

Associations of Obesity with Linear Growth and Puberty

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Abstract

Background: The prevalence of obesity in childhood has increased dramatically in recent decades with increased risk of developing cardiometabolic and other comorbidities. Childhood adiposity may also influence processes of growth and puberty. **Summary:** Growth patterns of obesity during childhood have been shown to be associated with increased linear growth in early childhood, leading to accelerated epiphyseal growth plate (EGP) maturation. Several hormones secreted by the adipose tissue may affect linear growth in the context of obesity, both via the growth hormone IGF-1 axis and via a direct effect on the EGP. The observation that children with obesity tend to mature earlier than lean children has led to the assumption that the degree of body fatness may trigger the neuroendocrine events that lead to pubertal onset. The most probable link between obesity and puberty is leptin and its interaction with the kisspeptin system, which is an important regulator of puberty. However, peripheral action of adipose tissue could also be involved in changes in the onset of puberty. In addition, nutritional factors, epi-

genetics, and endocrine-disrupting chemicals are potential mediators linking pubertal onset to obesity. In this review, we focused on interactions of obesity with linear growth and pubertal processes, based on basic research and clinical data in humans. **Key Message:** Children with obesity are subject to accelerated linear growth with risk of impaired adult height and early puberty, with its psychological consequences. The data highlight another important objective in combatting childhood obesity, for the prevention of abnormal growth and pubertal patterns. © 2021 S. Karger AG, Basel

Introduction

Obesity during childhood and adolescence remains one of the most important issues in global health. Over the past 4 decades, obesity in children of all ages has increased worldwide [1]. The prevalence of obesity varies according to racial, ethnic, and socioeconomic factors [2] and increases with advancing age [3]. Childhood obesity has been tracked into adulthood.

Pediatric obesity results from various factors, starting with genetic predispositions and the gestational environ-

ment, and progressing from early childhood through adolescence. Socioeconomic status and health literacy also affect obesity. However, the current obesity epidemic seems to be driven mainly by evolving food practices (increased energy-dense and ultraprocessed foods and sweetened beverages) [4] and reduced physical activity [5].

Obesity during childhood has important short- and long-term consequences. These include risks of diseases and disorders that previously occurred almost exclusively in adults, such as type 2 diabetes, hypertension, dyslipidemia, nonalcoholic fatty-liver disease, obstructive sleep apnea, and systemic low-grade inflammation [6–8]. In the long term, obesity during childhood increases risks of developing cardiovascular diseases and some cancers and premature death [9].

Several lines of evidence support the interplay of nutritional status, energy balance, and hormones in the regulation of growth and pubertal development. Frequently, children with obesity are taller for their age, with accelerated linear growth and advanced skeletal maturation, and tend to mature earlier than lean children [10].

Adipocytes are an active secretory tissue that release many endocrine and paracrine factors termed adipokines; these affect peripheral tissues and the central nervous system. Adipokines are involved in energy homeostasis [11], bone growth [12], and pubertal processes [13]. This review provides an overview of the complex interactions between obesity in childhood and the processes of linear growth and puberty, based on basic research and observational studies in humans.

Obesity and Linear Growth

Growth in Offspring of Mothers with Obesity

Intrauterine growth of the fetus is affected by placental function and by fetal and maternal factors. Preclinical animal studies and human translational studies suggest that increased chronic inflammation, oxidative stress, and insulin resistance related to maternal obesity create an intrauterine environment that can lead to altered fetal growth, with long-term “programmed” detrimental effects on the offspring [14].

The placenta is an important source of leptin, tumor necrosis factor (TNF)- α , and interleukin (IL)-6. Placentas of pregnant women with obesity are characterized by enhanced infiltration of macrophages and expression of inflammatory markers [15]. An association is widely recognized of maternal obesity with fetal growth from as early as the second trimester of pregnancy [16] and with signifi-

cantly higher fat mass of the offspring [17]. Thus, the relatively increased proinflammatory cytokine production by the adipose tissue and placentas of women with obesity may amplify physiological adaptations in pregnancy, leading to increased availability of nutrients for the fetus.

Insulin sensitivity decreases by 50–60% during normal pregnancy; insulin resistance is even more marked in obese pregnancy [18]. Moreover, the relative inability of insulin to suppress whole-body lipolysis results in increased plasma free fatty acid (FFA) [19]. These processes substantially augment the energy available for transport to fetuses in pregnant women with obesity. The increased IL-6 and TNF- α levels in the placentae of mothers with obesity have been suggested to increase amino acid transport to the fetus [20] and may also contribute to fetal overgrowth.

Leptin and adiponectin are 2 main cytokines released by white adipose tissue and involved in energy homeostasis. Secreted mainly from white adipose tissue, leptin signals the brain of the body's energy stores. In conjunction with other adipokines and hormones, leptin's action in the hypothalamus inhibits food intake and increases energy expenditure by increased thermogenesis. The soluble leptin receptor, the major circulating binding protein of leptin, is a potential marker of leptin sensitivity [21]. During pregnancy, leptin tends to increase [22], whereas adiponectin rises in early pregnancy and then decreases corresponding to decreased maternal insulin sensitivity [23].

A prospective longitudinal study demonstrated an association of prepregnancy obesity with higher leptin and lower soluble leptin receptor levels, suggestive of leptin resistance [24]. The upshot could be longer neonates in women with prepregnancy obesity. Adiponectin was inversely associated with neonatal length only in women with obesity.

Another prospective longitudinal study revealed longer bone lengths in fetuses born to women with rather than without obesity [16]. Such differences were apparent as early as 21 weeks' gestation and remained through delivery. Moreover, from 32 weeks' gestation, abdominal circumference was greater in fetuses of women with obesity than of normal weight. This suggests a role for maternal adipokine levels in the differences in fetal bone growth between women with and without obesity.

