20 Obesity and the Endocrine System, Part II: The Effects of Childhood Obesity on Growth and Bone Maturation, Thyroid and Adrenal Function, Sexual Development, and Bone Mineralization

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Introduction

The accumulation of excess body fat has profound effects on somatic development and endocrine function. Here I review the effects of obesity on linear growth and bone maturation, thyroid function, sexual development, adrenal function, calcium homeostasis, and bone mineralization.

Effects of Obesity on Linear Growth and Bone Maturation

Final adult height in otherwise normal obese children generally falls within two standard deviations of parental target height. However, rates of linear growth and bone maturation are often increased in obese pre- and peri-pubertal children despite marked reductions in basal and stimulated plasma growth hormone (GH) concentrations and a reduction in circulating GH half-life [1]. The reduction in GH secretion in obese children and adults has been ascribed to negative feedback by free fatty acids, a reduction in plasma ghrelin (a GH secretagogue produced by the stomach), and nutrient-stimulated increases in IGF-1 production. Total IGF-1 and IGF binding protein (BP)-3 concentrations in obese subjects are typically normal or mildly elevated; this may reflect in part the production of IGF-1 and IGFBP-3 by white adipose tissue [2, 3] and/or an increase in hepatic GH sensitivity, resulting from induction of hepatic GH receptors by hyperinsulinemia (Fig. 20.1).

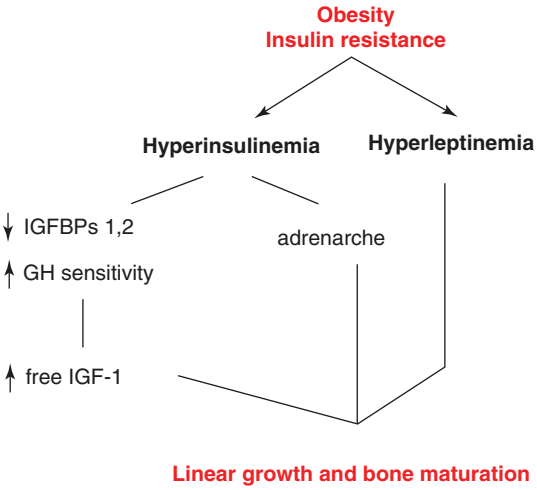

Fig. 20.1 Mechanisms that may explain why linear growth and bone maturation are normal or increased in prepubertal and peripubertal obese children despite a decrease in GH secretion.

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M.S. Freemark (ed.), *Pediatric Obesity*, Contemporary Endocrinology,
https://doi.org/10.1007/978-3-319-68192-4_20

Induction of GH receptor expression in obesity is suggested by an increase in levels of GH binding protein [4], the circulating form of the extracellular GH receptor domain, and by heightened production of IGF-1 following a single dose of GH [5].

Total IGF-2 concentrations were elevated in obese adults in two studies but were normal in a study of obese adolescents [6]. Many investigations have found reductions in serum IGF binding proteins 1 and 2 (IGFBP-1 and BP-2), which correlate inversely with plasma insulin concentrations and liver fat content [7–12]. The decreases in IGFBPs 1 and 2 are postulated to increase the bioavailability of IGF-1, which may maintain or increase linear growth in obesity despite diminished GH secretion [13–15] (Fig. 20.1). "Free" IGF-1 levels have been found to be elevated in some, but not all, studies of obese adults [13, 14]. Interestingly, increased rates of linear growth and reductions in fat mass have been observed in mouse models engineered to make endogenous IGF-1 incapable of binding to IGF binding proteins [16].

Reductions in plasma IGFBP-1 or IGFBP-2 concentrations in insulin-resistant obese subjects may facilitate weight gain because overexpression of IGFBP-1 or IGFBP-2 in transgenic mice reduces adipogenesis and prevents diet-induced obesity. Interestingly BP-1 excess reduces insulin sensitivity but BP-2 excess improves glucose tolerance [8, 17, 18].

