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Endocrine Control of Body Composition in Infancy, Childhood, and Puberty

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Body composition exhibits marked variations across the early human lifetime. The precise physiological mechanisms that drive such developmental adaptations are difficult to establish. This clinical challenge reflects an array of potentially confounding factors, such as marked intersubject differences in tissue compartments; the incremental nature of longitudinal intrasubject variations in body composition; technical limitations in quantitating the unobserved mass of mineral, fat, water, and muscle *ad seriatim*; and the multifold contributions of genetic, dietary, environmental, hormonal, nutritional, and behavioral signals to physical and sexual maturation. From an endocrine perspective (reviewed here), gonadal sex steroids and GH/IGF-I constitute prime determinants of evolving body composition. The present critical review examines hormonal regulation of body composition in infancy, childhood, and puberty. (*Endocrine Reviews* 26: 114–146, 2005)

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Abbreviations: BMD, Bone mineral density; BMI, body mass index; CT, computed tomography; DEXA, dual-energy x-ray absorptiometry; ER, estrogen receptor; FFA, free fatty acid; FM, fat mass; FFM, fat-free mass; GHRP, GH-releasing peptide; IGFBP, IGF binding protein; MRI, magnetic resonance imaging; rh, recombinant human; TBW, total body water; TBW/FFM, percentage of TBW normalized to FFM; UCP, uncoupling protein.

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I. Timing and Tempo of Normal Human Growth

A. Linear growth and body weight

AUXOLOGY [Gk. *auxesis*, to increase or grow; *logos*, study] is the scientific analysis of physical growth and development. Growth is a complex process that is sustained throughout *in utero* development, infancy, childhood, puberty, and early adulthood. Dynamic control of growth is endowed by age- and gender-dependent interactions among key genetic, environmental, dietary, socioeconomic, developmental, behavioral, nutritional, metabolic, biochemical, and hormonal factors. Thus, normative data must be developed from age-specific, gender-matched, and genetically comparable healthy populations.

Although normative isobars are widely used for comparisons of static height, the endocrinologist and pediatrician should also evaluate the velocity of linear growth velocity (annual increment in height), chronological and apparent biological age, pubertal status, family history, and psychosocial adjustment. From a clinical perspective, biological age is often assessed indirectly as radiographic bone age.

The velocity of *in utero* linear growth is maximal at about 18 wk of gestational age in the human. At this time, the fetus grows four times more rapidly than at any time postnatally. Increases in body weight follow a similar temporal pattern, except that the zenith occurs at about 34 wk. The growth rate declines sharply during the last weeks of gestation. The maternal-placental environment dictates the infant's birth weight more than the fetal genotype (1). In the newborn, height velocity adjusts toward the genetically predicted trajectory. Linear growth averages approximately 25 cm in the

first year and 12.5 cm in the second year of life (see Refs. 2 and 3 for distributional estimates). The annual height velocity decreases to 8 cm (ages 2–4 yr) and 6 cm (ages 4–6 yr) during childhood. A plateau-like phase emerges in midchildhood, wherein height velocity approaches 5.5 cm/yr before puberty. Especially in the male, there is an incompletely understood decline in height velocity before onset of the pubertal growth spurt.

1. Sex differences in the fetal period. Unborn humans exhibit two gender-related auxological distinctions: 1) males exhibit more rapid linear growth than females early *in utero*; and 2) girls manifest greater skeletal maturation than boys after 15 wk of gestational development. For example, the crown-rump length in boys exceeds that in girls by 1.0 mm at 8 wk and by 2.6 mm at 14 wk gestation (4). Ultrasonographic records of fetal head circumference show an analogous gender difference early in development. At term, the foregoing sex-related distinctions approach 2% of the population mean. Conversely, skeletal maturation (*e.g.*, defined by radiological bone age) proceeds more rapidly in the female than male fetus, which disparity yields a bone age advance of 1.5 wk in girls by the early third trimester of pregnancy (5). Weight diverges in the sexes at approximately 24 wk of gestational age, such that boys weigh 70 g more than girls at 30–32 wk of *in utero* life. The absolute male-female weight difference approximates 130 g (4% of the mean) at birth.

2. Sex differences in the postnatal period. Figure 1 presents population-based projections of linear growth velocity by gender in North American children. Healthy cohorts are heterogeneous in genetic background, biological development, nutrition, exercise, and psychosocial adaptation. Accordingly, in an effort to incorporate expected genetic nonuniformity in height trajectories, normative data include

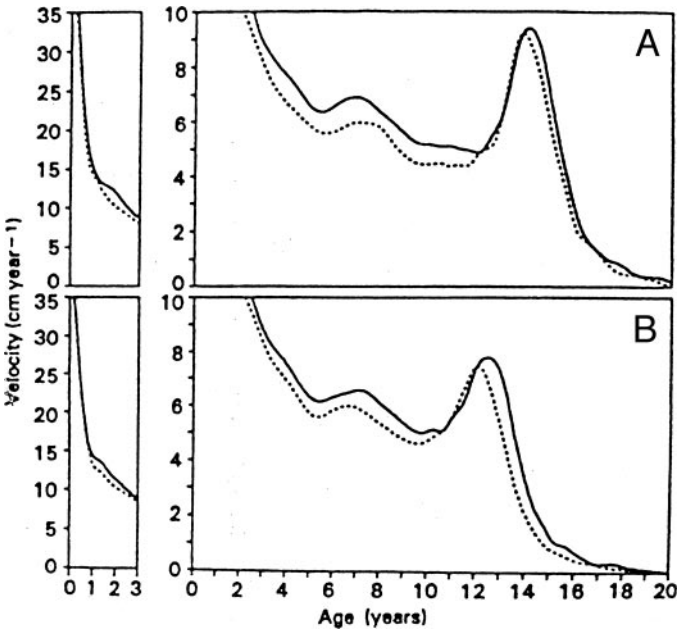


FIG. 1. Normative height velocity (centimeters per year) data in healthy boys (A) and girls (B) of Western European ethnicity, who subsequently become tall (*solid line*) or short (*dotted line*) as adults. Adapted from Ref. 2 with permission.

observations in children destined to become relatively tall or short as adults.

In the first one-half year of life, boys gain height more rapidly than girls. This velocity difference recedes after 8 months of age (2). During the age interval of 1–4 yr, girls increase in stature slightly more rapidly than boys. Thereafter, mean linear growth velocities converge in the sexes until approximately age 9, when girls (but not boys) begin a pubertal growth spurt. In North American and West European cohorts, during the interval of 9–14 yr of age, girls on average are taller than boys (3).

Girls attain a peak height velocity of 8.3 cm/yr at an average chronological age of 11.5 yr. This growth milestone corresponds to pubertal Tanner breast stages 2 and 3. Boys gain height at a prepubertal rate until age 11 (instead of 9), when testis volume begins to increase beyond 7–10 ml. Adolescent males then achieve a peak height velocity of 9.5 cm/yr at about 13.5 yr of age. The latter chronology coincides with pubertal genital stages 3 and 4. Maximal height velocity, but not total duration of linear growth, tends to be greater in youths who mature early. In both sexes, the pubertal growth rate declines rapidly after the gender-specific zenith; *e.g.*, girls gain 1 cm/yr or less in height after age 14.5 yr, and boys gain 1 cm/yr or less after age 17 yr. The net pubertal increment in stature in the male exceeds that in the female by 3–5 cm in Western cultures. Accordingly, the mean adult height difference of 13 cm between the sexes primarily reflects the gain of an additional 8–11 cm during a more prolonged prepubertal interval (~2 additional years) in boys.

3. Interindividual auxological variations. Height isobar projections (static distance curves) are shown for both sexes in Figure 2. Such population-defined data belie significant nonuniformities among individual children in the timing (onset) and tempo (rate) of sexual maturation and attendant physical development. Known genetic and environmental factors predispose to pubertal pathophysiology (6–12). However, precisely how heredity and environment control normal variations in physical maturation in healthy individuals is less well understood (13). Mechanistic considerations include mutations or microsequence polymorphisms of genes encoding (at least) the LH β-subunit, the aromatase enzyme, and the GH, LH, leptin, glucocorticoid, estrogen, and androgen receptors (14–19). Additional studies will be important to elucidate the impact of molecular diversity on physical, sexual, and psychological phenotypes.

Standardized growth curves assume a population-based mean timing of pubertal onset and progress. However, any given child may exhibit a delay or advance in sexual maturation and thus diverge at least temporarily from group predictions (2, 20, 21). A relevant family history should help in interpreting the clinical significance of serial growth measurements. As an additional aid, reference height-velocity predictions are available for average, early-, and late-maturing children in Northern Europe (3).

Normative weight trajectories are illustrated in Figure 3. Newborns lose approximately 10% of birth weight over the first 7–10 d of life. The exact adaptive processes that mediate evident extracellular fluid loss and inferred tissue catabolism at this time have not been articulated fully, but presump-

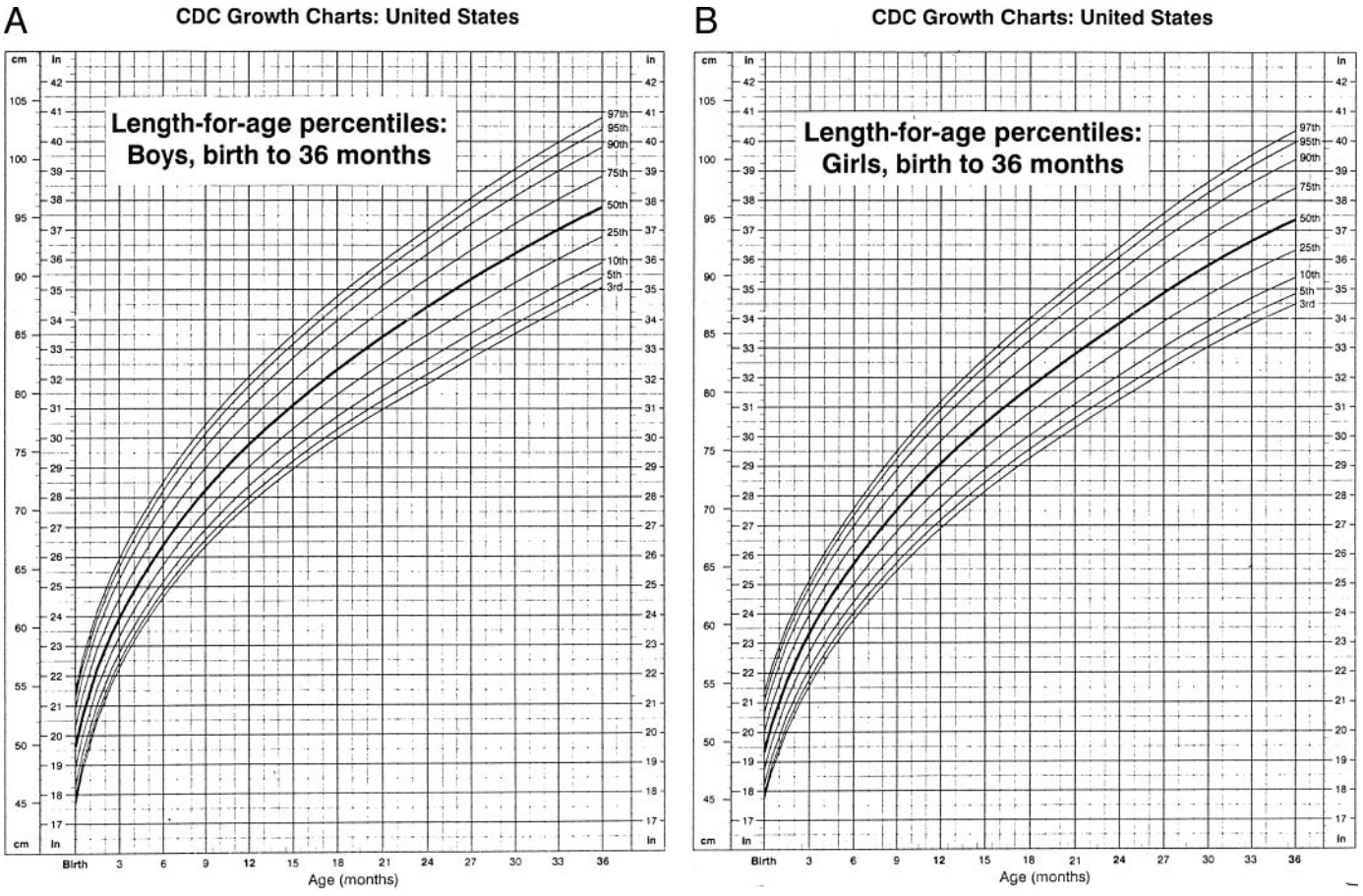


FIG. 2. Height (static distance) isobars in boys (A and C) and girls (B and D) from birth through adulthood in the United States. Data are adapted from the 2000 Center for Disease Control (CDC) Growth Charts (3).

tively entail combined nutritional and endocrine factors. Healthy neonates overcome the expected weight deficit within several weeks, and then gain approximately 30 g/d during the first 3 months of life. The latter mean increment declines to 20, 15, and 12 g/d over successive quarterly intervals until age 1 yr.