Obesity and Linear Growth in the Postnatal Years until Puberty

Postnatal linear growth is controlled by genetic, endocrine, and nutritional factors. Growth hormone (GH)

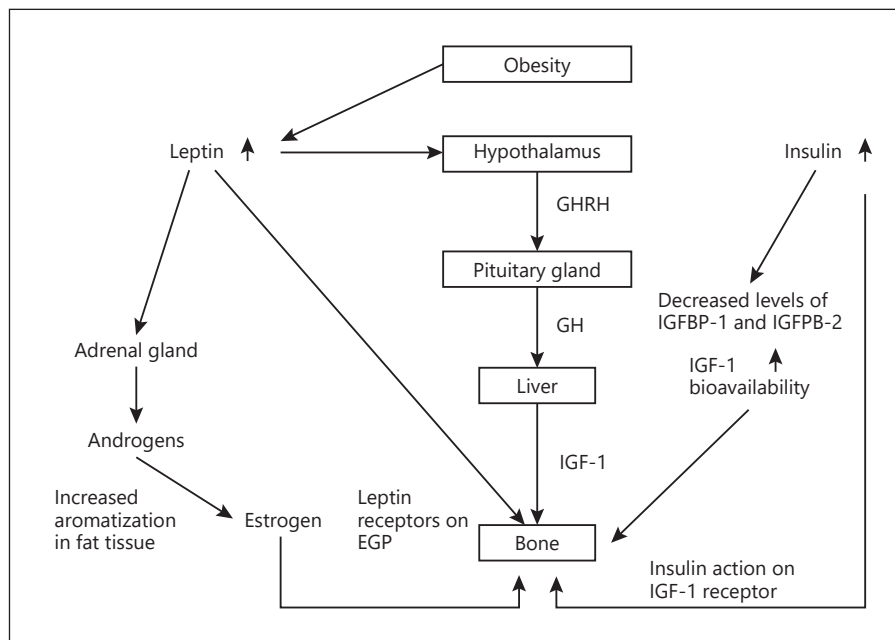


Fig. 1. Regulatory hormones affecting the process of linear growth in the constellation of obesity. GH, growth hormone; GHRH, growth hormone-releasing hormone; IGF-1, insulin-like growth factor; IGFBP-1/2, IGF-binding protein.

through insulin-like growth factor (IGF)-1 or by direct action on the epiphyseal growth plate (EGP) plays a major role in postnatal growth, together with thyroid hormones. Although adequate nutrition is essential for normal growth and children with obesity are usually taller than their normal-weight peers, they do not tend to attain taller height as adults [25]. Several regulatory hormones may affect linear growth in the constellation of obesity, as shown in Figure 1.

Long bones are formed through endochondral ossification, wherein a cartilage template is formed by condensed mesenchymal cells and later replaced by bone tissue. The process of endochondral ossification occurs within the EGP and is subjected to multiple regulatory mechanisms [26, 27].

The underlying mechanisms of obesity-related growth acceleration are still not fully resolved, and several factors secreted by adipocytes have been cited as possible mediators. Among them, insulin [28], leptin [13, 29], adiponectin [30], growth and differentiation factor (GDF)-5 [12], and estradiol [31] have demonstrated direct effects on EGP chondrocytes, as described below.

The GH-IGF-1 Axis in Obesity

An intact GH/IGF-1 axis is well recognized as the key regulator of somatic growth in humans. However, childhood obesity is characterized by normal or even accelerated linear growth during prepuberty despite abnormalities in the GH/IGF-1 axis. These abnormalities are main-

ly characterized by reduced GH secretion with normal IGF-1 levels compared to normal-weight peers.

Analysis of the 24-h secretion of GH has confirmed a decreased spontaneous GH release in persons with obesity [32]. Adiposity acts as a negative determinant of the frequency and amplitude of GH secretory bursts. Accordingly, increased GH clearance leads to a lower GH half-life; this suggests a defect in both secretion and clearance [33]. Alterations in GH receptors and increased GH-binding protein (GHBP) are consistent with these changes [34]. Therefore, children with obesity presumably present with normal growth despite reduced GH secretion. This is probably due to the combination of increased levels of total GHBP and the GH-GHBP complex that enable achieving normal production and bioavailability of IGF-1 [35].

Children with obesity also display blunted or absent responses to known GH stimuli, including fasting, exercise, and pharmacological stimulation [36]. Significant weight loss results in recovery of basal and stimulated GH release [37]. This indicates that metabolic alterations associated with weight gain precipitate low GH output, and these changes are reversible.

IGFs (IGF-1 and IGF-2) are involved in growth regulation [38]. In obesity, despite low GH values, IGF-1 levels are usually normal. This leads to the hypothesis that free elevated IGF-1 suppresses GH release. Studies in prepubertal children also support IGF-1's role in childhood obesity. These report increased GH sensitivity using an

Table 1. Main functions of hormones/adipokine mediators in growth and puberty

Hormones/adipokines	Impact on growth	Impact on puberty	Levels in obesity
Insulin	Decreases IGFBP1 and increases levels of total and free IGF-1 Increases action on the IGF-1 receptor [54] and the IR [59] Increases chondrocyte proliferation and differentiation [28, 56, 57] Accelerates linear growth and bone maturation with earlier EGP closure [104]	Stimulates GnRH and LH secretion [143, 144] Stimulates ovarian and adrenal steroidogenesis [145] (increases 5 α -reductase and 21-hydroxylase activity and lowers 11 β HSD1 activity) [154] Reduces SHBG and increases sex steroid bioavailability [82] May cause premature pubertal onset and premature adrenarche [144, 145]	↑
Leptin	Stimulates spontaneous GH secretion and the GH response to GHRH [68] Stimulates EGP cartilage proliferation and differentiation [76–78] Augments aromatase mRNA expression and estrogen receptor gene expression in chondrocytes [99] Accelerates bone maturation, with earlier epiphyseal closure	Stimulates secretion of kisspeptin and activates the HPG axis and accelerates GnRH secretion [126] Increases gonadotropin secretion [131] Increases sex hormone secretion [132, 133] Increases synthesis of adrenal androgens [138] Accelerates pubertal onset	↑
Ghrelin	Increases GH secretion		↓
Adiponectin	Increases chondrocyte proliferation and differentiation, proteoglycan synthesis, and matrix mineralization [64]	Inhibits secretion of kisspeptin and GnRH and release of LH, thereby inhibiting puberty onset [140, 141]	↓
GDF-5	Regulates cartilage cell differentiation and proliferation [85, 86]		↑
Estrogen/androgens	Estrogen increases EGP maturation and fusion [95–97] Increases aromatization in adipose tissue, of androgens into estrogens, with accelerated growth and accelerated epiphyseal fusion [96]	Increased androgen concentrations enhance GnRH secretion, possibly leading to earlier pubertal onset [150]	↑

EGP, epiphyseal growth plate; GH, growth hormone; GHRH, growth hormone-releasing hormone; GDF-5, growth and differentiation factor; GnRH, gonadotropin-releasing hormone; HPG, hypothalamic-pituitary-gonadal; HSD, 11 β hydroxysteroid dehydrogenase; IGF-1, insulin-like growth factor; IGFBP1, insulin-like growth factor-binding 1; LH, luteinizing hormone; SHBG, sex hormone-binding globulin. The numbers in the brackets denote the relevant references.

