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REVIEW

Role of obesity and leptin in the pubertal process and pubertal growth—a review

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The prevalence of obesity is increasing alarmingly to epidemic proportions in children and adolescents, especially in industrialized countries. The finding that overweight children, especially girls, tend to mature earlier than lean children has led to the hypothesis that the degree of body fatness may trigger the neuroendocrine events that lead to the onset of puberty. Obese children have high leptin levels, and these may play a role in their earlier onset of puberty. Leptin receptors have been identified in the hypothalamus, gonadotrope cells of the anterior pituitary, and ovarian follicular cells, as well as Leydig cells. Leptin accelerates gonadotropin-releasing hormone (GnRH) pulsatility in hypothalamic neurons, and it has a direct effect on the anterior pituitary. Leptin administration at low doses may have a permissive, threshold effect on the central networks that regulate gonadotropin secretion. However, at high levels, such as those in obese people, it can have an inhibitory effect on the gonads. Children with obesity also have increased adrenal androgen levels, which may be involved in the accelerated growth of these children before puberty. Recent data indicate that leptin has a specific role in stimulating the activity of enzymes essential for the synthesis of adrenal androgens. Children with exogenous obesity frequently show an increase in height velocity with tall stature for age despite low growth hormone levels. Our group has shown that leptin acts as a skeletal growth factor, with a direct effect on skeletal growth centers, in the mice mandibular condyle, a model of endochondral ossification. In summary, obesity is associated with early puberty. Elevated leptin levels might have a permissive effect on the pubertal process and pubertal growth.
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Introduction

Obesity is a major public health problem that has grown to epidemic proportions throughout the world.[1,2] Rates in adults range from 10 to 25% in most Western European countries and from 20 to 25% in some parts of the United States. In children and adolescents, the National Health and Nutrition Examination Survey (NHANES III) reported an estimated 20% prevalence of obesity, defined as a body mass index (BMI) greater than the 85th percentile.[1] For all age groups and degrees of obesity, girls are at higher risk than boys.

Obesity is not restricted to a single ethnic, age, or socioeconomic group, although cultural, environmental, and genetic factors clearly play a role.[1] The environmental factors that contribute to the development of a high degree of body fatness early in life include a high proportion of sedentary activities (eg, TV viewing), low proportion of physical activity, and a shift in diet towards more fast foods with high fat and calorie content. Among the genetic factors, polymorphism or mutations in any of the following genes may be involved in the pathophysiology of obesity: β-adrenergic receptor, tumor necrosis factor (TNF), pro-opiomelanocortin (POMC), neuropeptide Y (NPY), NPY-receptor, melanocortin receptor (MC4R), leptin, and leptin receptor.[3]

Severe obesity is associated with a higher likelihood of continued overweight. This risk is much higher in children with obese parents. Studies have shown that parental obesity is the most important risk factor of obesity in children,[4,5] owing to both the genetic influence and the shared environment (lifestyle, nutritional habits, food preferences, etc).

Among the most common sequelae of childhood obesity are hypertension and dyslipidemia, with increased risk of coronary heart disease, type II diabetes, respiratory problems, pseudotumor cerebri, and orthopedic and psychosocial problems. Since 85% of obese youngsters will become obese adults, the comorbidity exerts an important toll on industrialized societies.

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Several critical periods in childhood have been identified in the development and persistence of obesity.[6] In the gestational period, there is a direct association of high birth weight with subsequent adiposity.[7] Thereafter, in the first year of life, children undergo changes in nutritional behavior which may influence adiposity in later life. Another crucial period is ages of 5-8 years, where adiposity increases after its nadir in childhood ('adiposity rebound'). An early adiposity rebound may serve an index of further obesity.[8,9] The final risk period for the development of persistent obesity is adolescence.[10]