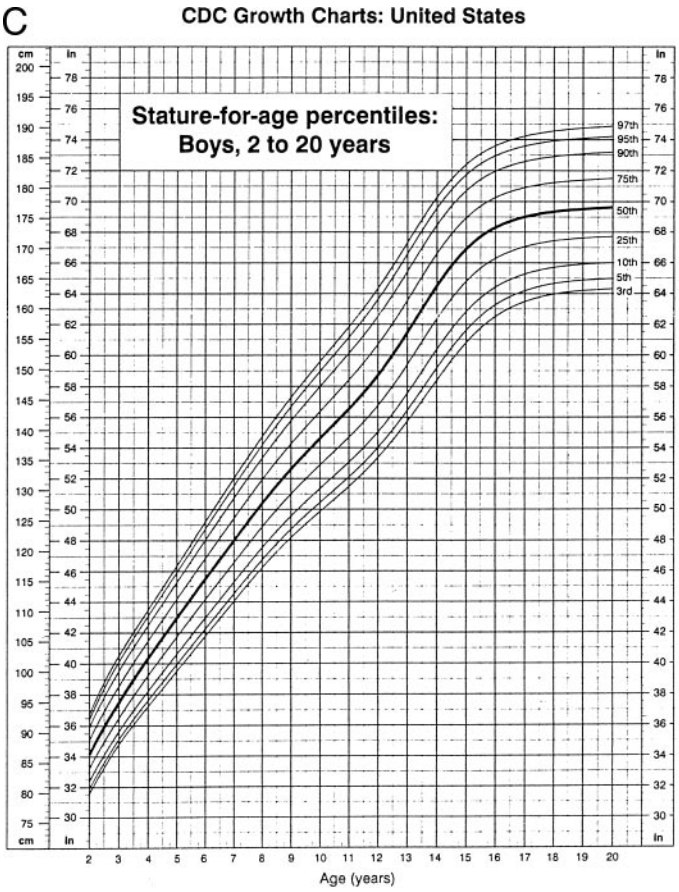
In the first year of life, male infants gain weight slightly more rapidly than female counterparts, such that at 12 months of age boys weigh an average of 10 kg and girls 9.5 kg. Over the next 2 yr, mean weight velocity approximates 8 g/d in both sexes. Weight gain diminishes to 6–7 g/d (2 or 2.5 kg/yr) in midchildhood. At age 7 yr, boys usually weigh 23 kg and girls 22 kg. Weight velocities accelerate by nearly 2-fold in the gender-specific years of puberty, wherein males gain 5 kg/yr (13.7 g/d) and girls 4.2 kg/yr (11.5 g/d).

B. Body composition in childhood and puberty

Extended, prospective, ethnicity-specific, and population-based normative body composition data stratified by gender in childhood are lacking. However, important (albeit longitudinally delimited and/or cross-sectional) observations are available in the fetus, neonate, child, and adolescent (22–28). Comprehensive body-compositional investigations will require the use of validated quantitative procedures, minimal (if any) radiation exposure, high procedural reproducibility, and repeated application in randomly selected cohorts of healthy children.

Accurate estimates of and (population-based) statistical boundaries for fat mass (FM) are crucial to classify children accurately as lean, normal, overweight, or obese. Analogously, reliable quantitation of fat-free mass (FFM) is important to identify relative or absolute sarcopenia and osteopenia. Valid measures of regional adiposity (*e.g.*, sc and visceral fat) are essential to elucidate the pathophysiological basis and clinical impact of hyposomatotropism, insulin resistance, dyslipidemia, obesity, and cardiovascular morbidity (see *Section II.A*).

1. FM and FFM accrual. Projections of the gender-specific evolution of FM, FFM, and percentage body fat in Caucasian children are given in Fig. 4. These predictions aggregate the results of accurate multicompartmental analyses performed cross-sectionally at selected stages in infancy, childhood, puberty, and early adulthood (22, 29, 30). Interpolations are required to supplement incomplete body-compositional data in midchildhood and early adolescence. Although ethnic comparisons are limited, one pediatric investigation compared FM and FFM estimates among African-, European-, and Mexican-American children at or over the age of 4 yr (31) (Fig. 5). This analysis like several recent other studies re-



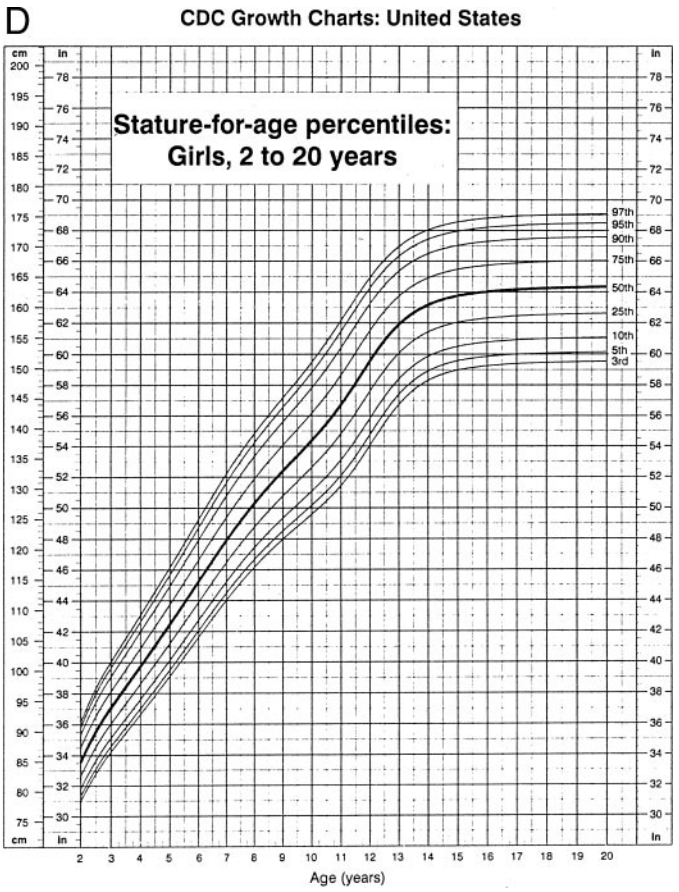


FIG. 2. *Continued*

ported a higher mean FM value than that typically observed earlier in children (32). Whether the latter (possible) increase in absolute FM reflects *de facto* historical trends, population selection, and/or technical differences is not clear.

The newborn boy has about 6.5% more (absolute) FFM than the newborn girl (33, 34). This gender difference mirrors the relative paucity of total body fat in the infant male (~13%), compared with the female (~15%), and the male's higher birth weight. FM increases to 25–30% of total body weight by age 6 months. Thereafter, FFM begins to accumulate preferentially. For example, 85% of the total weight gain over the second 6 months of life comprises FFM. Although fractional FFM remains comparable by gender across midchildhood, boys accrue about 1 kg more absolute FFM than girls before puberty (22, 29, 30). In puberty, boys acquire FFM at a greater rate (kilograms per year) and for a longer period than girls. In one analysis, stable (adult) values of FFM were attained by approximately 15–16 yr of age in girls and 2–3 yr later in boys (35).

In absolute terms, FM (kilograms) is comparable by sex in children ages 3–5 yr. Girls accumulate FM more rapidly than boys in midchildhood, such that 10-yr-old females have approximately 2 kg (6%) more FM than males. In adolescence, girls gain absolute FM at an average annual rate of 1.14 kg, whereas boys maintain a relatively fixed absolute FM. Hence, percentage body fat declines in pubertal boys (27).

2. Water, protein, and mineral accrual. Primary components of FFM (water, protein, and mineral) vary markedly in infancy and adapt further in childhood and adolescence (Fig. 6). The percentage of total body water (TBW) normalized to FFM (TBW/FFM) exceeds 80% at birth. The latter value decreases by 1% over the first year of life. TBW/FFM falls to 77% in boys and 78% in girls in early childhood and to 76% by age 10 in both sexes (22, 25, 29).

During the age interval of 10.5–12.5 yr, girls maintain a lower mean TBW/FFM than boys. This sex difference wanes until boys begin (and girls complete) puberty (25, 29, 30). Protein constitutes 15.7% of FFM at birth. The latter value increases to 18 and 19% at 2 and 10 yr of age, respectively, and approximates 20% in late adolescence (22, 25, 29).

Mineral comprises primarily (~82%) bone salts. The mineral fraction in FFM remains stable in infancy and early childhood, and then rises disproportionately (over protein and water) in midchildhood and early puberty (22, 25, 29). Bone mineral density (BMD) determined at near-peak height velocity is greater in boys than girls (25, 29, 30). BMD is higher in African-American than Caucasian individuals before and after puberty in both sexes (36, 37). The precise endocrine determinants of this consistent ethnic difference are not known. Nonendocrine genetic and environmental factors may contribute to some differences. One analysis revealed higher (overnight) serum concentrations of GH and

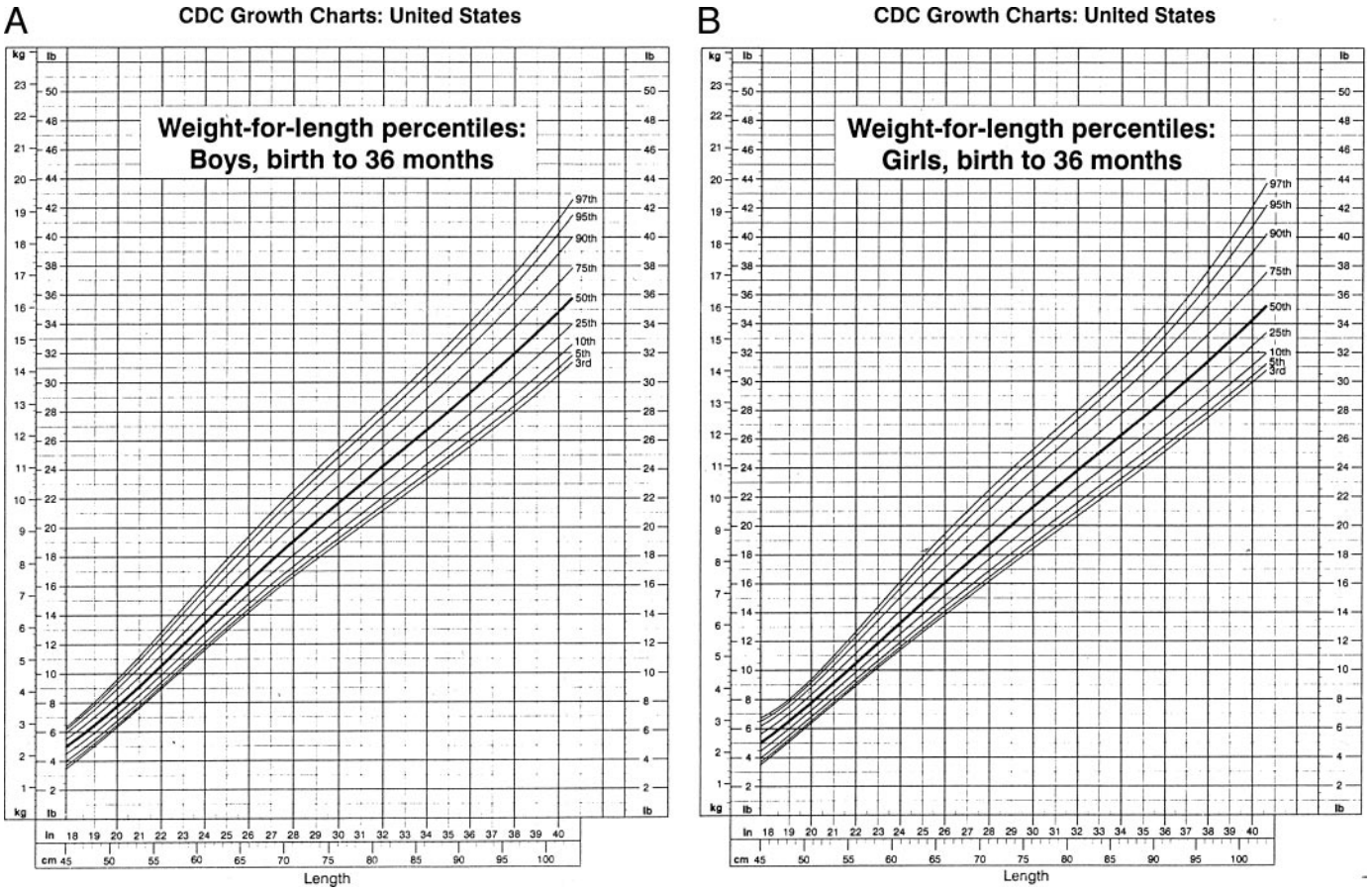


FIG. 3. Normative weight (kilograms) projections in boys and girls from birth through midchildhood. Data are presented as in Fig. 2.

estradiol in African-American than Caucasian men, which levels correlated positively with BMD (36). No comparable distinction was evident before puberty or in women (37). Other clinical studies have reported ethnic contrasts in plasma IGF-I/IGF binding protein (IGFBP) concentrations in the female (37–39). The foregoing epidemiological observations highlight the need to better understand the specific mechanisms by which ethnicity, gender, and developmental age modulate the endocrine control of human growth and body composition (40).