Growth and bone maturation in obesity may be potentiated by increases in adrenal androgen production (Fig. 20.1 and below) (see also Fig. 20.3); bone age may be advanced as much as 1–2 years in children with precocious adrenarche, which is more common in obese children. The hyperleptinemia of obesity also appears to play a role (Fig. 20.1). Circulating leptin levels rise in proportion to body (particularly subcutaneous) fat stores and are higher in girls than in boys. Leptin stimulates proliferation of isolated mouse and rat osteoblasts and increases the width of the chondroprogenitor zone of the mouse mandible in vivo. Conversely, leptin deficiency in ob/ob mice reduces cortical bone mass but increases trabecular mass [19]; leptin treatment increases femoral length, bone area, and bone mineral content [20] and may promote the differentiation of osteoblasts from bone marrow stem cells [19]. The effects of leptin may be exerted in concert with IGF-1 because leptin increases IGF-1 receptor expression in mouse chondrocytes [21]. Nevertheless, linear growth is normal in patients with congenital deficiencies of leptin or the leptin receptor [22, 23].

Effects of Obesity on Thyroid Function

Free T4 levels generally fall within the normal range in obese subjects but thyroid-stimulating hormone (TSH) and triiodothyronine (T3) concentrations are mildly, and variably, elevated. The increase in T3 reflects its peripheral conversion from circulating T4 [1, 24] (Fig. 20.2). Higher levels of T3 increase thermogenesis and energy expenditure [25, 26] and may thereby limit further weight gain; see also Chap. 7 on Brown Adipose Tissue. Conversely, caloric restriction and weight loss decrease T3 levels, reducing energy expenditure and thereby facilitating weight regain.

The effects of caloric excess and deprivation on thyroid hormone levels are mediated in part by leptin-dependent effects on hypothalamic TRH production (Fig. 20.2). Thyroid hormone levels

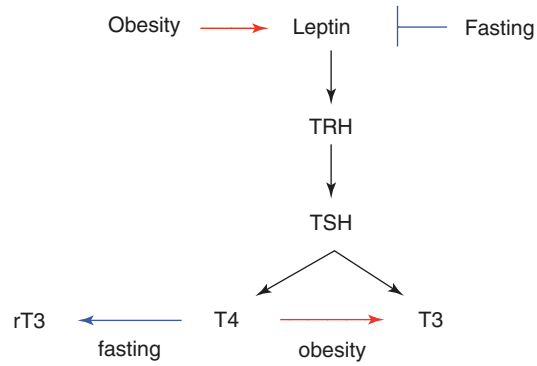

Fig. 20.2 Hyperleptinemia and nutrient-dependent conversion of T4 to T3 can increase T3 levels in obesity; fasting reduces T4 and T3 production and increases the conversion of T4 to inactive reverse T3 (rT3)

are variably low in leptin receptor-deficient humans and are reduced in leptin receptor-deficient db/db mice. Leptin treatment reverses the loss of TSH pulsatility that accompanies short-term fasting and normalizes thyroid hormone levels following longer-term caloric restriction. These actions are mediated by direct effects of leptin/STAT3 signaling on TRH transcription and indirect effects on TRH production mediated by increases in ∝MSH and reductions in agouti-related peptide (AgRP) and neuropeptide Y [27, 28]. By increasing sympathetic nervous system activity and deiodinase expression, hyperleptinemia may also promote peripheral T4 to T3 conversion [29, 30].

Some clinicians consider a mild elevation of TSH (typically in the range of 4.5–7 uIU/mL) in an obese child with normal free T4 to represent a state of subclinical hypothyroidism. However, the elevation of TSH may reflect hyperleptinemia rather than thyroid dysfunction. The author would consider thyroid hormone replacement in a child with elevated TSH if (a) there is a goiter, (b) the child is seropositive for thyroid antibodies, (c) the TSH exceeds 8–10 uIU/mL), (d) the T3 is not markedly elevated, *and/or* (e) the child's symptoms or physical findings (other than obesity) suggest a true hypothyroid state.