Leptin is a protein product of the obesity (ob) gene. It is secreted as a hormone mainly from white adipose tissue and serves as a signal for the brain of the body's energy stores.[11] By reducing food intake and increasing thermogenesis, leptin controls body fat tissue and, hence, body weight.[12,13] Studies of its physiologic action in humans have shown a strong positive correlation between serum leptin concentrations and the percentage of body fat.[14,15]

Puberty in mammals is physiologically gated by the body's energy resources. According to the classic studies of Kennedy and Mitra[16] and the work of Frisch *et al*,[17] the timing of sexual maturation is associated with body weight and composition. That is, accelerated linear growth and reproductive maturity are affected by peripheral metabolic factors, which signal the body size and fat content. Before puberty can occur, a critical body weight or fat mass must be achieved.[18] As such, alterations in diet and exercise exert a powerful influence on pubertal maturation.[19,20] The observation that overweight girls tend to mature earlier than lean girls[21] has led to the hypothesis that the degree of body fatness may trigger the neuroendocrine events that lead to the onset of menses.[22] Kaplowitz *et al*[23] reported that obesity, as measured by BMI, is significantly associated with early puberty in white girls and to a lesser extent in black girls. A correlation was also found between age at adiposity rebound and age at menarche.[24] As obese children have higher leptin levels than lean children, this may be an important factor in their earlier onset of puberty.

The present study reviews the findings clearly implicating the leptin hormone in the pathophysiology of obesity. Specifically, it focuses on the complicated interaction between obesity, leptin, the pubertal process, and the pubertal growth spurt (Figure 1).

Obesity and puberty

Normal puberty consists of two distinct processes: maturation of gonadal function, known as gonadarche, and increased adrenal androgen secretion, known as adrenarche.

Role of leptin in gonadarche (hypothalmic-pituitary-gonadal (HPG) axis)

The medial basal hypothalamus contains a pulse generator that is responsible for the onset of the episodic secretion of hypothalamic gonadotropin-releasing hormone (GnRH), which in turn, results in the pulsatile secretion of the pituitary gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) during puberty. LH stimulates Leydig cell secretion of testosterone in boys, but has little effect in girls until after ovulation occurs. FSH stimulates follicle formation and estrogen secretion in girls, with little effect in boys until spermarche.

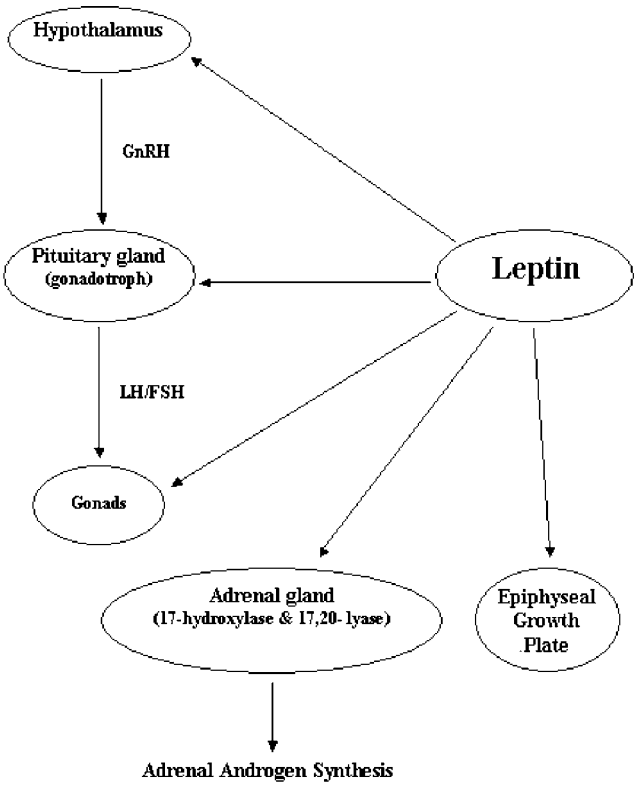

Figure 1 Leptin function at various target tissues.