II. Measurement of Body Composition

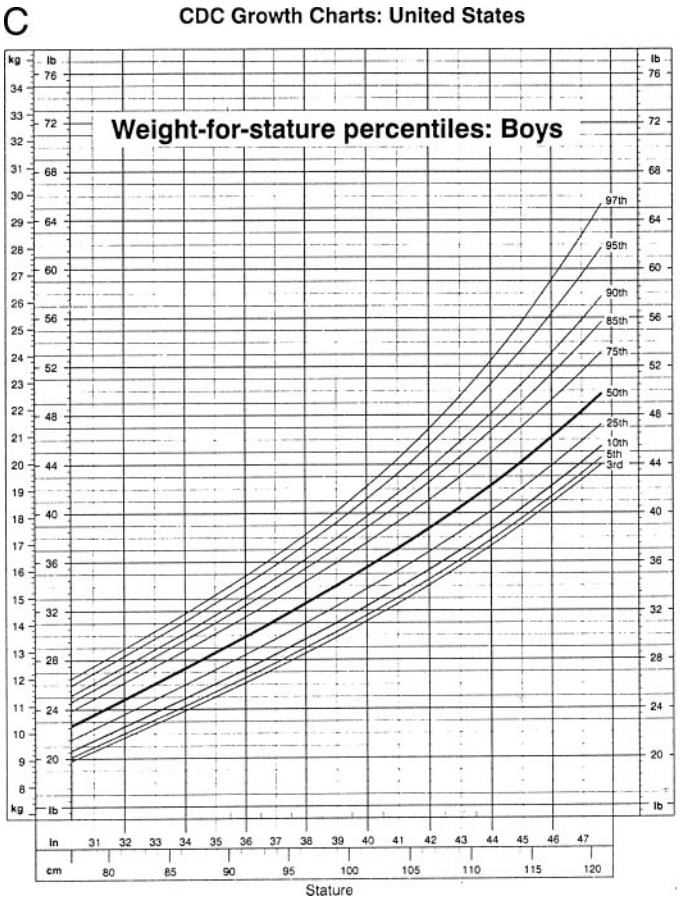
Body composition evolves dramatically *in utero* and across infancy, childhood, puberty, and adulthood and appears to be conditional on early developmental events (28, 34, 35, 41–45). Quantitation of body composition relies on auxological or anthropological attributes [*e.g.*, body mass index (BMI), skinfold thickness, abdominal girth], physical properties (*e.g.*, total body volume, bioelectrical impedance, dual-energy x-ray absorbance), and/or biochemical markers (*e.g.*, TBW, calcium, potassium, or nitrogen). Clinical measures are then applied in empirically constructed regression (correlation or prediction) equations to estimate unobserved features of body composition (26, 35, 46–50).

Primary estimates of body composition were derived by chemical analyses of adult cadaveric tissues (27, 31). Such data, albeit limited, provide validation for secondary estimates based on densitometry (*e.g.*, underwater weighing), dual-energy x-ray absorptiometry (DEXA), isotope dilution, bioelectrical impedance, BMI, and skinfold thickness (22, 24, 26, 27, 29, 31, 46, 47, 51, 52).

A. Body mass index

Height (meters) and weight (kilograms) are simple anthropological attributes. Algebraic combinations of these two measures are used to compute the BMI (kilograms per square meter), ponderal index (kilograms per cubic meter) or Benn index (kilograms per meter) (53). BMI has been applied to categorize children as lean, normal, overweight, or obese (54, 55). However, this metric varies with developmental age, gender, and ethnicity (27, 55–58). For example, BMI is high in the first year of life, decreases in early childhood (ages 2–5 yr), and then increases in puberty (54, 59). Accordingly, BMI should be compared via age-stratified standardized z-scores (or percentiles) defined in healthy populations, *e.g.*, as reported in North America, Holland, United Kingdom, France, and China (60–63).

BMI does not quantitate body composition. Indeed, this metric amalgamates frame size (mineral content), total FM (visceral and sc) and lean tissue (27, 28, 30, 52, 64). Thus, a short, muscular adolescent could be assigned a high BMI spuriously suggestive of obesity (47, 59). Moreover, treat-



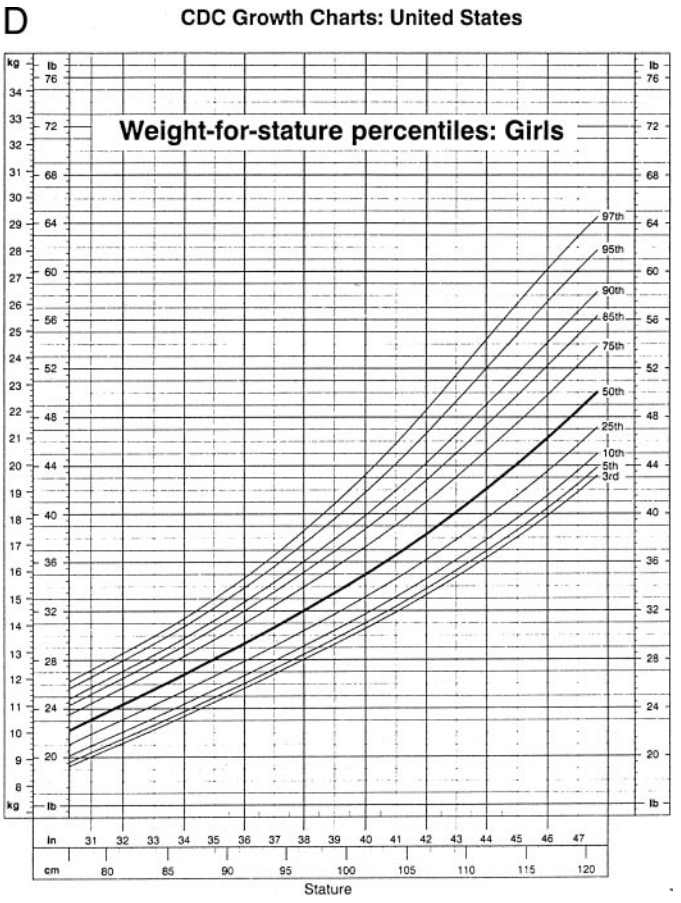


FIG. 3. *Continued*

ment with recombinant human (rh) GH often reduces FM by 2–3 kg and increases lean body mass comparably in the hypopituitary adult, while leaving BMI unchanged (65).

Indices like BMI also do not monitor the regional fat distribution (*e.g.*, visceral *vs.* sc) (57, 66–68). This distinction is significant epidemiologically, because visceral fat accumulation predicts higher risk of peripheral insulin resistance, dyslipidemia, adult cardiovascular disease, hypoandrogenemia, elevated free (salivary) cortisol, reduced concentrations of SHBG, IGFBP-1, LH, and high-density lipoprotein, and impoverished daily GH production (22, 26, 28, 69–76). Recent investigations suggest that deficiency of intrauterine growth factors, degree of fetal stress, low birth weight, relative hypercortisolemia, impaired glucose disposal in midchildhood, and premature adrenarche further forecast greater risk of insulin resistance, cardiovascular disease, dyslipidemia, and abdominal obesity in adulthood (39, 77–86).

B. Two-compartment models

1. Densitometry. Densitometric methods partition body composition into two mutually exclusive compartments, *viz.*, FM and FFM. Calculations relate whole-body density (weight divided by volume) to FM and FFM by way of average tissue-density constants (24, 87). To estimate whole-body density, weight is quantitated accurately on a dry scale, and volume is estimated by underwater weighing, clinical volumetry, or air plethysmography (26).

Water-displacement procedures are based on the principle of Archimedes, and thus require: 1) complete submersion of the volunteer in a suitable water-filled chamber to record underwater weight (hydrodensitometry) or quantitate water overflow into a burrette (clinical volumetry); and 2) accurate measurement of functional residual lung capacity by nitrogen washout to correct for the thoracic gas space. The latter determination introduces the majority of technical variability into the final estimate of percentage body fat. Within-subject coefficients of variation are approximately 3–4% of total body weight (26, 88). Limitations of hydrodensitometry include the requirement for a water tank, variable subject reluctance, and multiple (up to 10) submersions to ensure technical reproducibility.

Air-displacement plethysmography provides a complementary volumetric approach based on Boyle's law of the partial pressure of gases. This procedure may be less stressful to the subject than repeated immersion in a water chamber (89, 90). One plethysmographic unit comprises a sealed fiberglass capsule (or pod). The volunteer enters the chamber wearing a tightly fitting swimsuit and swim cap, views the room through a small window, and breathes quietly for several minutes while an internal diaphragm is oscillated to generate small changes in air pressure. The air-displacement

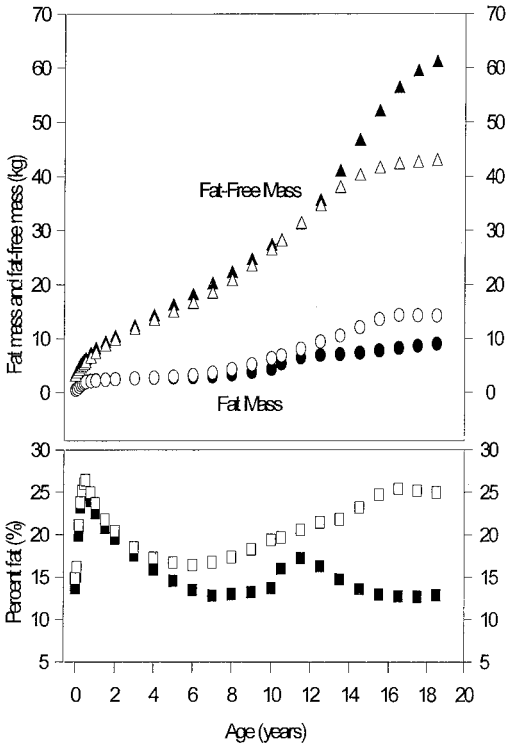


FIG. 4. Estimates of FFM, FM, and percentage body fat in European-American boys (*closed symbols*) and girls (*open symbols*) from infancy through early adulthood (age 20 yr). *Curves* reflect aggregate data compiled from and interpolated among cross-sectional analyses (22, 25, 29, 30, 35). Units are kilograms (FFM, FM) (31).

estimate is also corrected for thoracic gas volume (above). Cross-validating analyses indicate that air- and water-displacement methods perform comparably in young adults. However, air plethysmography may underestimate percentage body fat by 2–7% of total body weight (2–6 kg absolute FM) in children and older individuals (45, 52, 89–91).

In densitometric techniques, one calculates percentage body fat from the density estimate using an empirical regression model, such as that of Brozek *et al*. (51) or Siri (92). Both sets of equations assume a nominal adult tissue density of 0.9 g/ml for fat and 1.1 g/ml for FFM (24, 31). However, the use of adult tissue-density constants forces an overestimate of percentage body fat in children (Fig. 7). This artifact arises because the true density of FFM is as low as 1.063 g/ml in early childhood, whereas the contribution of water (density, 0.9937 g/ml) and mineral (density, 3.0 g/ml) to body density is higher and lower, respectively (27, 30). Accordingly, Lohman and colleagues suggest the use of age-specific tissue-density constants in the Siri model (24, 27). This adjustment obviates systematic overestimation bias in younger subjects. However, compared with multicompartmental methods (below), densitometry may yield inconsistent individual predictions (random procedural bias) (30).

2. Isotope dilution methods. Accurate quantitation of TBW facilitates reliable determination of body composition, because water represents 74–80% of FFM depending on age and gender (29). TBW is quantitated by the degree of dilution in the aqueous compartment of a known amount of a stable or radioactive isotope of water (*e.g.*, ^2H_2O, $H_2{}^{18}O$, or ^3H_2O) administered orally. Isotope concentrations are monitored in one or more timed (postequilibration) samples of serum, urine, saliva, or expired air by liquid scintigraphy (^3H_2O), infrared spectrometry (^2H_2O), or isotope-ratio mass spectroscopy (^2H_2O or $H_2{}^{18}O$) (68). Estimates are corrected for nonaqueous loss, because 4% of labeled hydrogen exchanges with nonaqueous hydrogen and 1% of labeled oxygen are removed via metabolic oxidation. The degree of final isotope dilution is proportionate to TBW. Given an estimate of TBW, one may calculate FFM and percentage body fat from age- and sex-specific constants for TBW/FFM (above). In isotope dilution studies, the coefficient of variation in the calculation of percentage body fat approximates 2–3% of body weight (31, 92).

C. Four-compartment models

Multicompartmental models are used to quantitate FM and the principal components of FFM (water, mineral, and protein) (29, 30, 59, 93–99). For example, one method determines TBW by isotope dilution (above) and quantitates FM and mineral mass by DEXA. Some compartmental models include the determination of body cell mass (*e.g.*, appraised by nonradioactive potassium spectrometry) or total body nitrogen and calcium (*e.g.*, assessed by whole-body neutron activation analysis) (100–105).