IGF generation test [39] and a correlation of IGF-1 levels with longitudinal growth in limb length and height [40].

Ghrelin is an endogenous GH-releasing peptide produced predominantly in the stomach, which acts on GH secretagogue receptors and as an orexigenic factor. Fasting increases and food intake decreases plasma ghrelin levels. Ghrelin is also known to stimulate insulin secretion [41]. Ghrelin levels are lower in children with obesity than with normal weight [42]; the levels are proportional to the degree of insulin resistance [43]. The feeding regulatory role of the ghrelin-GH axis was investigated in 2 studies that used a mouse model of isolated GH deficiency due to targeted GH-releasing hormone (GHRH) gene knockout (GHRHKO). The first study [44] demonstrated that isolated GH deficiency due to targeted ablation of the GHRH gene was associated with increased relative subcutaneous and intra-abdominal fat mass and higher food consumption that was not related to changes in circulating leptin. Adiponectin and visfatin mRNA levels were decreased in both intra-abdominal and subcutaneous fat.

The second study [45] evaluated the effects of intracerebroventricular ghrelin administration in mice homozygous for the GHRHKO allele ($-/-$) and heterozygous ($+/-$) control animals. Vehicle-treated GHRHKO mice showed greater food intake than heterozygotes; this was associated with increased circulating ghrelin levels. GHRHKO ($-/-$) mice showed elevated hypothalamic levels of neuropeptide Y (NPY) and agouti-related peptide (AgRP) mRNAs and decreased mRNA levels of corticotropin-releasing hormone (CRH). Ghrelin treatment significantly augmented food intake in both genotypes, but the relative increase compared to vehicle-treated animals was higher in $-/-$ than $+/-$ mice. In the hypothalamus, ghrelin increased AgRP and decreased CRH gene expression only in heterozygous mice and induced a significant reduction in proopiomelanocortin mRNA levels in $-/-$ mice. Thus, dysregulation of the ghrelin-GHRH-GH axis in GHRHKO mice could explain the increased feeding secondary to elevated circulating levels of ghrelin. Moreover, the obesogenic phenotype is likely mediated by elevated

NPY and AgRP and by decreased CRH gene expression in the hypothalamus.

Relations of adipose tissue with GH secretion are complex. Obesity induces hyperinsulinemia, hypoadiponec tinemia, and hyperleptinemia; reduces serum ghrelin; and increases FFA levels, thereby suppressing GH secretion from the pituitary [46]. GH can contribute to insulin resistance that may develop when the caloric supply exceeds demand. Therefore, the reduced GH secretion occurring with obesity may be an adaptive phenomenon that prevents insulin resistance [47]. Hypotheses of how obesity-associated hyperinsulinemia may suppress GH production include direct pituitary action on GH synthesis and release [48] and indirect action by (1) modulating hypothalamic function, (2) altering IGF-I availability, and (3) suppressing circulating ghrelin levels [49].

GH-Independent Growth in Obesity

Since children with obesity continue to grow despite their low levels of GH, their growth seems mainly GH independent. In some clinical conditions, normal growth persists or even accelerates in the presence of low GH serum levels. This “growth without GH” phenomenon has been observed in children with GH deficiency after surgery for craniopharyngioma, and their accelerated growth is associated with marked hypothalamic obesity. However, also children with exogenous obesity frequently show tall stature for their age, associated with accelerated bone age secondary to accelerated EGP maturation. This phenomenon can be explained by insulin resistance with hyperinsulinemia [50], bioactive but nonimmunoreactive GH [51], or increased levels of free IGF-1 [52] or of another unidentified “circulating factor” that stimulates growth independent of GH. The main functions of hormones/adipokine mediators in growth are presented below and summarized in Table 1.

Insulin

Insulin and IGF act through similar tyrosine kinase receptors [53]. Thus, in obesity, the increased insulin levels due to insulin resistance apparently increase insulin action on the IGF-1 receptor [54]. Indeed, in rats, the systemic injection of insulin has been shown to induce body growth [55].

The effect of insulin on EGP chondrocytes has been intensively studied. Adding insulin to cultured whole fetal metatarsal bones stimulated metatarsal linear growth in a concentration-dependent fashion [28]. In-

ulin increased the metatarsal EGP proliferative and hypertrophic zone heights. Adding insulin to the medium of cultured chondrocytes isolated from metatarsal EGPs significantly increased cell proliferation and differentiation compared to untreated chondrocytes. Several in vitro studies have demonstrated stimulatory effects of insulin on chondrocyte proliferation [56, 57] and chondrocyte differentiation [28, 56, 57]. Additionally, insulin was shown to modulate liver GH receptor expression [55], decrease circulating IGFBP-1 levels, and stimulate IGF-1 mRNA expression in cultured hepatocytes [58] even in the absence of GH. These findings support a growth-promoting effect of hyperinsulinemia through increased circulating levels of total and free IGF-1.

