Endocrinol Metab 2002; 87: 5830-5833.

21. Krohn K, Boczan C, Otto B, Heldwein W, Landgraf R, Bauer CP, Koletzko B. Regulation of ghrelin is related to estimated insulin sensitivity in obese children. Int J Obes (Lond) 2006; 30: 1482-1487.

22. Bellone S, Rapa A, Vivenza D, Castellino N, Petri A, Bellone J, *et al*. Circulating ghrelin levels as function of gender, pubertal status and adiposity in childhood. J Endocrinol Invest 2002; 25: 13-15.

23. Xiu-Min Wang, You-Jun Jiang, Li Liang, Li-Zhong Du. Changes of ghrelin following oral glucose tolerance test in obese children with insulin resistance. World J Gastroenterol 2008; 14: 1919-1924.

24. Chao-Chun Zou, Li Liang, Zheng-Yan Zhao. Factors associated with fasting plasma ghrelin levels in children and adolescents. World J Gastroenterol 2008; 14: 790-794.

25. Okamatsu Y, Matsuda K, Hiramoto I, Tani H, Kimura K, Yada Y, *et al*. Ghrelin and leptin modulate immunity and liver function in overweight children. Pediatr Int 2009; 51: 9-13.

26. Zhao CM, Furnes MW, Stenström B, Kulseng B, Chen D. Characterization of obestatin- and ghrelin-producing cells in the gastrointestinal tract and pancreas of rats: an immunohistochemical and electron-microscopic study. Cell Tissue Res 2008; 331: 575-587.

27. Furnes WM, Stenstrom B, Tommeras K, Skoglund T, Dickson SL, Kulseng B, *et al*. Feeding behaviour in rats subjected to gastrectomy or gastric bypass surgery. Eur Surg Res 2008; 40: 279-288.

28. Huda MS, Durham BH, Wong SP, Deepak D, Kerrigan D, McCulloch P, *et al*. Plasma obestatin levels are lower in obese and post-gastrectomy subjects, but do not change in response to a meal. Int J Obes (Lond) 2008; 32: 129-135.

29. Guo ZF, Zheng X, Qin YW, Hu JQ, Chen SP, Zhang Z. Circulating preprandial ghrelin to obestatin ratio is increased in human obesity. J Clin Endocrinol Metab 2007; 92: 1875-1880.

30. Reinehr T, de Sousa G, Roth CL. Obestatin and ghrelin levels in obese children and adolescents before and after reduction of overweight. Clin Endocrinol (Oxf) 2008; 68: 304-310.

31. Antunes H, Santos C, Carvalho S. Serum leptin levels in overweight children and adolescents. Br J Nutr 2008; 28: 1-5.

32. Holm JC, Gamborg M, Kaas-Ibsen K, Gammeltoft S, Ward L, Heitmann BL, *et al*. Time course and determinants of leptin decline during weight loss in obese boys and girls. Int J Pediatr Obes 2007; 2: 2-10.

33. Haqq AM, Farooqi IS, O'Rahilly S, Stadler DD, Rosenfeld RG, Pratt KL, *et al*. Serum ghrelin levels are inversely correlated with body mass index, age, and insulin concentrations in normal children and are markedly increased in Prader–Willi syndrome. J Clin Endocrinol Metab 2003; 88: 174-178.

34. Yoshinaga M, Sameshima K, Tanaka Y, Wada A, Hashiguchi J, Tahara H, *et al*. Adipokines and the prediction of the accumulation of cardio-vascular risk factors or the presence of metabolic syndrome in elementary school children. Circ J 2008; 72: 1874-1878.

35. Zhang S, Liu X, Brickman WJ, Christoffel KK, Zimmerman D, Tsai HJ, Wang G, *et al*. Association of plasma leptin concentrations with adiposity measurements in rural Chinese adolescents. J Clin Endocrinol Metab 2009; 94: 3497-3504.