D. Two- and three-compartment models

Two-compartment analyses of body composition use several means to evaluate the components of FFM (26, 46). In the water-density model, TBW is quantitated first to calculate FM (total weight minus TBW). Protein and mineral content of FFM are estimated secondly from age- and gender-specific prediction equations. In the mineral-density model, bone mineral content is determined so as to compute summed water and protein (mineral-free lean tissue) and FM (29). The water-density model performs more reliably in pediatric age groups, because water represents 73–80% (and mineral only 5%) of FFM in children (30). The mean bias of the water-density calculation of FM is approximately 0.75% when calibrated against four-compartment methods. On the other hand, the mineral-density model may overestimate percentage body fat by as much as 5–7.5% in individual children and adolescents (Fig. 8).

DEXA scanning is a contemporary three-compartment model. DEXA quantitates FM, mineral and mineral-free lean tissue (protein and water) based on differential tissue absorption of two distinct x-ray energy peaks (31, 35, 43, 50). The volunteer lies supine on a table under a detector panel placed over the x-ray source. X-rays are fractionated into 40 keV and 70–100 keV energy streams. Approximately 40–45% of recorded pixels (unit absorbance ratios) monitor x-ray attenuation by bone and soft tissue (combined), and 55–60% monitor x-ray absorbance by fat and mineral-free lean tissue (combined) (31). Prediction bias arises from DEXA determinations made near the surface of the body (due to disproportionate proximity of mineral and sc fat) and the appen-

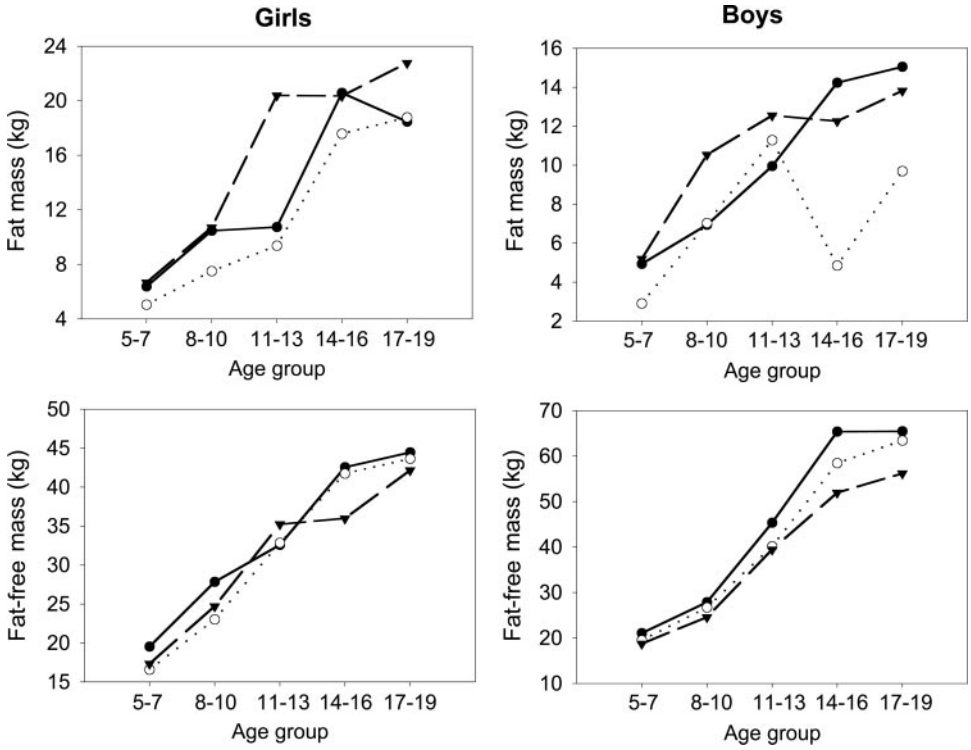


FIG. 5. Changes in FM and FFM of African-American (*filled circles*), Caucasian (*open circles*), and Mexican-American (*filled triangles*) girls (*left panels*) and boys (*right panels*) ages 5 to 19 yr. Data were collected cross-sectionally from 856 healthy youth. FFM was calculated from TBW data using age-appropriate constants for hydration of FFM. FM was determined by subtraction from total body weight. Note different y-axis ranges for girls and boys and reduction in pubertal FM in Caucasian boys only. Adapted from Ref. 31 with permission.

dicular skeleton (due to undue contiguity of muscle and connective tissue).

DEXA precision is higher when applied to calibration phantoms than to the human skeleton or the whole body (96, 106). In adults, the reproducibility of DEXA-based quantitation of BMD averages 0.7% or 0.01 g/cm^2; and, the absolute error in percentage body fat approaches ± 1.4% of body weight. The latter precision compares well with a value of ±1% in predicting absolute FM by four-compartment models (96, 107). In adults, estimates of percentage body fat based on DEXA usually fall within 3% of those determined by more complex models. Discrepancies typically reflect technical uncertainty in the DEXA calculation of body weight (which should agree with the scale weight within 1 kg) and/or errors in the isotopic determination of TBW.

DEXA scanning tends to predict falsely high percentage body fat in children (and older adults) (30, 95) (Fig. 8). DEXA likewise overestimated FM in two recent primary validation studies using the whole carcass of immature swine (108, 109). Practical limitations include equipment and technician costs and low-dose radiation exposure (1–3 mrad, or less than that contributed by cosmic background during a single 4000-km air flight). Nonetheless, DEXA technology offers a valuable means to estimate body composition. Additional important insights are achievable by way of computed tomography (CT) and magnetic resonance imaging (MRI), because these techniques allow one to appraise the regional distribution of fat.

E. Fat topography

Intraabdominal fat is a key epidemiological determinant of insulin resistance and cardiovascular risk (110). CT provides one well-validated means to quantitate intraabdominal adiposity. CT is technically precise in discriminating adipose tissue and affords a brief scan time that obviates motion artifact (111). To estimate abdominal fat, the CT examination is performed at the level of the fourth or fifth lumbar vertebrae, the corresponding intervertebral disc space, or (somewhat less reliably) the umbilicus. Data are expressed as the cross-sectional area (square centimeters) of a demarcated region of adipose tissue, such as visceral (mesenteric, pericolic, and perirenal), retroperitoneal, and sc fat (112, 113). A recent distinction between superficial and deep sc FM suggests that the latter may also predict increased cardiovascular health risk (114). MRI offers a complementary method to quantify regional FM that does not require x-ray exposure. Although not evaluated exhaustively in children, MRI outcomes correlate with those of CT (115). Table 1 summarizes available CT and MRI data in children as distinguished by peripubertal age, gender, and ethnicity in cross-sectional analyses. However, appropriately stratified longitudinal comparisons will be required to definitively assess the transpubertal control of regional fat distribution in girls and boys. Concomitant metabolic implications of visceral and sc accumulation and dissipation (*e.g.*, peripheral insulin sensitivity and lipoprotein composition) will be important to quantitate so well as practicable in pediatric populations. Finally, anatomic and metabolic adaptations across puberty need to be correlated with changing hormone outflow (*viz.*, GH, testosterone, estradiol, IGF-I, insulin, and leptin) or resting energy expenditure.

F. Clinic and field methods

Body composition may be assessed clinically by physical anthropometry (*e.g.*, BMI, the waist-to-hip ratio, anteroposterior abdominal dimension, skinfold thickness) and/or bio-

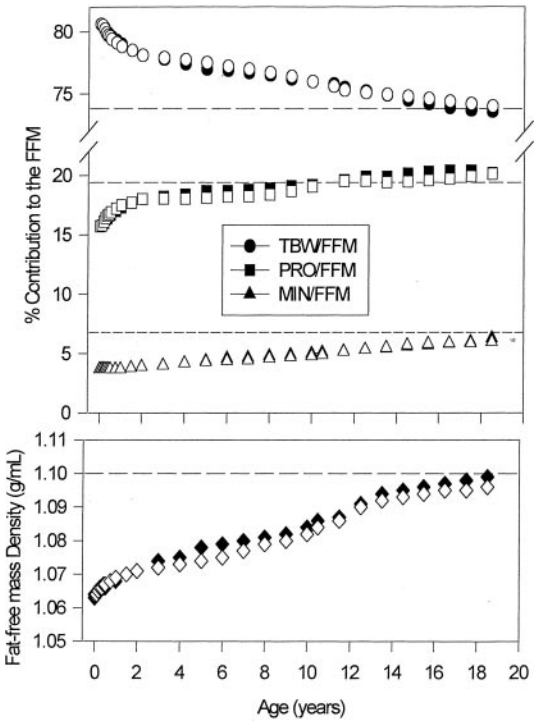


FIG. 6. Variations in TBW/FFM (*circles*), protein/FFM (PRO/FFM; *squares*), and mineral/FFM (MIN/FFM; *triangles*), and mean density of FFM (*diamonds*). Data apply to the newborn, prepubertal, and pubertal boy (*closed symbols*) and girl (*open symbols*). *Interrupted lines* reflect predictions based on a nominal adult (cadaveric) FFM density of 1.1 g/ml. Compiled variously from cross-sectional data reported in Refs. 22, 25, 29, 30, and 35.

electrical impedance (34, 49, 116–119). In some studies, average predictions of percentage body fat derived from summed skinfold thickness agree well with multicompartmental analysis (Fig. 9). However, anthropometric assessments may exhibit significant inter- and intraindividual variability (random bias), and bioelectrical impedance estimates may manifest marked (>25%) systematic bias compared with multicompartmental analyses (34, 75, 119–121).

III. Sex-Steroid and GH Interactions on Target Tissues in Puberty

A. Overview

From an endocrine vantage, normal physical growth and sexual maturation require time-evolving coordination among the somatotropic, gonadotropic, and adipostat systems (122–126). Time-varying somatic, visceral, endocrine, and metabotropic signals are integrated to a significant degree in hypothalamic centers (127–129). Additional interaxis control is accomplished by convergent and divergent actions of the corresponding hormones on the pituitary gland and peripheral target tissues (40, 130–133). States of mono- and bihormonal deficiency underscore the inferred interplay between somatotropic peptides and gonadal sex steroids in directing adult body composition and sexual maturation (134–137). For example, in the human, mouse, and rat, isolated GH deficiency reduces the production of major GH-dependent hepatic proteins, *viz.*, IGF-I, IGFBP-3, acid-labile subunit, and IGFBP-5, and retards the initiation of sexual development (138, 139). In particular, deprivation of GH and IGF-I: 1) delays the timely onset of puberty (in all species studied); 2) slows the pace of pubertal maturation (all species); 3) attenuates phallic growth (human); 4) reduces adult testicular size (rodent); and 5) impairs sperm motility (mouse); but 6) does not abrogate fertility in the mature individual (all species) (131, 135, 140–145).

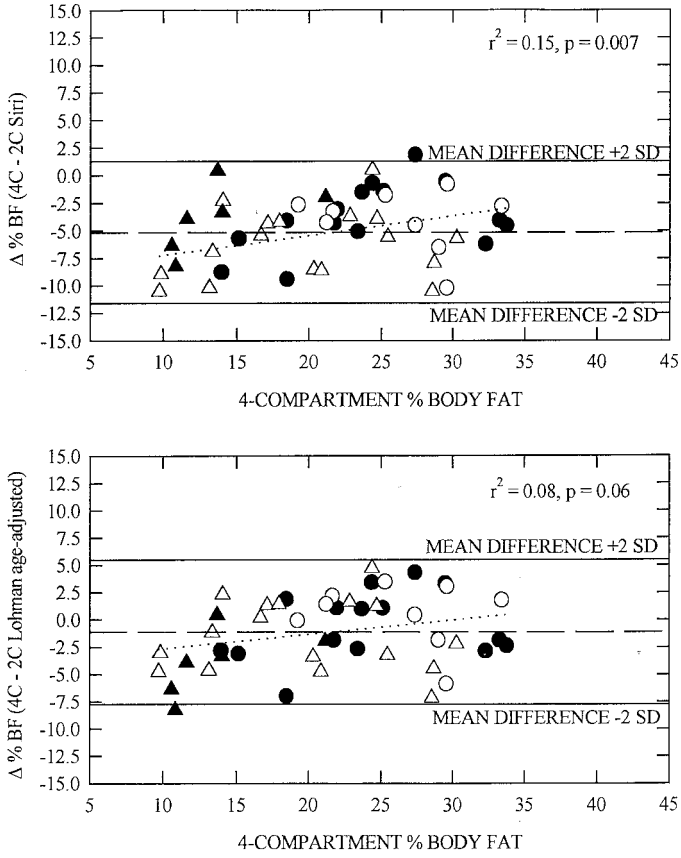


FIG. 7. Bland-Altman plots to compare predictions across the human lifetime of percentage body fat (% BF) by a two-compartment (2C) and a four-compartment (4C) model of body composition. The x-axis presents % BF determinations by the 4C criterion model, and the y-axis gives the bias [algebraic difference between the two methods (4C − 2C values)]. (Values for the 2C model are not shown directly, but are calculated readily by addition of the X and Y values.) Equivalent models would yield a zero mean bias (*interrupted lines*). Reliable correlations between the two methods would afford limited y-axis variance (random experimental variations). The implications of two assumptions are illustrated; *viz.*, a constant FFM density of 1.1 g/ml (*upper panel*) and Lohman's age-adjusted FFM density (*lower panel*) (see text). *Interrupted lines* depict mean (systematic) bias, and *dotted lines* define any trend in bias (slope of predicted linear regression ± 2 SD, continuous curves). Squared correlation coefficients (r^2) estimate the percentage variation in bias due to changing % BF. *P* values test a null hypothesis of no trend in bias. Symbols distinguish developmental strata; *viz.*, *open circles*, girls with Tanner breast stages I and II; *closed circles*, Tanner breast stages III and IV (female); *open triangles*, boys at genital stages I and II; and *closed triangles*, genital stages III and IV. Stages I and II correspond to pre- and early puberty, and stages III and IV to midpuberty and adulthood, respectively. Reproduced from Ref. 30 with permission. The Bland-Altman graphical representation was reported earlier.