Leptin receptors (ob-Rs) have been identified in the hypothalamus and in the gonadotrope cells of the anterior pituitary.[25] In the hypothalamus, leptin has a direct stimulatory effect on the HPG axis by accelerating GnRH secretion (but not pulse amplitude) in the arcuate hypothalamic neurons in a dose-dependent manner.[26] In the anterior pituitary, leptin directly stimulates the release of LH and, to a lesser extent, FSH via nitric oxide synthase activation in the gonadotropes.[27] The endocrine and direct paracrine effects of leptin on the gonads are implied by the expression of functional leptin receptors on the surface of ovarian follicular cells, including granulose, theca, and interstitial cells,[28] as well as Leydig cells.[29]

Other downstream effectors of leptin are important in the control of feeding, but their influence on puberty is less well defined. NPY, a potent stimulator of food intake, has an inhibitory effect on GnRH secretion.[30] Leptin administration has been shown to decrease the expression of NPY in the

arcuate nucleus, and consequently to remove the inhibitory action of NPY on pulsatile GnRH release.[31]

Leptin levels exhibit significant changes during progressive pubertal stages, with a distinct dimorphism between boys and girls. In boys, there is a prepubertal peak of serum leptin levels preceding the rise of free testosterone, growth hormone (GH), and insulin-like growth factor (IGF-1). Thereafter, about 3 y after the rise in serum testosterone levels, leptin levels fall to baseline concentrations.[32] In girls, leptin levels rise throughout puberty, concomitant with the rise in estrogen levels.[32] Even after correcting for body weight and fat mass, females have higher serum leptin levels than males.[33] This sexual dimorphism is related to several factors. First, the pulse amplitude of leptin secretion from adipose tissue is two- to three-fold higher in females than in males.[34] Second, fat mass is increased in females who have a differential fat distribution, with a higher subcutaneous/visceral fat ratio than males (leptin mRNA expression is higher in subcutaneous than visceral fat).[35] Third, females have higher total serum leptin levels and lower leptin-binding protein levels than males, indicating higher free leptin levels.[36] Finally, female adipose tissue may be more sensitive to hormones that stimulate leptin production, such as glucocorticoids. Halleux *et al*[37] demonstrated that physiological concentrations of glucocorticoids stimulated leptin secretion by enhancing the pretranslation process in human visceral and subcutaneous fat, especially in obese subjects.

Patients lacking leptin protein[38] or functional leptin receptors[39] do not attain pubertal maturity and have low serum FSH and LH. This finding suggests that hypogonadotropic hypogonadism is a feature of congenital leptin deficiency in humans. Farooqi *et al*[40,41] reported that administration of recombinant leptin in a child with leptin deficiency restored pulsatile gonadotropin secretion.

At high physiologic doses, leptin appears to antagonize the augmenting effect of growth factors (IGF-1) and hormones (insulin, glucocorticoids) on gonadotropin-stimulated steroidogenesis in follicular and theca ovarian cells throughout the menstrual cycles[42]; in Leydig cells, it exerts inhibitory effects on testosterone production.[29] Hence, leptin possesses a bimodal action on the HPG axis, depending on its serum levels. Specifically, leptin deficiency to the low levels seen in starvation or eating disorders results in HPG dysfunction, and leptin administration in low doses may have a permissive, threshold effect on the central networks that regulate gonadotropin secretion. By contrast, the high serum leptin levels seen in obese people may have an inhibitory effect on the gonads.

The findings of an earlier onset of the classic pubertal signs in female mice injected with leptin compared with controls[43] suggested that leptin is the signal that transmits the information to the brain that fat stores are adequate to cover the energy requirements of reproduction. Leptin, therefore, may participate in the timing of puberty. Another recent study in female rats showed that leptin is able to reverse the delayed onset of puberty in animals receiving less than normal quantities of food.[44] Thus, leptin is apparently not the signal that triggers the onset of puberty, but rather serves as a metabolic gate for puberty to progress.[44] Palmert *et al*[45] found that girls with central precocious puberty have slightly higher serum leptin levels than normal, healthy girls, even after correcting for BMI and Tanner stage. Furthermore, in a recent study of the relation between fat mass and age at menarche, researchers[46] found that rising leptin levels during puberty were associated with a decline in the age at menarche[46]: Every 1 ng/ml increase in serum leptin levels was associated with a 1-month decrease in age at menarche, and every 1 kg increase in body fat was associated with a 13-day decrease in age at menarche. Apparently, there is a critical concentration or threshold of leptin for the timing of menarche. Leptin deficiency may be the primary reason for delayed puberty and menarche in individuals accustomed to absolute or relative dietary energy deficiency.