In mice [28], a high-fat diet (HFD) led to greater body and tibial growth than did standard chow, concomitant with increased levels of serum insulin, IGF-1, leptin, and FFA. Administration of pioglitazone, an insulin sensitizer, to the HFD-fed mice led to lower body growth, tibial growth, and serum insulin levels; however, serum levels of IGF-1, IGFBP-1, IGFBP-3, leptin, and FFA were not significantly reduced [28]. HFD-fed mice also exhibited greater expression of phosphorylated, active, insulin receptor (p-IR) than did the mice fed with standard chow, but not in those treated with pioglitazone [28]. The same research team created transgenic mice with the IR gene ablated only in chondrocytes and exposed them to HFD. In the control mice, tibial length and whole EGP proliferative and hypertrophic zone heights of HFD-fed mice were all greater than in standard-diet-fed mice. In contrast, the effect of the HFD on the IR knockout (IR-KO) mice was significantly smaller. The tibial whole EGP and the proliferative and hypertrophic zone height were significantly greater in HFD control mice than in HFD IR-KO. In both lines, HFD led to greater serum insulin, leptin, and IGF-1 levels [59]. These findings indicate that the growth acceleration caused by HFD in rodents is due to insulin resistance-related hyperinsulinemia, by direct activation of the IR in the EGP.

Additionally, in cultured chondrocytes transfected with small interfering RNA, to selectively silence IR expression, the effects of insulin on cell proliferation and differentiation were completely abolished. This supports an IR-mediated regulatory role for insulin on skeletal growth and EGP chondrogenesis [28]. Thus, insulin resistance and hyperinsulinemia are related to accelerated skeletal growth and EGP chondrogenesis [59].

In humans, the anabolic effect of insulin has mainly been described in small-for-gestational-age infants, in

whom increased insulin secretion was found to be associated with increased catch-up linear growth, transiently followed by an increased rate of obesity [60]. Thus, insulin may contribute to increased linear growth in simple obesity in postnatal life.

Adiponectin

Adiponectin is secreted predominantly by differentiated adipocytes and involved in energy homeostasis [61]. Its level is reduced in adipose tissue of obese and diabetic mice and humans but restored to normal levels following weight loss [62].

Adiponectin and its receptors, AdipoR1 and AdipoR2, were expressed during chondrogenic differentiation of the mouse ATDC5 cell line, in an *in vitro* model of chondrogenesis [63]. However, data regarding the role of adiponectin in linear growth are conflicting. One study showed that adiponectin increased chondrocyte proliferation and differentiation, proteoglycan synthesis, and matrix mineralization, as reflected by upregulation of the expression of type II collagen, aggrecan, Runx2, and type X collagen, a unique marker of hypertrophic chondrocytes, and the activities of matrix metalloproteinase 9 and alkaline phosphatase [64]. However, a study in transgenic mice overexpressing human adiponectin in the liver found no effect of enhanced serum adiponectin levels on the length of long bones. This was despite increased bone volume and osteoblast activity [65].

Leptin

In humans, elevated serum leptin levels were found to be concomitant with central resistance to circulating leptin in simple obesity [66]. Leptin seems to mediate accelerated growth in the context of obesity [67].

Leptin receptors are expressed in hypothalamic nuclei known to be involved in GH regulation [68]. Leptin has a potent stimulatory action on both spontaneous pulsatile GH secretion and the GH response to GHRH [68]. Thus, leptin may be a critical hormonal signal of nutritional status in the neuroendocrine regulation of GH secretion.

In leptin-deficient *ob/ob* mice, leptin administration corrected metabolic abnormalities and also led to significantly increased femoral length [69, 70]. A recent study showed that chondrocytes are linearly arranged in the EGP of lean mice but not in *ob/ob* mice [71]. Tibias were significantly shorter in *ob/ob* mice than in lean controls;

the mean EGP height was reduced, and cell columns were fewer, shorter, and less organized, particularly the hypertrophying cells in the distal portion of the EGP. These differences may be attributed to the inhibitory effects of leptin deficiency on chondrocyte metabolism. Interestingly, the disturbed 2D columnar structure, with inhibited proliferation and extracellular matrix synthesis, was reversed in animals treated with leptin [71].

The role of leptin in regulating linear growth by affecting the EGP has been studied extensively [72, 73]. We have shown that leptin significantly increases tibial length in normal mice compared to pair-fed controls, probably acting through the parathyroid hormone-related protein/Indian hedgehog loop [74]. The leptin receptor is expressed by EGP chondrocytes; adding leptin to ATDC5 cells increases their differentiation, as evident by increased expression of type X collagen [29, 75, 76]. Leptin directly stimulates EGP cartilage proliferation and differentiation [76–78] through its active, long-form, receptor [29, 77]. Leptin administration was also shown to enhance levels of collagen type II, chondroitin-6-sulfate, and proteoglycans. This reflects the extent of leptin's effect on differentiation. Leptin strongly enhanced chondrocyte anabolic functions and induced synthesis of IGF-1 and transforming growth factor β -1 in the cartilage, at both the mRNA and the protein levels.

Few prospective cohort studies have addressed the relation of BMI with growth, from infancy to adolescence. Findings from population-based studies [79, 80] showed associations between higher BMI during early life and subsequent increases in length and height velocities. Consequent to faster linear growth, prepubescent children with obesity typically present with taller stature than their peers with normal weight [25]. Thus, we speculate that factors known to influence linear growth and previously shown to be positively correlated with BMI, such as IGF-1 [81], insulin, and leptin, may play important roles in the relation between higher BMI in early life and accelerated subsequent linear growth. Higher prepubertal BMI is also associated with insulin-induced reduction of sex hormone-binding globulin and increased sex steroid bioavailability, with marked influence on the GH-IGF-1 axis [82].

Growth and Differentiation Factor-5

An additional link between adipose tissue and longitudinal growth was identified in an *in vitro* model of 3T3L1 cells, induced to differentiate in culture into adipocytes and metatarsal bone rudiments [12]. The 3T3L1

preadipocyte cell line was originally isolated for its ability to undergo differentiation into adipocytes in vitro [83]. We showed that the conditioned medium of 3T3L1 adipocytes stimulates growth of metatarsal rudiment bones in culture; the principal mediator in this setting was identified as GDF-5, secreted by adipocytes [12, 84]. Histological examination showed significant increases in the length of the bones exposed to GDF-5, in hypertrophic cell number and height and in the overall length of the hypertrophic zone. The GDF subfamily of bone morphogenetic factors (BMP) plays a central role in cartilage formation and in regulating cell differentiation and proliferation [85]. GDF-5 is active during mesenchymal cell condensation and in initiating early stages of chondrogenesis by promoting cell adhesion [86] and can increase the size of skeletal elements [86]. GDF-5 also stimulates proteoglycan production in chondrocyte-like cells, thus leading to increased aggrecan and type II collagen gene expression and increased production of proteoglycans [87]. GDF-5 binds specifically to bone morphogenetic protein receptor type-1B (BMPRI1B), BMPRI2, and actin-related protein 2a (ACTR2a), forming a heterodimeric complex [88]. We have shown that BMPRI1B is present in the metatarsal bones, specifically in the hypertrophic zone, coinciding with its site of action [12].