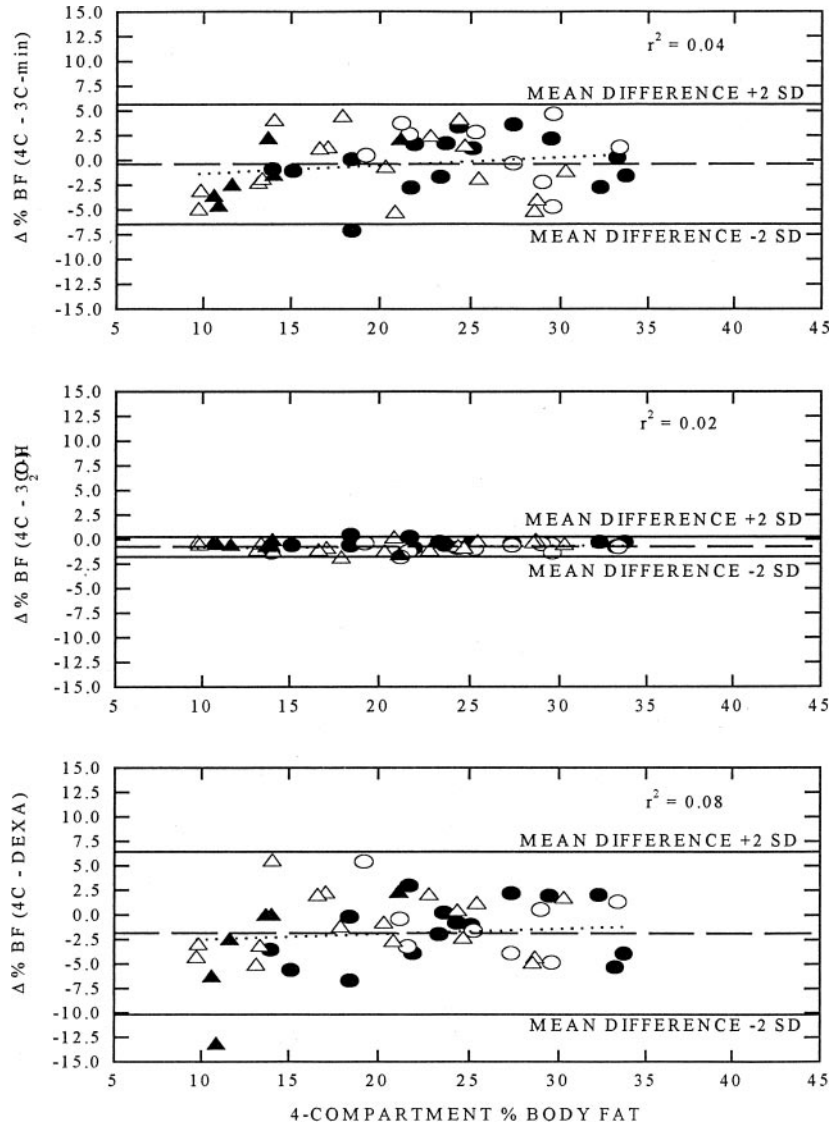


FIG. 8. Bland-Altman plots to examine possible bias in children between estimates of percentage body fat (% BF) based on: 1) a three-compartment mineral-density (3C-bone) model (*top*); 2) a three-compartment water-density (3C-H_2O) model (*middle*); and 3) DEXA (*bottom*) compared with a four-compartment criterion model (4C) applied in children. Predictions by DEXA showed systematic positive bias; *viz.*, predicted higher % BF at all measurement levels, as reflected in the zero slope of the linear regression. Data are presented as defined in the legend of Fig. 7. Adapted from Ref. 30 with permission.

Clinical treatment of precocious puberty highlights the inference that stimulatory effects of gonadal sex steroids on the GH/IGF-I axis are reversed in part when ovarian or testicular secretion is decreased medically (40, 146, 147). In particular, therapy with a GnRH analog suppresses concentrations of estradiol and testosterone profoundly and those of GH, IGF-I, and IGFBP-3 significantly, but does not affect measurements of cortisol or adrenal androgens (148, 149). Gonadal-axis down-regulation may thereby obviate rapid skeletal maturation not only by sex-steroid depletion but also by secondary inhibition of the somatotropic axis (150). Albeit originally hypothesized as a means to stimulate growth in the face of bone-age delay, combining rh GH supplementation with GnRH agonist therapy in children with sexual precocity may enhance predicted final stature (147, 151, 152).

From a simplified viewpoint, the timely onset and effectual progress of puberty would require, at a minimum, interaxis coordination of GH/IGF-I and GnRH/LH/sex-steroid production. Several mechanistic insights are relevant to this network-like concept. First, IGF-I and/or insulin act in an apparently species-specific manner to: 1) enhance hypothalamic GnRH outflow *in vivo* in the juvenile female monkey and rat and stimulate GnRH secretion *in vitro* by murine GT1–7 cells; 2) promote normal reproductive hormone secretion in the male and female mouse in part via the central nervous system insulin receptor substrate-2 signaling pathway; 3) potentiate GnRH-stimulated LH release *in vitro*; and 4) synergize with LH and FSH in stimulating ovarian and testicular steroidogenesis *in vitro* and *in vivo* (12, 132, 153–163). Second, endogenous gonadal sex steroids amplify the synthesis of GH and IGF-I and regulate the availability of IGFBPs and cognate proteases (90, 131–133, 164–170). Third, GH, IGF-I, IGF-II, insulin, and sex steroids interact via complex heterologous control of receptor-effector signaling pathways (135, 165, 171–182). And, fourth, sex steroids and insulinomimetic peptides act in combination to govern appetite, thermoregulation, behavior, and energy expenditure via central and peripheral pathways (183–186). Comprehensive formal integration of the foregoing multivalent mechanisms is not yet possible.

TABLE 1. Impact of childhood age, gender, and ethnicity on abdominal visceral and sc fat accumulation

Study cohort	N	Age (yr)	Fat accumulation (cm^2)		Total body fat (%)	Citation no.
			Visceral	Subcutaneous		
Prepubertal boys and girls[a]	16	6.4 (4–8)	8 (2–24)	65 (10–141)	25.8[e]	555
Prepubertal African-American boys[a]	27	7.3 (4–10)	22 (7–72)	61 (8–372)	26.6[e]	556
Prepubertal Caucasian boys[a]	16	8.2 (5–10)	27 (7–65)	65 (14–225)	24.5[e]	556
Prepubertal Caucasian boys and girls[a]	68	10.0 (7–12)	48 (16–142)	145 (15–420)	28.6	557
Prepubertal African-American boys and girls[a]	51	9.3 (7–12)	34 (7–118)	124 (9–436)	26.5	557
Prepubertal boys and girls[b]	21	N/A	27	98	N/A	558
Obese prepubertal boys and girls[b]	7	N/A	41	325	N/A	558
Obese prepubertal Caucasian boys[b]	10	9.7 (9–11)	69.8	274	42.1	559
Obese prepubertal African-American boys[b]	11	9.7 (9–11)	80.6	437	47.7	559
Prepubertal boys[c]	16	10.4 (9–12)	44 (18–93)	71 (30–127)	18.5	560
Pre- and early pubertal boys[b]	25	11–13	18 (6–58)	78 (21–214)	22.1[e]	
Pubertal boys[b]	5	N/A	15	42	N/A	558
Obese pubertal boys[b]	6	N/A	56	380	N/A	558
Pubertal boys[c]	13	13.4 (11–15)	62 (43–119)	96 (37–209)	18.8	560
Prepubertal African-American girls[a]	38	7.4 (4–10)	28 (7–73)	106 (14–272)	35.4[e]	556
Prepubertal Caucasian girls[a]	20	8.2 (5–10)	54 (12–102)	172 (30–341)	37.8[e]	556
Obese prepubertal Caucasian girls[b]	19	9.3 (9–11)	55.5	270	43.4	559
Obese prepubertal African-American girls[b]	24	9.5 (9–11)	48.1	321	44.4	559
Prepubertal girls[c]	12	10.4 (8–12)	44 (25–54)	103 (23–186)	24.0	560
Pre- and early pubertal girls[b]	25	11–13	25 (15–50)	81 (29–152)	27.0[e]	
Early pubertal girls[d]	13	11.5	24	44	N/A	561
Obese pubertal girls[b]	10	N/A	50	355	N/A	558
Pubertal girls[b]	5	N/A	17	72	N/A	558
Pubertal girls[c]	15	13.5 (11–15)	53 (36–72)	124 (53–285)	24.7	560
Late pubertal girls[d]	11	14	26	63	N/A	561

Data represent mean (range). N/A, Not available.
[a] CT (level of umbilicus).
[b] MRI.
[c] MRI (at L4–5 interspace).
[d] MRI (at minimal waist circumference).
[e] Recalculated from original data.

B. Actions of androgen, estrogen, GH, and IGF-I on bone

1. Hypogonadism overview. Prolonged deprivation of sex-steroid hormones at or after the time of expected puberty predisposes to reduced peak bone mass, attendant osteopenia, osteoporosis, and major fractures in the adult (56, 187–190). Cross-sectional epidemiological analyses demonstrate that total and bioavailable (non-SHBG-bound) estradiol concentrations predict bone mass in women and men more accurately than total or bioavailable testosterone concentrations (188, 191–194). Data from four longitudinal investigations corroborate the fundamental association between peripheral estrogen concentrations and bone mass in the aging individual (56, 188). Testosterone, GH, IGF-I, and (in some studies) leptin concentrations also correlate with TBW in some analyses (195, 196). Albeit incompletely defined, heterogeneous genetic factors are prominent determinants of bone mass in healthy individuals (197, 198). In addition, ethnicity may influence bone density by as much as 6–11% (199).

2. Male hypogonadism. Testosterone replacement in hypogonadal boys and men increases TBW incrementally in proportion to the degree of androgen deficiency at presentation (168, 200–202). The anabolic effects of testosterone *in vivo* are not fully understood but are associated with augmentation of at least: 1) pulsatile GH secretion, which drives longitudinal bone growth (166, 169, 170, 203, 204); 2) IGF-I synthesis in both liver and bone cells (169, 170, 205–207); 3) gastrointestinal absorption and skeletal retention of calcium and magnesium (201, 208–215); 4) muscle mass, mechanical loading, and energy expenditure, which in turn correlate with bone mineral content and density (90, 162, 164, 165, 168, 216–220); 5) biochemical markers of osteoblastic activity, such as osteocalcin (221); and 6) epiphyseal growth-plate maturation, which culminates in mineralization-dependent cessation of skeletal elongation (15, 222–224). *In vitro* studies affirm these inferences and further illustrate that (in rodent species) testosterone and 5α-DHT can stimulate osteoblastic activity, inhibit apoptosis of osteoblasts and osteocytes, suppress osteoclastogenesis, and promote cortical (periosteal) bone apposition (225–228). Androgen- and estrogen-dependent stimulation of epiphyseal mineralization underscores the clinical challenge of tailoring sex-hormone replacement in hypogonadal children to optimize total skeletal growth without inducing premature fusion of the growth plate (229–234).