Effects of Obesity on Gonadal Function and Pubertal Development

Recent studies show that obesity in early childhood (age 36–54 months) and excessive weight gain between 3–9 years of age increase the risks of precocious thelarche in girls and reduce by ~6–9 months the age of menarche [31]. Since leptin promotes gonadotropin secretion and rises transiently before the onset of puberty in normal weight children, it is possible that the hyperleptinemia of obesity promotes early sexual maturation, at least in girls.

More commonly, obese girls and boys develop precocious adrenarche without true puberty, and obese adolescent females are prone to ovarian hyperandrogenism with mild hirsutism, acne, anovulation, and menstrual irregularity. The pathogenesis of precocious adrenarche and ovarian hyperandrogenism in obesity remains poorly understood (Fig. 20.3). However, insulin and IGF-1 in excess act in synergy with adrenocorticotrophic hormone (ACTH) and luteinizing hormone (LH) to stimulate the production of androgens from adrenocortical cells and ovarian theca cells, respectively. These effects are

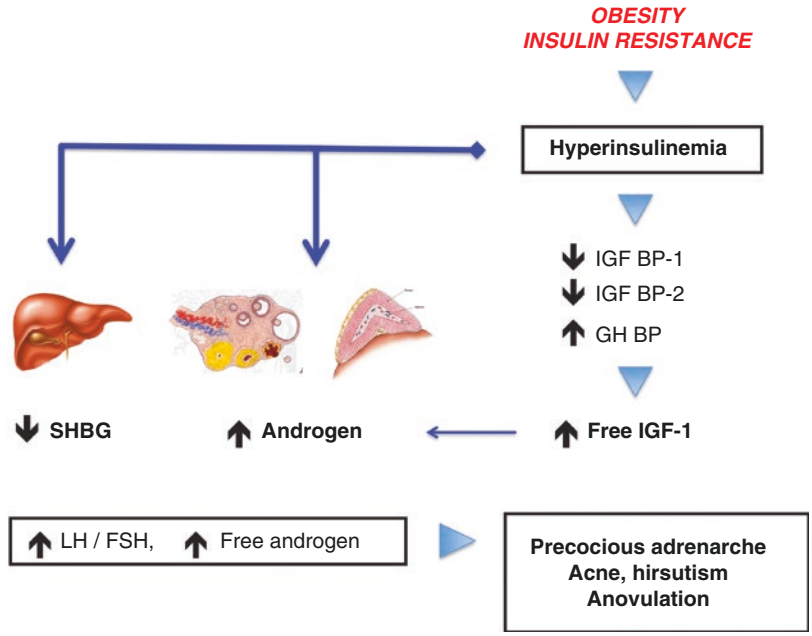

Fig. 20.3 Development of precocious adrenarche and ovarian hyperandrogenism in obese adolescents. IGF, insulin-like growth factor; BP, binding protein; GHBP, growth hormone-binding protein; SHBG, sex hormone-binding globulin; LH, luteinizing hormone; FSH, follicle-stimulating hormone

mediated through induction of P450c17α hydroxylase activity. The biologic availability of ovarian and adrenal androgens is increased because insulin suppresses hepatic sex hormone-binding globulin (SHBG) expression and reduces plasma SHBG concentrations. In obese girls with polycystic ovary syndrome, the free androgens (and, possibly, hyperinsulinemia) increase the frequency of LH pulses [32, 33] and the ratio of LH to follicle-stimulating hormone (FSH), thereby exacerbating thecal androgen production. The increase in free androgens can cause precocious adrenarche in prepubertal girls and boys and anovulation, hirsutism, and acne in adolescent girls and young women. Thus, obesity may mimic and clearly exacerbates the reproductive phenotype of the polycystic ovary syndrome [34–36] (Fig. 20.3); see also Chap. 36 by Dr. Barber and colleagues.