High-Fat Diet

Two rodent studies examined effects of HFD-induced obesity on linear growth. The first, performed in young male C57BL/6J mice, showed that HFD-induced obesity led to decreased trabecular bone density and slower cortical bone formation than standard chow. Serum leptin levels were correlated with trabecular but not cortical bone density. However, mean bone length did not differ between the 2 groups [89]. In contrast, in female C57BL/6J mice fed with a HFD, the obese mice had longer femurs in the early stages of the study, with no significant effect at age 20 weeks [90].

Another study investigated the effect of fast-food meals supplemented with caloric soft drink on linear growth in young fast-growing female rats. Two control groups enabled studying effects of the 2 main ingredients in fast-food diets: high levels of fat (corn oil) and sucrose (10% in drinking water). Only the fast-food meal led to damaged EGPs, shorter bones, and reduced bone strength. These harmful effects occurred initially through disruption of the normal endochondral ossification process in the EGP, leading to impaired growth and bone quality.

However, the deleterious effect on linear growth seems not to have been due to obesity nor to the high caloric intake/HFD but rather to the absence of the necessary nutritional elements critically required for normal development [91].

Obesity and Linear Growth during Puberty

Longitudinal studies [92] have reported inverse associations between high BMI for age in childhood and linear growth during adolescence. Furthermore, evidence suggests a relation between childhood obesity and the timing of pubertal milestones [93, 94]; the latter is known to influence adolescent linear growth. A large Swedish study [92] showed that puberty started earlier, and the height gain during puberty was reduced in children with obesity. This was despite an association of increased BMI during ages 2–8 years, with a parallel gain in height. Observational studies [25, 80] showed earlier pubertal development and slower linear growth among children with higher BMI during adolescence and a lesser growth spurt during puberty.

Increased adipose tissue can also release sex steroids that are involved in linear growth. Estrogen plays an important role in EGP maturation and fusion. EGP fusion is associated with senescence, which is manifested by a decline in the proliferative capacity of the resting chondrocytes with age [95] and which culminates in growth cessation. Changes in estrogen level are associated with tibial chondrocyte proliferation rate, EGP height, the number of proliferative chondrocytes, the number and size of hypertrophic chondrocytes, and column density [96, 97]. We previously reported that aromatase is expressed in chondrocytes of the EGP, and that applying the aromatase inhibitor, letrozole, to young male mice led to significantly increased body weight and tail and tibial lengths, together with a marked increase in EGP height [98]. In a subsequent study, we described crosstalk between leptin and aromatase in chondrocytes. Administration of leptin augmented aromatase mRNA expression and protein content and augmented leptin and estrogen receptor gene expression. The increased aromatase expression enhanced aromatization (conversion of testosterone to estrogen). The increased locally produced estrogen then bound to its receptors (also increased), enhancing the senescent decline in the EGP chondrocyte proliferation rate and reducing EGP height [99]. These results were also supported by a study that showed a significantly higher longitudinal growth rate in animals treated with leptin + (ER)- α inhibitor than only with leptin. This indicates that the concurrent increase in es-

trogen levels during leptin treatment antagonizes the growth-promoting actions of leptin [100].

Rapid weight gain in early childhood is often accompanied by bone age advancement [101]; this reduces the height attained in late adolescence and impairs the potential genetic adult height [102, 103]. Therefore, the increased insulin secretion that normally occurs in adolescence is probably involved in activating IRs at the EGP. Hyperinsulinemia was found to be a strong predictor of advanced bone age in children with obesity [104]. Since leptin also has a direct effect on skeletal growth centers, its increased levels in adolescents with obesity may also contribute to accelerated bone maturation, with earlier epiphyseal closure and impaired genetic growth potential. Accelerated EGP maturation in children may also result, due to an early effect of estrogen on the EGP. Another pathway is the increased aromatization in adipose tissue, of androgens into estrogens, which may accelerate growth but also cause accelerated epiphyseal fusion in children with obesity [96].

Linear Growth in Monogenetic Obesity and Syndromic Obesity

Several genes, such as proopiomelanocortin, leptin receptor (*LEPR*), leptin (*LEP*), proconvertase 1 prohormone convertase 1, and melanocortin 4 receptor (*MC4R*), have been confirmed as harboring mutations that are causal to the onset of monogenic obesity with very early onset of weight gain. These genes are involved in the leptin/melanocortin axis, which has an essential role in human energy homeostasis and endocrine function. Homozygous mutations in the *LEP* and *LEPR* genes cause hyperphagia and severe early-onset obesity from the first year of life. This is associated with pubertal delay due to hypogonadotropic hypogonadism. These patients also have hyperinsulinemia and insulin resistance. Gibson et al. [105] reported normal stature in their patient with *LEP* deficiency.

Farooqi et al. [106] reported normal linear growth in children with *LEPR* mutations and similar standard deviation scores for height to those of children with the same degree of obesity and without *LEPR* mutations. Serum levels of IGF-1 were age appropriate, and GH was secreted in a pulsatile fashion. However, the final height was reduced in adults with *LEPR* mutations, probably due to the lack of a pubertal growth spurt.

Mutations in the *MC4R* are the most common mutations in children with monogenic early-onset obesity. Lubrano-Bertheliet et al. [107] reported accelerated growth in children with the *MC4R*^{-/-}; this feature was also found in individuals with heterozygous *MC4R* mutations. This

result suggests that in humans, the positive effects of leptin on linear growth may not be mediated through the melanocortin pathway.