Androgen receptors are expressed in human osteoblastic cells and mature osteocytes (235). A normal linear growth spurt is described in 46XY patients with complete androgen insensitivity (testicular-feminization syndrome) due to inactivating mutation of the cognate receptor (145, 236). Nonetheless, loss of androgen-receptor function limits adult height and skeletal volume (bone size) in the genotypic male to values intermediate between those of the unaffected male and female (237). A reduction in bone mineral content is reported in some (but not other) patients with testicular feminization syndrome. Low bone mineral content may reflect: 1) a younger age at prophylactic orchidectomy; 2) suboptimal estrogen replacement; 3) the postgonadectomy fall in

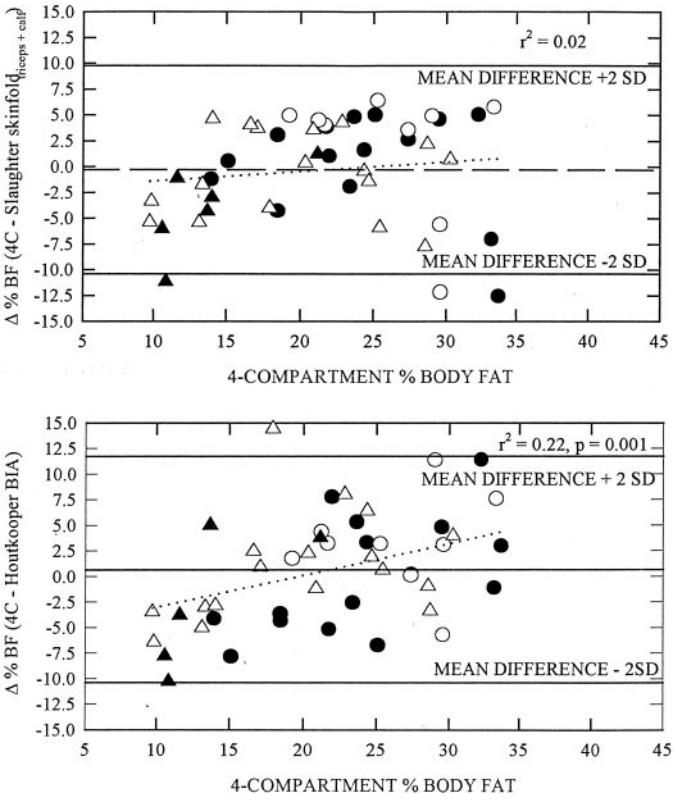


FIG. 9. Systematic and nonsystematic bias inherent in two particular field models compared with a four-compartment criterion model (4C) in quantitating percentage body fat in children. *Top*, Skinfold-thickness prediction (equation originally estimated from a 4C criterion model); *bottom*, bioelectrical impedance prediction (equation derived from a 4C criterion model). Data presentation is described in the legend of Fig. 7.

IGF-I availability; 4) a role for the androgen receptor in early bone development; 5) reduced supplementation with aromatizable androgens, which provide substrate for estrogen synthesis *in situ*; and/or 6) more severe inactivation of androgen-receptor function (135, 223, 238–240).

Supraphysiological amounts of aromatizable and nonaromatizable androgens stimulate osteoblast proliferation, antagonize the osteoclast-activating effect of PTH, and elevate markers of bone growth (228, 241–244). In experimental animals, 5α-DHT especially stimulates periosteal (appositional) skeletal growth and thereby increases cortical bone formation (228, 245–247). However, available data are not facile to interpret, because 5α-reduced products of testosterone activate the androgen receptor and simultaneously impede estrogen action in some tissues (248–250). In the human, the androgen receptor may mediate up to 30% of sex steroid-induced skeletal remodeling, as inferred by combined administration of a down-regulating dose of a GnRH agonist, testosterone, and placebo, or an aromatase-enzyme inhibitor in healthy older men. In the sex steroid-depleted setting, transdermal repletion of testosterone or estradiol alone suppressed indices of bone resorption, increased markers of bone formation, and stimulated production of osteoprotegerin, a potent inhibitor of osteoclastogenesis (below). Each of the effects of testosterone was blunted by pharmacological aromatase blockade, with the exception of increased synthesis of osteocalcin, a marker of osteoblast function. Comparable mechanistic investigations of sex steroid-specific control of skeletal development are not available in childhood. Moreover, no studies have extended discrete receptor agonist and antagonist analyses over prolonged intervals (years) in the human.

3. Estrogenic effects. Estrogenic steroids repress osteoclastogenesis, promote epiphyseal maturation, stimulate endosteal and trabecular bone formation, augment mineralization, and increase tensile bone strength (136, 137, 211, 240, 251–254). Selective estrogen receptor (ER) modulators (*e.g.*, raloxifene) appear to act analogously (but not necessarily identically) to enhance overall bone mineral content. Estrogen supplementation also stimulates the intestinal absorption and skeletal retention of calcium, which processes contribute to bone mineralization (255–257). Estrogens drive proliferation and differentiation of the entire osteoblastic-cell lineage; enhance the anabolic actions of other trophic signals (*e.g.*, PTH, GH, IGF-I, and prostaglandin E_2); limit osteocyte apoptosis; inhibit osteoclastic resorption under osteolytic stress (*e.g.*, by PTH, prostaglandin $F_2\alpha$, interferon γ, IL-1, and TNF-α); and induce osteoblast synthesis of osteoprotegerin. The last-named glycoprotein is a potent inhibitor of osteoclastogenesis and inducer of osteoblast cytodifferentiation (77, 136, 245, 251, 258–262).

4. ER subtype and aromatase-enzyme expression. Gene transcripts encoding truncated and full-length ERα and ERβ are detectable in osteoprogenitor cells, differentiated osteoblasts, and mature osteocytes (259, 263, 264). Expression of ERβ predominates in immature bone and wanes with skeletal maturation (265, 266). As highlighted in Table 2, inactivating mutations of ERα or the aromatase gene (but not ERβ) cause severe osteoporosis and impair epiphyseal mineralization in the human and mouse (10, 237, 240, 243, 244, 246, 267–270). In several patients with rare inborn aromatase deficiency, repletion of estradiol stimulated prompt epiphyseal maturation and bone mineralization, whereas testosterone supplementation did not (243, 271). Albeit less well studied, certain molecular polymorphisms of the estrogen-receptor gene also predict reduced BMD epidemiologically.

Experiments based on short-term pharmacological inhibition of the aromatase enzyme are consistent with genetic inferences. In older men and aged male rats, administration of specific aromatase antagonists increased biochemical markers of bone resorption and (where assessed in the ro-

TABLE 2. Skeletal changes associated with genetic inactivation of ER, androgen receptor (AR), or aromatase enzyme

Gene knockout	Skeletal change
ERα	↓ ↓ Trabecular/cancellous bone (human and mouse); ↓ ↓ cortical bone, male > female (mouse)
ERβ	No human data; NL male (mouse); ↑ female cortical bone (mouse)
AR	NL rodent; ↓ bone volume (human)
Aromatase enzyme	↓ ↓ Skeletal mass; ↑ markers of bone turnover (human and mouse)

Arrows denote relative changes compared with wild-type. See text for detailed discussion and references. NL, Normal.

dent) impaired the pubertal gain in skeletal calcium and (in the human and rodent) accelerated the age-related decline in mineral density (242, 246, 272, 273). One prospectively randomized study in boys with constitutionally delayed puberty combined placebo or a potent, orally active, selective aromatase-enzyme inhibitor (letrozole) with testosterone supplementation. The combination delayed radiographic bone maturation significantly compared with testosterone administration alone.

Interpretation of target-tissue responses to ostensibly isolated interruption of a single sex-steroid signaling pathway *in vivo* is not straightforward, as indicated by the following considerations. First, in one analysis, supplementation with testosterone partially restored appendicular skeletal size in the orchidectomized mouse harboring transgenetic inactivation (knockout) of the ERα subtype (α-ERKO model) (240). In a strict technical context, this novel finding might be explained by androgen-receptor and/or ERβ-mediated drive of longitudinal bone growth; confounding by supraphysiological androgen addback; and/or species, gene-dosage, or strain effects inherent in the transgenic model (101, 165, 174, 235, 243, 253, 264, 274). Second, pharmacological muting of sex-steroid negative feedback in the human and rodent stimulates (systemic) testosterone and estradiol secretion by 1.5- to 3-fold, thereby secondarily altering the systemic sex-hormone milieu (275–279). Third, androgen and estrogen exert both delayed genomic and rapid nongenomic effects on diverse target cells. Such bipartite actions mediate an array of complementary neuronal and extraneuronal effects. For example, in the central nervous system, estrogen acts on membrane receptors that facilitate IGF-I signaling via Akt and MAPK, thereby plausibly altering negative feedback by peripheral IGF-I (280–282). Fourth, androgens and estrogens regulate sex-steroid metabolism by inducing or inhibiting aromatase, 5-α reductase and 17β-hydroxysteroid dehydrogenase isoenzymes, which interconvert androgens and estrogens. Fifth, age and gender appear to influence the skeletal effects of aromatase deficiency in transgenic murine models (246). Sixth, species modulates neuroendocrine adaptations to the sex-steroid milieu; *e.g.*, estradiol but not 5α-DHT in the human (and, conversely, in the rodent) drives GH secretion (127, 128). GH output is significant as a stimulus of both systemic and skeletal synthesis of IGF-I (166). Seventh, inactivation of ERα in the mouse depletes systemic IGF-I concentrations (237). Transgenic depletion of blood-borne IGF-I indicates that this peripheral source of growth-factor drive also contributes to adult bone growth (283). Eighth, androgen depletion heightens the capacity of estrogen to stimulate osteoblastic synthesis of the potent osteoclastogenesis-inhibiting peptide, osteoprotegerin (251, 259, 284–286) (Fig. 10). And, lastly, the relative availabilities of estrogen and androgen can determine promoter-specific gene transcription due to incompletely characterized heterologous interactions among ERα, truncated ERα, ERβ, and the androgen receptor (237, 240, 243, 287–292). In view of extensive complementation of osteogenic and osteolytic signals, the biological effects of interrupting the action of a single agonist-receptor linkage, such as disabling ERα, could reflect nonexclusively: 1) impairment of ERα-dependent drive; 2) collateral actions via ERβ and/or the androgen receptor; 3) reduced availability of systemic and *in situ* IGF-I; 4) altered sex-steroid synthesis and metabolism; and/or 5) heterologous receptor-receptor interactions.

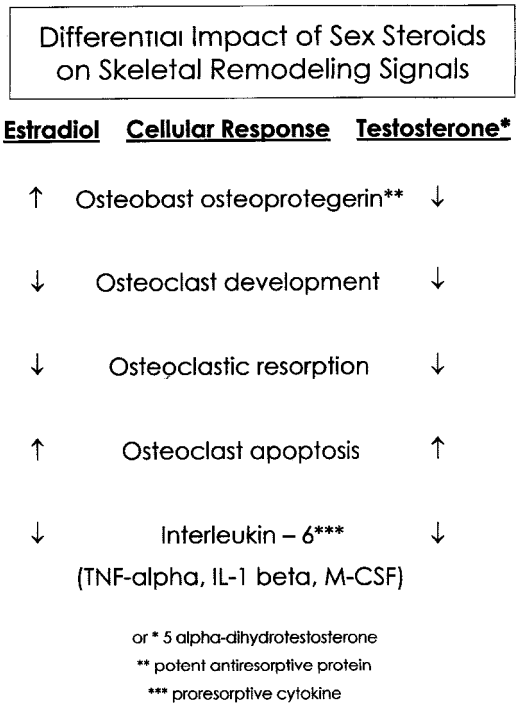


FIG. 10. Schematic summary of roles of estradiol and testosterone inferable on key stages in bone remodeling.

5. GH and IGF-I. GH, IGF-I, IGF-II, and IGFBPs control growth, remodeling, and mineralization of the skeleton in part via direct actions on bone (7, 241, 293–302). A classic study showed that unilateral infusion of GH into the tibial artery of the GH-deficient male rat stimulates ipsilateral longitudinal bone growth. Mechanistically, GH drives a number of local bone effects; *viz.*, skeletal IGF-I synthesis; proliferation of prechondrocytes; hypertrophy of osteoblasts; bone remodeling; and net mineralization (after a time lag of 1–2 yr in the human) (101, 303–305). In addition, exogenous GH suppresses osseous production of IGFBP-4 (which antagonizes the actions of IGF-I in bone) and stimulates *in situ* synthesis of IGFBP-2, -3, and -5 (which stimulate bone cells directly and/or via IGF-I) (306–309).

Sex steroids, IGF-II, T_4, and glucocorticoids not only modulate the secretion of GH and IGF-I (127, 128), but also impact the direct effects of GH and IGF-I on skeletal growth (146, 147, 310, 311). For example, testosterone stimulates GH and IGF-I production systemically; induces IGF-I synthesis in the skeleton; enhances GH-driven IGF-I accumulation in osteoblasts; promotes epiphyseal cartilage growth; increases mineralization of bone matrix; and, augments net trophic effects of selected IGFBPs (306–308, 312, 313). Estradiol amplifies GH receptor-mediated signaling in osteocytes, up-regulates osteoblast IGF-I production, down-regulates inhibitory binding proteins (IGFBP-4 and -6), induces the type I IGF receptor in bone, and uniquely stimulates osteoblastic synthesis of osteoprotegerin, a potent antiresorptive signal that is not induced by nonaromatizable androgens (15, 136, 165, 174,

207, 237, 265, 308, 309, 313–318). Apparently joint trophic roles of GH and estradiol in bone accrual are inferable indirectly in clinical studies. In particular, maximal BMD correlates with 24-h GH concentrations in young men and with overnight GH and estradiol concentrations in the African-American (but not Caucasian) male (36, 37, 221).

Height, weight, and genetic endowment are strong epidemiological determinants of bone mineral content (191, 199). However, height and weight mirror multiple convergent genetic, environmental, and trophic-hormone interactions (319–321). The rate of skeletal calcium and magnesium accretion is maximal at ages 11–14 yr in girls and 16–18 yr in boys (322–324). On the other hand, total IGF-I, but not sex-steroid, concentrations reach a zenith 1.5–2 yr later. In young women, 99% of maximal BMD and 99% of total mineral content are attained at ages 22 ± 2.5 yr and 26 ± 3.7 yr, respectively (325). Skeletal mass at age 20, which amalgamates the conjoint impact of height, weight, environment, and genetics, predicts more than 50% of the statistical variability in bone mineral content in later adulthood (326). Nonetheless, some bone growth and mineralization continue in selected skeletal sites into the fourth or fifth decade of life (56, 188, 221, 323, 325, 327).