Free and total testosterone levels are generally normal in boys with mild to moderate obesity but decline with dramatic weight gain in association with normal or low gonadotropin levels. Among a group of obese teenage boys [37] aged 14–20 years, free testosterone levels were inversely related to BMI and measures of insulin resistance (HOMA-IR). LH, FSH, and estradiol levels were normal or low, suggesting suppression of the hypothalamic-pituitary-gonadal axis.

The mechanisms driving the fall in testosterone in obese adolescents (and adults) are unclear (Fig. 20.4); potential mediators include hypothalamic resistance to insulin and leptin and increases in circulating proinflammatory cytokines, which in concert reduce gonadotropin releasing-hormone (GnRH) secretion and LH pulse amplitude [38]. In addition, resistance to insulin action in bone may reduce circulating levels of osteocalcin (see below), an osteoblast hormone that in mice promotes Leydig cell testosterone production [39]. Testosterone levels in obese boys and men can be restored with weight loss.

Obesity is now the most common cause of gynecomastia in teenage boys. Aromatization of androgens by adipose tissue likely increases local estrogen concentrations (Fig. 20.4), causing true

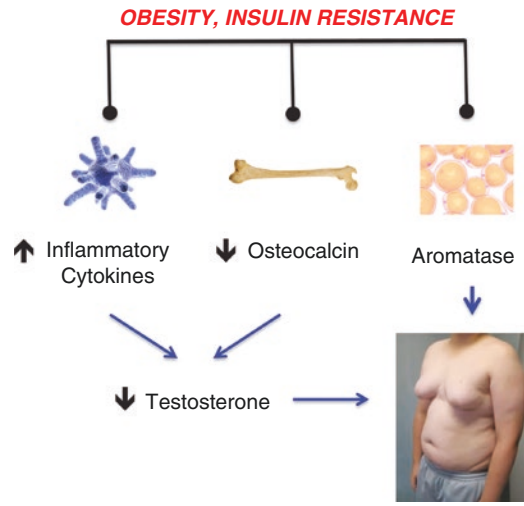

Fig. 20.4 Pathogenesis of testosterone deficiency and gynecomastia in obese males

breast enlargement (commonly superimposed upon adipomastia). In rare cases, gynecomastia in obese boys and ovarian hyperandrogenism in obese teenage girls are caused by hyperprolactinemia. Prolactin levels are typically normal or low in obese children [40]. However, hyperprolactinemia in children with pituitary tumors may be associated with weight gain in children as well as adults [41, 42]. Studies in rodents suggest that prolactin-dependent weight gain derives from increases in food intake and white adipogenesis [43–49]; alternatively, hyperprolactinemia may cause weight gain and fat deposition in pubertal and postpubescent boys and girls by suppressing sex steroid production [50].

Effects of Obesity on Glucocorticoid Production and Turnover

The abdominal weight gain, striae, hirsutism, and menstrual irregularity that may accompany obesity are often confused with Cushing's syndrome. In contrast to "exogenous" obesity, Cushing's syndrome is typically associated with linear growth failure and delayed bone maturation (unless a primary adrenal tumor produces excess androgens as well as glucocorticoids) as well as broad (>1 cm diameter), atrophic, and/or hemorrhagic/violaceous

striae, rather than thin (<1 cm diameter) pink striae. Basal plasma, salivary, and urinary free cortisol concentrations and basal ACTH levels in obese, non-Cushingoid children generally fall within the normal range, and diurnal variation and the response to dexamethasone are maintained [51]. However, body fat mass correlates with total excretion of glucocorticoid metabolites, suggesting that obesity is accompanied by increased cortisol secretion and turnover.