Height standard deviation score was found to be significantly greater in children who were *MC4R* deficient compared with controls, at age 5 years and continuing throughout childhood. Fasting IGF-I, IGF-II, acid-labile subunit, and IGFBP-3 concentrations were similar in the 2 groups. GH levels were markedly suppressed in children in the control group who were with obesity, but pulsatile GH secretion was retained in *MC4R* deficiency [108]. In individuals with *MC4R* deficiency, increased linear growth in childhood leads to a greater adult final height, which exceeds that predicted by obesity alone. GH pulsatility is maintained in *MC4R* deficiency and suggests a role for *MC4R* in controlling hypothalamic somatostatinergic tone. Fasting insulin levels are significantly higher in children with *MC4R* mutations [109]. Both these factors may contribute to the accelerated growth phenotype characteristic of *MC4R* deficiency.

In contrast to monogenic disorders, obesity in syndromic conditions typically develops after infancy. Examples include Prader-Willi syndrome (PWS), Bardet-Biedl syndrome (BBS), Alström syndrome, and Albright's hereditary osteodystrophy syndrome. These syndromes are often associated with impaired growth.

In PWS, following a period of limited catch-up weight gain at age 6–18 months, children develop an insatiable appetite, resulting in obesity by age 6 years. In children with PWS compared to healthy children with obesity, the following parameters are significantly higher: ghrelin levels, total adiponectin, high molecular weight (HMW) adiponectin, and the HMW adiponectin:leptin ratio; fasting insulin levels are lower [110, 111]. The relatively high levels of ghrelin in these children may contribute to hyperphagia and excess weight gain [112]. Affected children often also have poor linear growth, with short stature and delayed puberty [113]. GH deficiency in the context of PWS has been documented in many studies. The GH deficiency is independent of obesity and manifests in low spontaneous and pharmacologically stimulated GH secretion and low serum concentrations of IGF-I [114, 115]. This contrasts with overnutrition in common obesity, which is associated with normal or increased IGF-I levels.

In BBS, energy dysregulation is thought to arise from a greater degree of leptin resistance than presents in individuals with obesity who do not have BBS [116]. A study of 50 individuals with BBS [117] showed shorter height than individuals with obesity in a control group. However, the height of the BBS group approximated the pop-

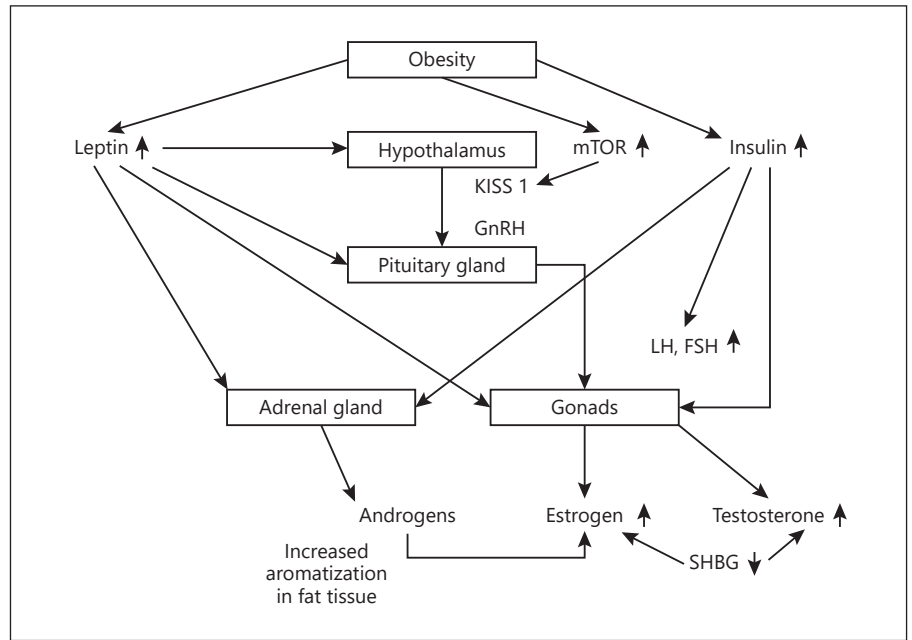


Fig. 2. Regulatory hormones affecting the process of puberty in the constellation of obesity. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; kiss1, kisspeptin-1; LH, luteinizing hormone; mTOR, mammalian target of rapamycin; SHBG, sex hormone-binding globulin.

ulation mean for age and sex. This indicates that they were not abnormally short, but rather lacked the bone age advancement and accelerated growth typically seen in healthy individuals with obesity.

Obesity and Puberty

Multiple factors affect pubertal development, including genetic and environmental conditions. The genes that are involved control gonadotropin-releasing hormone (GnRH) hypothalamic secretion, pituitary development, hormone synthesis and bioactivity, energy homeostasis and growth, and potential peripheral feedback from sex steroids [118]. Adequate nutrition is a key permissive factor for the normal timing and tempo of pubertal development.

The strong relation between childhood BMI and the earlier timing of puberty supports the critical mass theory of sexual maturation [119]. Obesity may alter secretion and sensitivity of hormones, including leptin and insulin. Leptin levels rise gradually with age, prior to puberty in adolescents, thus suggesting that a threshold effect may trigger puberty [13, 120].

Adipose tissue is a source of a large number of secreted signals and is a site for the conversion of cortisone to active cortisol [121] and of androgens to estrogen [122]. Accumulated adipose tissue may therefore contribute to the orchestrated controls for pubertal development, as presented in Figure 2. The main functions of hormones/adipokine mediators in puberty are presented below and summarized in Table 1.

Kisspeptin

Hypothalamic neurons that produce kisspeptins, encoded by *Kiss1*, have been shown to play a master role in the neuroendocrine pathways controlling puberty. The *Kiss1* system is highly sensitive to changes in metabolic and nutritional cues, as well as to alterations in leptin levels and signaling. This suggests an effect of body energy reserves and leptin levels on the reproductive axis, via modulation of *Kiss1* neurons [123].

Excess adiposity appears to have a biphasic impact on the *Kiss1* system. Overfeeding during the postnatal/peripubertal period increases hypothalamic *Kiss1* expression and advances puberty onset. However, in rodents, an association was shown of persistent energy excess and obesity in adulthood with suppression of *Kiss1* expression and reproductive dysfunction [124].