In hyposomatotropic children and adults, GH replacement therapy facilitates the timely onset of sexual development and therewith increased sex-steroid secretion (140). GH treatment in such patients uniformly elevates biochemical indices of bone remodeling (within weeks), promotes marked (so-called catch-up) linear growth in the first year, augments skeletal mineralization after 1.5 to 2 yr, and (in children) increases final adult stature (97, 241, 298, 328–334) (Table 3). Albeit less well documented, administration of IGF-I also stimulates bone growth, skeletal remodeling, and mineral deposition in the IGF-I-deficient setting in man and animals. Estrogen blunts the actions of GH on biochemical markers of skeletal remodeling in the hypopituitary female, postmenopausal woman, and male-to-female transsexual patient (335–337). Estradiol replacement also attenuates the rh GH-induced rise in IGF-I concentrations and decline in visceral FM (127, 337). Whether the foregoing GH/sex-steroid interactions apply equally to other long-term tissue effects is not known.

TABLE 3. Primary actions of GH and sex steroids on body composition[a]

	GH	Estradiol	Testosterone
Visceral fat[b,c]	↓ ↓	[d,e]	↓
Subcutaneous fat[b,f]	↓	↑	↓
Bone mineral[b,g]	↑	↑ ↑	↑ ↑
Muscle mass[b,c]	↑	[d]	↑ ↑
Extracellular water	↑ (acutely)	[d]	↑ (acutely)
Linear bone growth[b,c,g]	↑	↑ ↑	↑ ↑
Epiphyseal fusion[c,g]	[d]	↑ ↑	↑ ↑
Energy expenditure	↑	[d]	↑ ↑

[a] Refs. 194, 244, 393, 562–571.
[b] Possible synergy between somatotropic and gonadotropic signals.
[c] Nonaromatizable androgens also effectual.
[d] Limited or inconsistent data.
[e] Only in combination with a (synthetic) progestin.
[f] May differ in children and adults.
[g] Maximal effects require aromatization.

Genetic GH receptor defects and primary IGF-I deficiency states are associated with osteopenia, sarcopenia, and visceral adiposity in the adult (338). In the GH receptor-defective patient, replacement therapy with rh IGF-I facilitates the onset of pubertal development and stimulates musculoskeletal growth (339). Nonetheless, systemic delivery of IGF-I does not normalize growth velocity or body composition in children with inborn GH receptor defects. The precise factors that account for incomplete tissue responses in this setting are not yet evident (141, 340–348). One consideration is that GH and IGF-I exert both singular and combined trophic effects in a target tissue-specific fashion (349–357). For example, GH but not IGF-I induces synthesis of the complete 150-kDa ternary complex comprising IGF-I, IGFBP-3, and the acid-labile subunit (358). Systemic concentrations of the ternary complex correlate well with somatic growth in normal puberty and during GH treatment in hyposomatotropic children (338). Conversely, hepatic-specific IGF-I-deficient transgenic mice exhibit diminished BMD in adulthood despite elevated GH concentrations (283). The latter important observation suggests that postnatally induced IGF-I deficiency impairs skeletal growth in the rodent. In support of this experimental inference, peripheral IGF-I administration can stimulate markers of skeletal remodeling and increase BMD.

6. Multisignal endocrine control. Sex steroids, GH, IGF-I, cortisol, T_4, and other systemic hormones act on bone collaboratively via potent local effector molecules, such as IGF-I/IGFBPs, cytokines, prostaglandins, and osteoprotegerin. This nonexclusive ensemble of *in situ* regulators directs skeletal growth (increased volume), remodeling, and mineralization (259). The importance of multihormonal trophic control of bone growth and maturation is illustrated in children with Turner syndrome. Osteopenia in this setting is attributable to 3-fold deficiency of estrogen, GH/IGF-I, and androgen along with important but incompletely characterized genetic factors that disrupt bone development. TBW in gonadal dysgenesis is reduced detectably in the third decade, and fracture risk is increased significantly by the fourth decade of life (40, 77, 136, 137, 201, 243, 359–363). Clinical interventional trials have combined physiological estrogen replacement (based on developmental age), dose-titrated repletion of androgen, and supraphysiological amounts of GH to accelerate height velocity. Final statural gain in Turner syndrome is influenced principally by age at initial treatment, duration of hormonal intervention, doses of GH (higher) and androgen (low), degree of growth failure, and incompletely defined genetic factors (98, 175–177, 209, 210, 232, 233, 364, 365).

C. Adiposity and sex-steroid hormones

Sex-steroid hormones, GH, insulin, glucocorticoids, and β-3 adrenergic agonists are dominant determinants of adipocyte mass (Fig. 11). A corollary thesis is that fat topography is controlled by regionalized expression and activity of sex steroid-metabolizing enzymes, growth factors, and cognate receptors (366–368). For example, estradiol receptors predominate in mammary and gluteofemoral fat, whereas androgen receptors are more abundant in intraabdominal (omental) fat (367). At the level of target cells, GH, β-3-

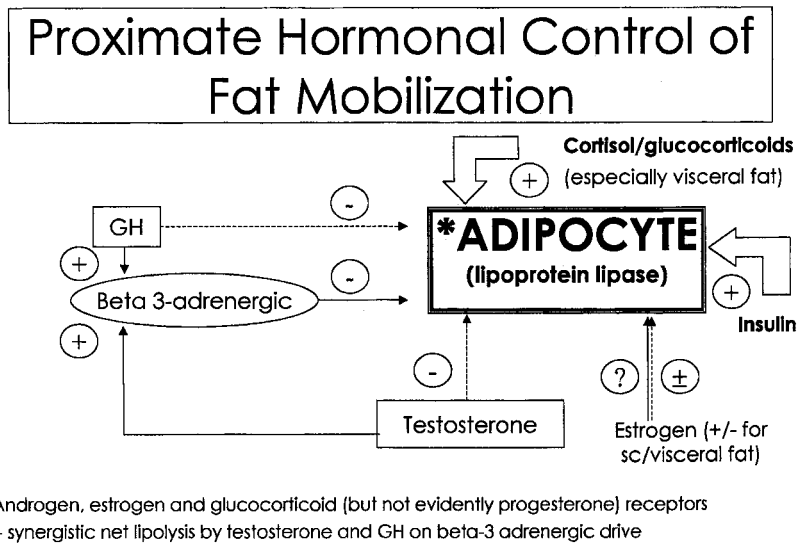


FIG. 11. Simplified schema of the conjoint effects of GH, testosterone, estradiol, and β-adrenergic signaling on human adipose tissue. Unpublished compilation.

adrenergic agonists, and testosterone induce greater lipolysis of visceral than sc adipose tissue. In contradistinction, insulin and cortisol stimulate lipogenesis in diverse fat depots (76, 100, 365–367, 369–372).

The liporegressive actions of testosterone reflect the 4-fold ability of androgens to: 1) amplify the direct lipolytic effects of GH and adrenergic agonists; 2) up-regulate androgen receptors homologously (positive autofeedback effect) and β-3 adrenergic receptors heterologously (sensitization effect); 3) oppose the lipogenetic effects of insulin and cortisol; and 4) inhibit lipoprotein lipase-dependent esterification of triglycerides, which biochemical step is required to enlarge fat cells (253, 351, 365, 373–377). Collectively, such mechanisms could contribute to pubertal redistribution of fat stores. However, the details of such putative actions have not been mapped.

Estradiol up-regulates its own receptor and that of insulin in fat cells *in vitro* and *in vivo* (378, 379). These effects would be consistent with the statistical association between (unopposed) estrogen replacement therapy and intraabdominal adiposity in postmenopausal women (366, 380). However, correlations may be invidious, inasmuch as the route of estrogen supplementation also determines the magnitude of metabotropic effects; *e.g.*, oral compared with transdermal estradiol replenishment inhibits lipid oxidation more (thereby predisposing to fat retention) and blocks glucose disposal less (thus facilitating insulin action and fat synthesis) (98, 381). Conversely, a history of combined use of estrogen and a synthetic progestin postmenopausally predicts less visceral fat accumulation (98, 175, 177, 180, 382, 383). The apparent lipolytic effect of adding a synthetic progestin may be due to weak intrinsic androgenicity of such agents. According to this reasoning, greater availability of androgens in menstruating than ovariprival women may contribute to relatively less intraabdominal (visceral) fat (365, 383, 384). In addition, nonwithdrawal of adrenal androgenic sex steroids during long-term GnRH agonist therapy of precocious puberty may account for some changes in total body fat despite estrogen depletion (73, 385).

Estradiol inhibits proliferation of immature fat cells via ERα and stimulates growth of preadipocytes via ERβ (366). The foregoing distinction applies in the rodent, inasmuch as transgenetic α-ERKO and aromatase knockout induce hyperplasia and hypertrophy of (white) adipocytes with a resultant 80–100% increase in total body fat (368, 386). Conversely, high-dose estradiol administration in the immature mouse, rat, and cow reduces FM. The topography of adipose tissue presumably depends further on (nonexclusively) tissue-specific differences in the expression of α- (inhibitory) and β- (stimulatory) ER, aromatase enzyme, 11-hydroxysteroid dehydrogenase (types I and II), and 17β-hydroxysteroid dehydrogenase (isotypes 2 and 3) (384). The foregoing enzymes control interconversion of testosterone and estradiol, as well as cortisol and (inactive) cortisone. Understanding how the ensemble of IGF-I, GH, insulin, cortisol, sex steroids, adipocyte topography, gender, and species determines regional and total FM in pubertal development presents a daunting investigative challenge.

D. Adiposity and GH/IGF-I

GH increases lipolysis acutely (within minutes), and decreases adiposity over the short-term (days to months) in children and adults (387, 388) (Table 3). The whole-body lipolytic effect of a given dose of GH is attenuated in estrogen-replete young or postmenopausal women compared with estrogen-insufficient women and androgen-sufficient men (175, 180, 345). Such distinctions suggest that estrogen induces partial resistance of adipose tissue to GH. In one mechanistic analysis of this relationship, estradiol down-regulated GH signaling *in vitro* by inducing cellular expression of the negative-feedback signal, suppressor of cytokine signaling (389).

GH induces rapid loss of fat due to stimulation of lipolysis and reciprocal antagonism of the lipogenetic actions of insulin (97, 119, 175, 299, 339, 353, 390–395). Although the initial reduction of adipose-tissue mass persists during continued GH replacement in hyposomatotropic patients, the rate of decrease in FM slows over time. The basis for evident

down-regulation of fat-cell responsiveness to the lipolytic action of GH is not well defined.

GH replacement therapy in the adult initially elevates (days to weeks) and then suppresses (months to years) insulin and leptin concentrations. The delayed decline in insulin and leptin concentrations parallels a gradual reduction in visceral fat and total adiposity induced by exogenous GH (98, 144, 180, 299, 351, 391, 396–400). The key lipolytic role of GH is indicated in a murine model of transgenically enforced postnatal depletion of liver-derived IGF-I concentrations. In this experimental context, hypersecretion of GH reduces total-body fat in the face of elevated leptin and insulin concentrations. Hepatic IGF-I gene silencing also impairs muscle sensitivity to insulin and stimulates hepatic gluconeogenesis. Such outcomes would secondarily modulate *in vivo* glucose and fat metabolism (401, 402).

Mature adipocytes express GH, but not IGF-I, receptors (338). Indeed, in clinical studies, combining rh IGF-I and GH replacement fails to reduce FM further (355). In addition, long-term rh IGF-I treatment of children with GH receptor defects decreases intraabdominal FM only over the first 6 months of therapy (339). A plausible notion is that this short-lived liporegressive effect reflects IGF-I action on less mature fat cells and/or the known capability of exogenous IGF-I to suppress endogenous insulin secretion (403).

Adiposity suppresses GH production markedly in the human and experimental animal (59, 72, 404–408). In men and women, intraabdominal FM is a primary negative determinant of pulsatile GH secretion (71, 409, 410). On the other hand, for reasons that are not known, sc rather than visceral adiposity is a major negative correlate of GH production in children (93). However, as observed in the adult, intraabdominal adiposity in the child presages insulin resistance and dyslipidemia, and presumptively elevates long-term atherosclerotic risk (47, 76, 411). In fact, hyposomatotropism, topography of fat distribution, ethnicity, gender, sex hormones, IGF-I, IGFBP-1, and insulin concentrations jointly influence predicted risk of cardiovascular disease (58, 366).

Low GH concentrations in obesity result from reduced secretion and increased elimination rates (412, 413). In particular, adiposity in some manner represses GH secretory-burst mass, impedes the stimulatory effects of secretagogues, expands the GH distribution volume, and accelerates the metabolic clearance of GH (71, 405, 407, 409, 412–417). Reduced absolute GH secretion constitutes the major (>85%) basis for low GH concentrations in obesity (127). More rapid elimination of GH correlates with intraabdominal (upper body) rather than sc (lower body) adiposity in young women (71). The mechanistic basis for this association has not been delineated.