Soluble leptin receptor (sOB-R), the major leptin-binding protein in human circulation, may modulate leptin bioavailability and function. Kratzsch *et al*[47] found inverse relations of sOB-R with age, pubertal stage, and body composition parameters, as well as with leptin concentrations. The increased sOB-R levels in subjects with hypoleptinemia may represent a mechanism to temporally preserve the reduced hormone levels in the circulation. Correlation analysis demonstrated that the parameters of growth and sexual maturation were more closely related to the ratio between leptin and sOB-R, free leptin index (FLI), than to leptin alone, predominantly in boys. Therefore, sOB-R levels may serve as another valuable tool to investigate the leptin axis during growth and sexual maturation.

In summary, leptin plays a dual role in gonadarche. First, it may be one of several factors that induce cellular maturation of the GnRH pulse generator. Maturation of the neuroendocrine networks may occur when fat stores are sufficient to maintain a threshold leptin concentration. Second, leptin may act as a signal of metabolic fuel availability to the GnRH pulse generator, such that the continuation of puberty in the adolescent is dependent on adequate leptin feedback from fat and muscle.

Role of obesity and leptin in adrenarche

According to cross-sectional observations, adrenarche begins about the same time as the preadolescent rise in BMI, gradual increase in plasma insulin, and increase in IGF-I serum levels.[48] Remer and Manz[49] reported a temporal proximity in individuals of the greatest increase in dehydroepiandrosterone (DHEA) sulfate (DHEAS) levels in early adrenarche with the greatest increase in BMI. This observation provided evidence that a change in nutritional status, measurable in the form of ΔBMI, is an important physiological regulator of adrenarche, regardless of individual adrenal androgen excretion level, age, and developmental stage. Although ΔBMI is associated with serum leptin levels, it may also be an

integrated measure of the combined long-term actions of IGF-I and insulin, which have been shown to augment adrenal androgen production and the expression of steroidogenic enzymes in human adrenocortical cells.[49] Adrenal androgen levels are increased in children with obesity[50] and may therefore be responsible for their accelerated growth before puberty.[51] This assumption is supported by data pointing to a specific, dose-dependent, stimulatory activity of leptin on 17-α-hydroxylase and 17–20 lyase, both enzymes essential for the synthesis of adrenal androgens.[52]

In view of these findings, we may assume that marked weight gain and obesity (associated with insulin resistance and high insulin levels) are probably involved in the development of premature adrenarche and the subsequent manifestations of functional ovarian hyperandrogenism and polycystic ovary syndrome. Cizza *et al*[53] reported that girls with premature adrenarche had a higher BMI and a more than two-fold elevation in plasma leptin levels compared to nonadrenarchal, age-matched girls. They also had elevated levels of salivary and plasma cortisol, DHEA, DHEAS, androstenedione, estradiol, and esterone. The authors proposed that girls with premature adrenarche are characterized by features of increased adiposity and hypothalamic-pituitary-adrenal axis activity. In contrast, however, another study[54] found that in patients with premature adrenarche, neither BMI nor leptin levels were correlated with the increased androgen levels.[54]

Prader–Willi syndrome (PWS) is the most frequent form of syndromal obesity. The phenotype is linked with a genetic hypothalamic defect. GH insufficiency and hypogonadism are described in PWS, and the gonadal development at puberty is typically delayed or incomplete. Surprisingly, however, premature adrenarche may be observed in affected children,[55] eventhough their insulin and IGF-1 levels are below the normal average because of insufficient GH secretion.[56] In addition, the mean adrenal androgen levels in patients with PWS are elevated above the normal range,[57] like in healthy obese children. The typically delayed gonadal maturation in PWS may be contrasted by elevated androgen levels and premature adrenarche. These hormonal changes are amplified by obesity and related metabolic alteration, independent of the hypothalamic regulation.