Key cellular metabolic sensors, including the mammalian target of rapamycin, AMP-activated protein kinase, and the fuel-sensing deacetylase, sirtuin (SIRT)-1, have also been shown to be involved in the metabolic modulation of puberty. AMP-activated protein kinase and SIRT1 operate as major molecular effectors for metabolic control of *Kiss1* neurons and, thereby, puberty onset. The central mechanisms whereby early-onset obesity with elevated circulating leptin levels may advance pubertal maturation are likely to involve changes in SIRT1 activity in *Kiss1* neurons. Thus, premature removal of SIRT1 from the *Kiss1* promoter would contribute to an earlier

change in the epigenetic landscape of this promoter toward a more permissive configuration. This would increase *Kiss1* expression with earlier activation of GnRH neurosecretion and, thereby, puberty onset [125].

Leptin

Several explanations are plausible for the association of obesity with earlier puberty [13]. The higher leptin levels in children with obesity than lean children may contribute to their earlier onset of puberty. In the hypothalamus, leptin can stimulate the secretion of kisspeptin and subsequently activate the hypothalamic-pituitary-gonadal (HPG) axis and accelerate GnRH secretion in the arcuate hypothalamic neurons in a dose-dependent manner, thereby hastening puberty [126].

The relation between leptin and gonadotropins has been reported to be sex specific. In girls entering puberty, a peak in leptin concentrations preceded peaks in luteinizing hormone (LH) and follicular-stimulating hormone concentrations [127]. Leptin concentrations increase before the onset of puberty in boys, but the concentrations fall in midpuberty, in contrast to girls [128]. This refutes a direct relation between leptin and puberty in boys. The sex difference in leptin concentrations in puberty may explain the later puberty onset in boys with obesity and the earlier puberty onset in girls with obesity. An important sexual dimorphism has also been shown of the interaction of kisspeptin with GnRH secretion [129].

Leptin receptors have been identified in the hypothalamus and in the gonadotroph cells of the anterior pituitary [130]. In the anterior pituitary, leptin directly stimulates release of LH and, to a lesser extent, follicular-stimulating hormone, via activation by nitric oxide synthase in the gonadotrophs [131]. Effects of leptin on the gonads are implied by expression of functional leptin receptors on the surface of ovarian follicular cells, including granulosa, theca, and interstitial cells [132], as well as Leydig cells [133].

NPY, a potent stimulator of food intake, has an inhibitory effect on GnRH secretion [134]. NPY expression in the arcuate nucleus is decreased by leptin administration, which disrupts its inhibitory action on pulsatile GnRH release [135].

At high physiological doses, leptin appears to antagonize the augmenting effect of growth factors (IGF-1) and hormones (insulin and glucocorticoids) on gonadotropin-stimulated steroidogenesis in follicular and theca ovarian cells throughout the menstrual cycle [136]. In Leydig cells, leptin exerts inhibitory effects on testosterone production

[133]. Hence, leptin possesses a bimodal action on the HPG axis, depending on its serum levels. Specifically, low leptin levels result in HPG axis dysfunction, and leptin administration in low doses may have a permissive, threshold effect on the central networks that regulate gonadotropin secretion. On the other hand, high serum leptin levels in people with obesity may have an inhibitory effect on the gonads.

Adrenarche generally begins parallel to the preadolescent rise in BMI, the gradual increase in plasma insulin, and the increase in IGF-1 serum levels [137]. Specific, dose-dependent, stimulatory activity of leptin on enzymes has been shown as essential for the synthesis of adrenal androgens [138]. Furthermore, adrenal androgen levels are increased in children with obesity [139] and may therefore also be responsible for their accelerated growth before puberty.

Adiponectin

Individuals with obesity often develop a chronic low-grade inflammatory state, indicated by a high level of circulating inflammatory cytokines (TNF- α and IL-6). TNF- α and IL-6 inhibit the expression of adiponectin, and indeed individuals with obesity often have low levels of adiponectin.

Adiponectin can affect the HPG axis due to the expression of adiponectin receptors in the hypothalamus, pituitary gland, and gonads [140]. Adiponectin regulates puberty onset, as it inhibits secretion of kisspeptin and GnRH in the hypothalamus and the release of GH and LH in the pituitary gland, thereby inhibiting puberty onset [141]. Total adiponectin was found to be significantly lower and HMW adiponectin higher in girls with than without central precocious puberty [142]. Total adiponectin correlated negatively with the progression of puberty in girls. Therefore, a low level of total adiponectin or high levels of inflammatory cytokines in individuals with obesity can promote the onset of puberty.

Insulin

Insulin has been shown to be involved in the modulation of GnRH neurons and reproductive development [143]. An *in vivo* experimental model demonstrated that increasing insulin concentrations stimulated LH secretion, while an *in vitro* model showed direct dose-dependent stimulation of GnRH secretion by insulin [144]. This suggests that greater insulin resistance/hyperinsulinemia

associated with obesity may lead to premature pubertal onset. Hyperinsulinemia may also increase LH-stimulated ovarian and adrenal steroidogenesis and its association with precocious adrenarche [145].

Peripubertal obesity with insulin resistance and compensatory hyperinsulinemia augments ovarian/adrenal androgen production and also leads to decreased sex hormone-binding globulin. This leads to increased androgen bioavailability and bioavailability of sex steroids including estradiol [146]. In addition, aromatase action of adipose tissue increases androgen conversion to estrogens. Aromatase activity within the adipocyte is dependent on fat mass. Thus, obesity may result in greater peripheral conversion of androstenedione to estrone and testosterone to estradiol, independent of gonadotropins.

Adrenal Androgens

Prepubertal children with obesity have increased adrenal androgens [147]. Therefore, presumably, marked weight gain and obesity (associated with high insulin levels) are involved in premature adrenarche [148]. Girls with premature adrenarche were shown to have higher BMI and elevated levels of plasma leptin, cortisol, androgens, estradiol, and estrone compared to age-matched girls without adrenarche [149]. This indicates that girls with premature adrenarche are characterized by features of increased adiposity and hypothalamic-pituitary-adrenal axis activity.