Polymorphisms in the glucocorticoid receptor have been associated with obesity, hypertension, and insulin resistance in some studies in adults. However, in contrast to the mineralocorticoid receptor (which binds cortisol with very high affinity), the glucocorticoid receptor is not overexpressed in white adipose tissue of obese adults [52]. Regulation of tissue glucocorticoid metabolism, rather than circulating cortisol levels per se, may be a critical determinant of fat distribution and peripheral insulin sensitivity in non-Cushingoid obese subjects [53]. Many investigations find overexpression of 11βHSD-1 in visceral adipose tissue of obese adults. In theory, the resulting overproduction of cortisol may either cause or aggravate pre-existing visceral adiposity and insulin resistance. On the other hand, some studies find lower expression of 11βHSD-1 in preadipocytes of obese, nondiabetic adults [54]; the expected reduction in tissue cortisol concentrations is postulated to reduce adipogenesis, stabilize or reverse pre-existing weight gain, and increase insulin sensitivity. Conversely, an increase in 11βHSD-1 expression after weight loss might in theory facilitate adipose cortisol production, adipogenesis, and weight rebound.

Effects of Obesity on Calcium Homeostasis, Bone Mineralization, and Fractures

25-OH Vitamin D, Parathyroid Hormone (PTH), and Vitamin D Binding Protein in Obesity

Adolescents and adults with severe obesity, particularly those with dark skin, often have subnormal circulating levels of 25-hydroxyvitamin D (25-OHD). One study [55] found that 25-OHD levels were less than 20 ng/mL in 78.4% of markedly obese (BMI 43.3) African American teenage girls (mean age 14 years). Reductions in 25-OHD are less frequent in obese white than in black or Hispanic children [56]: in a total of 127 obese adolescents (mean age 13 years, BMI 36.4), low levels of 25-OHD were noted in 43.6% of Hispanics and 48.7% of African Americans but only 10.2% of Caucasians. In that study, levels of 25-OHD correlated inversely with serum parathyroid hormone (PTH). A more recent investigation [57] showed that 17 of 58 obese adolescents (mean 14.9 years, BMI 36, 66% female, 14% black) had 25-OHD levels below 20 ng/mL; however, none had elevated (>65 ng/mL) PTH levels, and bone mineral content and density fell within the normal range.

In theory, the reductions in 25-OHD levels in obese children may be explained by decreased intake of vitamin D-containing dairy products, decreased cutaneous synthesis of vitamin D3 (in persons of color), and/or reduced bioavailability of vitamin D3 owing to sequestration in adipose tissue [58]. However, recent investigations suggest that rates of "vitamin D deficiency" in obese subjects may be drastically overestimated by standard measurements of 25-OHD, which encompass the fraction bound with high affinity to vitamin D binding protein (85–90% of total circulating 25-OHD), the fraction bound with low affinity to albumin (10–15% of total), and the unbound or "free" 25-OHD (<1% of total). A number of investigators consider free and albumin-bound 25-OHD to be "bioavailable" and therefore biologically active. Studies in Italian and American adolescents [59] and American adults [60] found normal levels of "bioavailable" 25-OHD and PTH in obese subjects with low total 25-OHD; moreover, unlike total 25-OHD, the levels of bioavailable 25-OHD did not correlate with either BMIz or the metabolic syndrome. The differences between total and bioavailable 25-OHD in obesity were explained by downregulation of vitamin D binding protein. Interestingly, vitamin D binding protein levels were ~50% lower in African American

than in Caucasian teenage girls and, in contrast to bioavailable 25-OHD, correlated inversely with plasma insulin and HOMA-IR [61]. These findings suggest that levels of biologically active 25-OHD are maintained in obesity and insulin resistance through reductions in vitamin D binding protein. Given that vitamin D treatment neither prevents nor reverses weight gain or insulin resistance in obese subjects [62–64], the widespread treatment of obese children of color with *mild* reductions of (total) 25-OHD should be reconsidered pending development of standard assays for vitamin D binding protein and bioavailable 25OH D.