36. Kim IK, Kim J, Kang JH, Song J. Serum leptin as a predictor of fatty liver in 7-year-old Korean children. Ann Nutr Metab 2008; 53: 109-116.

37. Licinio J, Caglayan S, Ozata M, Yildiz BO, de Miranda PB, O'Kirwan F, *et al*. Phenotypic effects of leptin replacement on morbid obesity, diabetes mellitus, hypogonadism, and behavior in leptin-deficient adults. Proc Natl Acad Sci USA 2004; 101: 4531-4536.

38. Aprath-Husmann I, Rohrig K, Gottschling-Zeller H, Skurk T, Scriba D, Birgel M, *et al*. Effects of leptin on the differentiation and metabolism of human adipocytes. Int J Obes Relat Metab Disord 2001; 25: 1465-1470.

39. Weigle DS, Cummings DE, Newby PD, Breen PA, Frayo RS, Matthys CC, *et al*. Roles of leptin and ghrelin in the loss of body weight caused by a low fat, high carbohydrate diet. J Clin Endocrinol Metab 2003; 88: 1577-1586.

40. Rosenbaum M, Goldsmith R, Bloomfield D, Magnano A, Weimer L, Heymsfield S, *et al*. Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight. J Clin Invest 2005; 115: 3579-3586.

41. Cambuli VM, Musiu MC, Incani M, Paderi M, Serpe R, Marras V, *et al*. Assessment of

adiponectin and leptin as biomarkers of positive metabolic outcomes after lifestyle intervention in overweight and obese children. J Clin Endocrinol Metab 2008; 93: 3051-3057.

42. Bruun JM, Lihn AS, Verdich C, Pedersen SB, Toubro S, Astrup A, *et al.* Regulation of adiponectin by adipose tissue-derived cytokines: In vivo and in vitro investigations in humans. Am J Physiol Endocrinol Metab 2003; 285: E527-533.

43. Panagopoulou P, Galli-Tsinopoulou A, Fleva A, Pavlitou-Tsiontsi E, Vavatsi-Christaki N, Nousia-Arvanitakis S. Adiponectin and insulin resistance in childhood obesity. J Pediatr Gastroenterol Nutr 2008; 47: 356-362.

44. Jeffery AN, Murphy MJ, Metcalf BS, Hosking J, Voss LD, English P, *et al*. Adiponectin in childhood. Int J Pediatr Obes 2008; 3: 130-140.

45. Murphy MJ, Hosking J, Metcalf BS, Voss LD, Jeffery AN, Sattar N, *et al.* Distribution of adiponectin, leptin, and metabolic correlates of insulin resistance: a longitudinal study in British children; 1: Prepuberty (EarlyBird 15). Clin Chem 2008; 54: 1298-1306.

46. Eyzaguirre F, Mericq V. Insulin resistance markers in children. Horm Res 2009; 71: 65-74.

47. Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. Endocr Rev 2005; 26: 439-451.

48. Arita Y, Kihara S, Ouchi N, Maeda K, Kuriyama H, Okamoto, *et al*. Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-BB-binding protein and regulates growth factor-induced common postreceptor signal in vascular smooth muscle cell. Circulation 2002; 105: 2893-2898.

49. Arnaiz P, Acevedo M, Barja S, Aglony M, Guzman B, Cassis B, *et al*. Adiponectin levels, cardio-metabolic risk factors and markers of subclinical atherosclerosis in children. Int J Cardiol 2008; Sep 5: [Epub ahead of print].

50. Koistinen HA, Bastard JP, Dusserre E, Ebeling P, Zegari N, Andreelli F, *et al*. Subcutaneous adipose tissue expression of tumour necrosis factor-alpha is not associated with whole body insulin resistance in obese nondiabetic or in type-2 diabetic subjects. Eur J Clin Invest 2000; 30: 302-310.

51. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 1993; 259: 87-91.