Increased androgen levels can, in turn, promote pubertal development, acting peripherally or centrally on the HPG axis. In prepubertal girls, increased androgen concentrations have been suggested to facilitate pubertal increase in GnRH secretion, possibly leading to early pubertal onset [150].

Potential mechanisms of obesity-associated hyperandrogenemia include insulin resistance, enhanced androgen production in an expanded fat mass, and potential effects of abnormal adipokine/cytokine levels. Kinyua et al. [151] suggested that insulin upregulates steroidogenic factor-1 (transcriptional factor) and the steroidogenic genes directly, independent of the CRH-ACTH-MC2R-PKA pathway. This increases the generation of adrenal gland hormones.

Adipose tissue contains several steroidogenic enzymes. A number of studies have demonstrated significant steroid hormone uptake and conversion by adipose tissues. Activities and mRNAs of aromatase, 3beta-hydroxysteroid dehydrogenase (HSD), 3alpha-HSD, 11beta-HSD, 17beta-HSD, 7alpha-hydroxylase, 17alpha-hy-

droxylase, and 5alpha-reductase have been detected in adipose tissue [152].

Insulin resistance in childhood obesity is characterized by higher 5alpha-reductase and lower 11betaHSD1 [153]. The enzyme 5alpha-reductase converts testosterone to the highly potent androgen dihydrotestosterone. Thus, increased 5alpha-reductase activity related to an expanded fat mass represents another mechanism by which obesity may promote hyperandrogenism. An additional hypothesis holds that altered peripheral cortisol metabolism related to obesity leads to a compensatory increase of ACTH drive. This contributes to increased adrenal androgen production. Specifically, reduced cortisol negative feedback on ACTH secretion could be related to (1) augmented cortisol inactivation by increased 5alpha-reductase activity and (2) decreased activity of 11beta-hydroxysteroid dehydrogenase type 1 (11HSD1), which converts cortisone to cortisol. Recently, Gawlik et al. [154] reported that children with obesity and insulin resistance were characterized by high adrenal androgens, glucocorticoids, and mineralocorticoid metabolites; higher 5alpha-reductase and 21-hydroxylase activity; and lower 11betaHSD1 activity.

Obesity and Pubertal Onset and Advancement

The onset and timing of puberty in humans are dependent on numerous factors, including genetic variability, energy balance, multiple neuroendocrine pathways, and hormonal profiles. Moreover, successful reproduction is acknowledged as requiring suitable energy stores to support the associated physiological functions [155]. Therefore, puberty is “metabolically gated” to prevent fertility in conditions of energy insufficiency, such that metabolic conditions and energy reserves play important roles in modulating puberty timing [155].

In the last centuries, pubertal timing has changed dramatically. An association has been shown between obesity and earlier puberty onset among adolescent girls [156, 157]. Data of American girls observed the onset of thelarche at younger ages than previously documented, with important differences according to ethnicity and BMI, thus confirming and extending patterns seen previously [158]. Nonetheless, the tempo from breast development to menarche appears to have lengthened. Furthermore, girls with overweight and obesity are more likely to experience menarche at younger ages [159].

In contrast to these well-documented findings in girls, less is known of secular trends in pubertal maturation in boys and possible relations to obesity. An inverse linear relation has been reported between BMI and male pubertal onset [160, 161]. However, others reported delayed

onset in boys with obesity compared to boys with overweight, thus indicating a nonlinear, J-shaped association [162]. However, according to recent data, the previously held notion that boys with obesity might progress to puberty at a slower pace than their peers without obesity is no longer substantiated [161, 163, 164].

Impaired fertility markers, reduced reproductive functions with low sperm counts, and reduced sperm function have been observed in males with obesity [165]. Adipocytokines and inflammatory cytokines have all been shown to impact reproductive function [166].

Environmental Factors and Associations with Puberty

Both pubertal timing and obesity are influenced by the environment, and the interaction between genes and environments is strong during critical periods of development such as puberty. This interaction is due to substances such as dietary factors and endocrine-disrupting chemicals (EDCs) that derail the normal hormonal process. Potential dietary factors include total caloric intake, fat intake, protein intake, and fiber intake. Several studies have suggested that earlier onset of breast development may occur independent of HPG axis activation, perhaps through EDCs acting on adipocytes or on other hormonally responsive tissues [167].

Several epidemiological studies [168, 169] have reported an association of high total energy intake, as well as a high animal (red meat) versus vegetable protein ratio, with early menarche. Total dietary fat consumption may lead to earlier menarche, although the literature is inconsistent [169]. Dietary protein was associated with earlier onsets of the pubertal growth spurt, the age at peak height velocity, and the age at menarche/voice break [170]. EDCs can also act as obesogens and promote early adiposity rebound, changing metabolic or peripheral signals and increasing adrenal androgen levels, thus inducing early pubertal development [171]. An example of such an EDC is bis (2-ethylhexyl) phthalate (DEHP), a plasticizer that is noncovalently bound to plastics and easily released. Children are particularly vulnerable and susceptible to DEHP effects due to higher exposure levels and developmental processes. A juvenile toxicity study was performed to characterize the DEHP hazard and mode of action in rats of both sexes during the peripubertal period – corresponding to the childhood phase – from weaning, postnatal day 23, to full sexual maturity (postnatal day 60). DEHP was administered by gavage for 28 days.

The main targets of DEHP during the juvenile period were the liver and metabolic system in both sexes, while sex-specific effects were recorded in the reproductive system (male rats) and the thyroid (female rats). Thus, DEHP exposure during the peripubertal period at dose levels derived from a biomonitoring study in children can induce sex-specific imbalances [172]. Recent studies in humans and animals have shown that metabolic pathways involved in regulating growth, body weight gain, and sexual maturation are largely affected by epigenetic programming that can impact both current and future generations.

Conclusions

The escalating prevalence of obesity is currently observed among children and adolescents in the majority of countries. In addition to other obesity-related comorbidities, children and adolescents with obesity are subject to accelerated linear growth and the risk of impairment of their potential genetic adult height and early puberty, with its psychological consequences. These findings may prove helpful to clinicians in their efforts to raise motivation among young people with obesity to comply with lifestyle modifications.

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Conflict of Interest Statement

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