Further research is needed to fully elucidate the role of increased leptin levels in these physiological and pathophysiological processes.

Role of obesity and leptin in pubertal growth

Growth in childhood depends on an intact and functioning GH-IGF-I axis. Androgens and estrogens do not contribute substantially to normal growth before the onset of puberty, but they play an important role in the pubertal growth spurt. In adolescents, the rising sex hormone levels may exert a growth-promoting effect via their stimulatory effect on the GH–IGF-I axis. However, in some clinical conditions, normal growth persists or is even accelerated in the presence of low GH serum levels. This has been observed in children with GH deficiency secondary to craniopharyngioma surgery. In these cases, the accelerated growth is associated with the development of marked obesity.[58,59] Children with exogenous obesity also frequently show tall stature for age in association with an acceleration of epiphysial growth plate maturation.[60] However, the linear growth often stops prematurely because of the advanced bone age, and in some cases, final height is below the adult height potential.

During the phase of normal or accelerated height velocity in obese children, plasma GH levels remain low, apparently as a result of both decreased GH secretion by the pituitary gland and increased GH clearance from plasma.[61–63] Measurements performed during sleep and over 24 h have shown that GH secretion in obese children is reduced not only under physiological conditions, but also following pharmacologic stimulation with insulin, clonidine, arginine, levodopa, glucagon, GH-releasing hormone, and opiate peptides, much like in children with GH deficiency.[64] Despite the reduction in circulating GH levels, obese children may have normal, increased or reduced, plasma IGF-I and GH-binding protein levels.[65–67]

The mechanism whereby obese children continue to grow despite the low levels of GH is not known. Several explanations have been postulated, such as obesity-induced hyperinsulinemia,[68] hyperprolactinemia,[68] induced bioactive but nonimmunoreactive GH molecules,[69] and an increase in free IGF-I levels.[67] The possibility that children with obesity may have an as yet unidentified 'circulating factor' that stimulates growth independent of the presence of GH has also been suggested.[59]

In an animal study, Maor *et al*[70] reported on the presence of leptin receptors in cartilaginous skeletal growth centers involved in leptin-induced skeletal growth. Leptin is known to stimulate, in a dose-dependent manner, the width of the proliferative zone of the epiphysial growth plate and to increase the expression of chondroitin sulfate within the cartilaginous matrix. Thus, leptin induces both proliferation and differentiation of chondrocytes. Apparently, leptin acts as a skeletal growth factor with a direct peripheral effect on skeletal growth centers. Some of these effects on the growing bone may be mediated by the IGF system through an increase in local IGF-I receptor expression.

In humans, obesity is associated with central resistance to circulating leptin. A differential sensitivity between the center (hypothalamus) and periphery (epiphysial growth plate) to the effect of leptin might serve as an explanation for the accelerated growth in obese children.

Conclusions

The prevalence of obesity is increasing alarmingly among children and adolescents, especially in industrialized countries. Many of the metabolic and cardiovascular complications that are commonly associated with adult obesity begin

in childhood. Among the most common sequelae of childhood obesity are hypertension, dyslipidemia, insulin resistance with increased risk of type II diabetes, and orthopedic and psychosocial problems (poor self-image, social isolation). However, physicians treating children and adolescents need to bear in mind that childhood obesity is associated with additional phenomena, namely, early puberty, premature adrenarche and the subsequent manifestation of polycystic ovary syndrome, and accelerated growth with impaired final height potential, all of which can already affect their quality of life. Understanding the antecedents of obesity-related complications in obese children is therefore of great importance.

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