52. Hotamisligil GS, Spiegelman BM. Tumor necrosis factor: A key component of the obesity-diabetes link. Diabetes 1994; 43: 1271-1278.

53. Greenberg, AS and McDaniel ML. Identifying the links between obesity, insulin resistance and ß-cell function: Potential role of adipocyte-derived cytokines in the pathogenesis of type 2 diabetes. Eur J Clin Invest 2002; 32: 24-34.

54. Angin Y, Kuralay F, Arslan N. Evoluation of metabolic, antioxidant and oxidant systemic determinants in nonalcoholic fatty liver disease relevant to pediatric obesity. *In:* Sahin MF, Zefirov NS, editors, 1st Turkish-Russian Joint Meeting on Organic and Medicinal Chemistry; 2009 October 14-17; Antalya, Turkey, p. 64.

55. Lyon CJ, Law RE, Hsueh VA. Minireview: Adiposity, inflammation, and atherogenesis. Endocrinology 2003; 144: 2195-2200.

56. Gtowinska B, Urban M. Selected cytokines (Il-6, Il-8, Il-10, MCP-1, TNF-alpha) in children and adolescents with atherosclerosis risk factors: obesity, hypertension, diabetes. Wiad Lek 2003; 56: 109-116.

57. Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, *et al*. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. J Clin Endocrinol Metab 1997; 82: 4196-4200.

58. Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J Clin Endocrinol Metab 1998; 83: 847-850.

59. Fernandez-Real JM, Vayreda M, Richart C, Gutierrez C, Broch M, Vendrell J, *et al*. Circulating interleukin 6 levels, blood pressure and insulin sensitivity in apparently healthy men and women. J Clin Endocrinol Metab 2001; 86: 1154-1159.

60. Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol 2001; 280: 745-751.

61. Yeste D, Vendrell J, Tomasini R, Broch M, Gussinyé M, Megia A, *et al*. Interleukin-6 in obese children and adolescents with and without glucose

intolerance. Diabetes Care 2007; 30: 1892-1894.

62. Vozarova B, Weyer C, Hanson K, Tataranni PA, Bogardus C, Pratley RE. Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion. Obes Res 2001; 9: 414-417.

63. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation 2000; 101: 1767-1772.

64. Tsigos C, Papanicolaou DA, Kyrou I, Defensor R, Mitsiadis CS, Chrousos GP. Dose-dependent effects of recombinant human interleukin-6 on glucose regulation. J Clin Endocrinol Metab 1997; 82: 4167-4170.

65. Fasshauer M, Kralisch S, Klier M, Lossner U, Bluher M, Klein J, *et al*. Adiponectin gene expression and secretion is inhibited by interleukin-6 in 3T3–L1 adipocytes. Biochem Biophys Res Commun 2003; 301: 1045-1050 .

66. Boden G, Shulman G I. Free fatty acids in obesity and type 2 diabetes: Defining their role in the development of insulin resistance and β-cell dysfunction. Eur J Clin Invest 2002; 32: 14-23.

67. Sacheck J. Pediatric obesity: an inflammatory condition? J Parenter Enteral Nutr 2008; 32: 633-637.

68. Bhagat K, Balance P. Inflammatory cytokines impair endothelium dependent dilatation in human veins in vivo. Circulation 1997; 96: 3042-3047.

69. Gunnett CA, Heistad DD, Faraci FM. Interleukin-10 protects nitric oxide-dependent relaxation during diabetes: Role of superoxide. Diabetes 2002; 51: 1931-1937.

70. Esposito K, Giugliano D, Nappo F, Marfella L. Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus: Campanian Postprandial Hyperglycemia Study Group. Circulation 2004; 110: 214-219.

71. Waters AK, Mast BT, Vella S, De La Eva R, O'Brien LM, Bailey S, *et al*. Structural equation modeling of sleep apnea, inflammation, and metabolic dysfunction in children. J Sleep Res 2007; 16: 388-395.