Bone Density and Fracture Rates in Obese Children

Bone quality depends on sex, age, pubertal development, and nutritional status and is modulated by hormones, growth factors, cytokines, and a variety of genetic and environmental factors including vitamin and micronutrient intake, sun exposure, weight bearing, and physical activity, which promote bone accrual and strength. In general, bone density is more closely related to lean body mass than to fat mass [65]; the increases in lean as well as fat mass in obesity are associated with increased bone mass in boys and with increased bone density and bone mass in girls [66]. Nevertheless, the literature is inconsistent and its findings are highly variable. Some studies show mild reductions in bone mineral content in obese subjects; others find that overweight and obese children have normal or increased bone mass compared with lean controls. One investigative group finds that bone mineral content, bone density, and bone mass are reduced in obese children with insulin resistance or prediabetes but not in otherwise healthy obese children [67].

It is likely that hormones and cytokines produced by adipose tissue and infiltrating immune cells mediate effects of obesity on bone development [65]. High levels of leptin and inflammatory cytokines (including TNF-α and interleukin 6) and low levels of adiponectin and ghrelin in obese subjects with insulin resistance and glucose intolerance act in concert to promote bone resorption and reduce bone density. Resistance to insulin in bone reduces both bone formation and osteoclast differentiation and impedes the release of osteocalcin (see below). These effects are countered by sex steroids, which inhibit bone resorption and promote bone growth by recruiting osteoblast precursors from a common osteoadipogenic stem cell and by inhibiting the trans-differentiation of osteogenic to adipogenic precursors [65]. The effects of sex steroids in males as well as females are mediated by estrogen receptor signaling.

It is unclear if changes in bone density or mass in obesity alter current or future fracture risk. A retrospective review of medical records of more than 900,000 children [68] found that obesity was associated with a modest increase in fracture risk (odds ratio 1.23–1.42). In contrast, a prospective cross-sectional study of 2213 otherwise healthy children [69] found that obesity reduced fracture risk (OR 0.75). Experiments in mice suggest that high-fat feeding increases bone density but reduces bone strength, bending stiffness, and fracture resistance [70].

Osteopontin, Osteocalcin, and the Complications of Obesity

Bone cells produce a number of proteins that appear to play important roles in the pathogenesis of obesity and its metabolic complications. The *osteoclast* matrix glycoprotein *osteopontin* is markedly upregulated in adipose tissue of obese humans and mice [71]. It reduces insulin sensitivity in adipocytes and hepatocytes through recruitment of tissue monocytes and macrophages and local production of inflammatory cytokines [72, 73]. Plasma levels are increased in adults with obesity, insulin resistance, and type 2 diabetes [74, 75]. In contrast, serum osteopontin was not increased in a single study of obese adolescents [76]. It should be noted, however, that circulating osteopontin levels vary widely in the normal population and decline sharply during and after puberty, making comparisons among varying age groups difficult.

Like osteopontin, the plasma levels of the *osteoblast* protein *osteocalcin* decline with age [77]. Plasma osteocalcin is downregulated by leptin and the glucocorticoids; levels are reduced in children as well as adults with obesity, diabetes, and other insulin-resistant states [65, 78–80].

The carboxylated form of osteocalcin is stored in bone matrix; in response to bone resorption induced by insulin or parathyroid hormone, the protein is decarboxylated and released into the circulation, where it boosts energy expenditure through induction of BAT thermogenesis, reduces white adipose mass, increases insulin sensitivity, and improves glucose tolerance [80, 81]. A knockout of osteocalcin or its receptor in mice [80, 81] reduces energy expenditure, increases abdominal fat mass, reduces pancreatic beta cell mass and insulin production, decreases insulin sensitivity, impairs glucose tolerance, and reduces Leydig cell testosterone production. The fall in plasma osteocalcin in obese children and adults would therefore be expected to exacerbate the metabolic and reproductive phenotypes associated with obesity. Potential adaptive benefits of low osteocalcin in obesity might include a reduction in insulin-dependent bone resorption; this would implicate a functional axis with feedback loops involving the bone, pancreas, gonad, and adipose tissue.

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