In the human and experimental animal, several factors appear to repress GH production in obesity: 1) direct inhibition of somatotrope secretion by elevated systemic concentrations of free fatty acids (FFAs), free IGF-I, insulin, and, less plausibly in the human, leptin (83, 418–427); 2) proximate suppression of GH release by excessive hypothalamic somatostatin outflow, which in the obese Zucker rat differs by gender; 3) impaired release and blunted actions of GHRH; and 4) an obesity-associated reduction in systemic ghrelin concentrations (17, 409, 414, 428–433). These considerations are supported in part by the increase in GH secretion in obese subjects following: 1) short-term fasting or weight reduction, which suppresses IGF-I and insulin and elevates ghrelin concentrations; 2) pharmacological inhibition of somatostatin outflow, which drives GH secretion; and 3) infusion of GHRH and/or GH-releasing peptide (GHRP), which stimulates GH release (420, 429, 432, 434–437). Notably, none of the foregoing individual interventions is able to reinstate GH output equivalently in the obese and lean individual. However, the combination of L-arginine (to repress somatostatin) or acipimox (to block FFA release) and GHRH or GHRP will induce significant GH secretion in obese subjects, which outcome is consistent with a presumptively multifactorial basis for relative hyposomatotropism (127, 128). In fact, all three of the insulin, FFA, and free IGF-I concentrations are elevated in the obese adult, thus conferring potentially combined repression of GH secretion (430).

Acute nutrient deprivation in obese volunteers fails to stimulate maximal GH release (127). Attempting to interpret this outcome illustrates the complexity of metabolic control of the GH-IGF-I axis. For example, fasting lowers insulin and free IGF-I concentrations, thereby potentially disinhibiting feedback on GH output. At the same time, nutrient deprivation increases FFA concentrations, which presumptively suppress somatotrope secretion (76, 423, 438–443).

Linear growth appears to be accelerated in obese children. The precise basis for this observation is unknown. However, unbound IGF-I concentrations are elevated in the obese human, which is presumably due to hyperinsulinemia-dependent suppression of hepatic IGFBP-1 production (100, 439). Elevated total and free IGF-I concentrations correlate with exogenous IGF-I-induced inhibition of GH secretion in individuals of normal body weight (282, 419, 444, 445). Conversely, partial (34%) reduction of total IGF-I concentrations by hepatic GH receptor blockade with pegvisomant amplifies GH secretory-burst mass significantly (by 1.8-fold) in healthy young adults (280, 281). Likewise, liver-specific postnatal IGF-I gene inactivation in mice and a single case of mutational truncation of the IGF-I gene in the human increased GH concentrations by 2- to 10-fold and more than 30-fold, respectively (358, 401). These ensemble data would support the postulate that excessive IGF-I availability contributes to reduced GH secretion in obesity.

The role of hyperinsulinemia in promoting skeletal growth or in repressing GH secretion in obesity is not clear. In the latter context, free IGF-I and insulin concentrations both correlate inversely with GH output (430). For example, in one study, an acute euglycemic hyperinsulinemic clamp that achieved insulin concentrations observed in fasting obese adults did not inhibit GH secretion in healthy young men (419). This important outcome does not exclude the corollary notions that: 1) insulin may potentiate IGF-I feedback inhibition; and 2) more prolonged hyperinsulinemia may suppress GH secretion. Such issues are relevant in view of indirect clinical data that are consistent with negative feedback by both insulin and IGF-I (426, 427, 440, 444, 446, 447).

Marked weight loss is required to normalize suppressed GH secretion in obese individuals (448). For example, several weeks of caloric restriction, which were sufficient to reduce visceral FM by more than 30% in obese premenopausal

women, failed to reinstate normal 24-h GH production (71). This outcome raises the question whether intraabdominal obesity and hyposomatotropism arise individually, exacerbate each other, or reflect a common defect in metabotrobic or appetite-regulating signals (17, 71, 366, 368, 418, 449–451). Knowledge of this issue could aid in formulating how long GH replacement should be continued in adult GH-deficient patients with visceral adiposity and increased cardiovascular risk defined on *a priori* epidemiological grounds. A corollary interventional query in children with idiopathic visceral obesity is the possible utility of short-term supplementation with rh GH. The question is made difficult by possible toxicity, significant cost, uncertain compliance, unknown perpetuity of therapy, and the availability of alternative treatments that reduce intraabdominal FM, enhance peripheral insulin sensitivity, and engender more favorable lipid profiles (32, 65, 98, 144, 348, 351, 391, 396, 399, 452–460).

In the human, monkey, sheep, dog, and guinea pig, fasting stimulates GH secretion. These responses contrast with those in the rodent, in which caloric deprivation represses GH production (127, 357, 391, 442, 461–470). The basis for the latter clarion species difference remains to be clarified.

E. Control of muscle by sex steroids and GH/IGF-I

Few prospective interventional studies have examined the impact of sex steroids and GH/IGF-I on muscle mass and function in infancy, childhood, or puberty. In one analysis, short-term testosterone supplementation in prepubertal boys increased whole-body proteolysis by 18%, reduced amino-acid oxidation (catabolism) by 49%, and stimulated net protein synthesis by 35% (211). In laboratory experiments, androgens promote hypertrophy of type IIA (rapid-twitch, glycogenolytic, highly oxidative) muscle fibers and protect against immobilization-induced muscle atrophy (210). Physiological amounts of testosterone stimulate lean-tissue accrual, augment total muscle volume, accelerate protein synthesis, retard protein breakdown, increase isokinetic strength and induce *in situ* muscle IGF-I gene expression in hypogonadal boys or men (23, 167, 201, 209–211, 370, 471–478). However, pharmacological doses of androgen are required to enhance isometric strength or maximal aerobic capacity in eugonadal young adults. This distinction could indicate that euandrogenemia operates near or above the genetically determined upper bound of the physiological testosterone concentration-muscle response function (334, 370, 473). According to the foregoing collective data, increased androgen availability in puberty would provide a proximate (but nonexclusive) stimulus to muscle growth (25, 479) (Table 3). On the other hand, estrogen repletion does not measurably affect whole-body protein synthesis or oxidation in combined estrogen- and androgen-deficient (ovariprival) girls with Turner syndrome (480, 481). These data suggest that endogenous androgens may be required to drive pubertal anabolism in girls.

Androgens and muscle loading stimulate myofibrillar protein synthesis, myoblast proliferation, and myocyte hypertrophy (211, 392, 471, 482). Anabolic and growth-promoting effects of testosterone and muscle contraction occur in significant part via the induction of *in situ* IGF-I and the inhibition of IGFBP-4 gene expression (472). One study in older men reported that repletion of testosterone also transiently induced the androgen-receptor gene in muscle (472). The significance of this finding has not been demonstrated. Intramuscular IGF-I accumulation driven by testosterone and other factors promotes myoblast proliferation from satellite cells and stimulates myocyte hypertrophy, as established by direct local infusion of IGF-I peptide into senescent skeletal muscle and transfer of the recombinant IGF-I gene into developing smooth muscle, respectively (212–214, 483–486).

Testosterone induces expression of the myostatin gene in skeletal muscle. Myostatin is a 26-kDa glycoprotein that opposes myocyte apoptosis (215, 486, 487). Mutations of the myostatin gene result in marked muscle hypertrophy in the transgenic mouse and in the Belgian double-muscled Piedmontese cow. Muscle unloading and catabolic syndromes like AIDS-associated wasting also stimulate skeletal-muscle myostatin gene expression (488). The foregoing adaptations were postulated to reflect compensatory autocrine or paracrine mechanisms in muscle. However, the nature of such mechanisms is elusive. In a small number of studies, administration of either GH or IGF-I in elderly humans did not consistently up-regulate this antiapoptotic signal (489, 490). Therefore, additional studies will be required to clarify precisely how testosterone and GH promote myostatin-dependent and -independent muscle growth (392).

Anabolism occurs when the rate of amino-acid incorporation into proteins exceeds that of oxidative metabolism (392). Net protein accumulation is determined positively by amino-acid availability, muscle loading, and the myotrophic hormones, GH, IGF-I, and testosterone. Protein loss is accentuated variously by: 1) amino-acid depletion (491–493); 2) aging (472, 493–495); and 3) systemic inflammatory disease (496). Systemically delivered hormones stimulate protein synthesis (androgen, GH, and high plasma concentrations of IGF-I) and/or retard protein breakdown (testosterone and lower blood-borne concentrations of IGF-I and insulin) (124, 201, 253, 334, 349, 453, 472, 476, 496–502). In one analysis, exercise enhanced the biosynthesis of myofibrillar proteins in part by enhancing translation of existing mRNA.

Testosterone supplementation promotes whole-body nitrogen retention in eugonadal and hypogonadal men and in individuals with heightened catabolism; *e.g.*, fasting, AIDS-associated muscle wasting, and severe burns (166). Administration of GH or IGF-I increases lean body mass in organically hyposomatotropic patients (356, 393) and limits protein catabolism in patients with multiorgan failure, major surgery, protracted critical illness, male hypogonadism, and glucocorticoid excess (357, 392, 499, 500, 503–509). In a recent study in postmenopausal women, supplementation with rh GH for 6 months stimulated whole-body protein synthesis and breakdown by 9 and 8%, respectively; and administration of a high dose of rh IGF-I increased the same measures by 18 and 17%, respectively. Although net protein synthesis rose by 48% (GH) and 196% (IGF-I), exact comparison of GH and IGF-I dosimetry in the human is not yet possible. The importance of continuing trophic peptide drive is evident in young-adult hypopituitary patients, in whom discontinua-

tion of GH replacement therapy results in measurable attrition of muscle mass (510).

An implicit clinical thesis is that testosterone, GH, and IGF-I promote anabolism synergistically (323, 511–515). This concept has not been explored definitively in human pubertal physiology (Table 4). In particular, the precise cellular and molecular mechanisms that transduce putative hormonal synergy are unexplained.

IV. Energy Expenditure in Puberty

Energy expenditure is quantitated by way of whole-room calorimetry, portable closed- or open-circuit calorimetry, and the metabolism of doubly labeled water (387, 408, 516–518). The benchmark method has been quantitation in a closed respiratory chamber (519). Calorimetry relies on the respiratory quotient (ratio of oxygen and carbon dioxide content in expired air) (72). Portable systems are used commonly, but may be less reliable in children or apprehensive adults (516). The innovative doubly labeled-water technique can be applied in community-dwelling individuals to monitor total energy utilization during normal daily physical activity and rest (293, 519).

Energy expenditure over 24 h reflects principally basal metabolic costs (517). Energy is expended at rest to maintain core body temperature via heat generation in internal organs (liver, kidney, muscle, fat, and brain). Heat production proceeds through mitochondrial uncoupling protein (UCP), such as muscle UCP-3, and in the maintenance of transmembrane ionic gradients and other ATP-dependent metabolic reactions. Nonbasal contributions to energy balance arise from the thermogenic effects of metabolizing glucose and mixed nutrients (specific dynamic action of food) and physical activity (520–522). In correlational studies, FFM and aerobic exercise capacity are the principal positive determinants of resting energy expenditure (518, 523, 524). Fasting leptin concentrations also predict basal energy expenditure to some degree (525). Although a causal relationship is not established in the human, leptin promotes central sympathetic outflow experimentally, which in principle would elevate basal energy expenditure (526). In young adults, acute aerobic exercise increases energy expenditure without altering leptin concentrations (527).

Healthy aging, food restriction, and limited physical activity lower total energy expenditure (520, 528–531). Resistance exercise, aerobic physical training, and sympathoadrenal outflow stimulate energy utilization in an age-, nutrient-, gender-, and ethnicity-related fashion (521–523, 532, 533). In the human, endurance training drives heat production, enhances insulin action, increases noradrenergic outflow, augments maximal oxygen consumption, elevates 24-h GH secretion, facilitates muscle glucose uptake, reduces visceral FM, and lowers leptin concentrations (520, 532, 534, 535).

Longitudinal analyses will be important to clarify the precise impact of sexual maturation and gender on energy expenditure, inasmuch as current data are limited and contradictory. For example, in a study of adolescent girls, the resting metabolic rate (adjusted for FFM) averaged 1418 ± 186 kcal/d before puberty, tended to decline in early puberty, and then decreased significantly to 1179 ± 189 kcal/d 4 yr after menarche (536). In another comparison of 12- to 14-yr-old children, resting energy expenditure was significantly higher during adolescence than before puberty (537).

Resting energy utilization under free-living conditions is lower in women than men (293). The gender distinction presumably reflects the capacity of testosterone, nortestosterone, and to a lesser degree androstenedione or DHEA to significantly augment basal energy expenditure (524, 538, 539). In addition, energy expenditure rises consistently (by 4–16%) in the luteal phase of the normal menstrual cycle (540–545) and falls in amenorrheic states (546). Whether increased progesterone or androgen availability contributes to the former association is not evident. In women, estradiol does not affect the basal metabolic rate or whole-body anabolism (408, 547). However, transgenic disruption of ERα in the male mouse significantly (11%) reduced basal energy expenditure via unknown mechanisms (368).

Energy expenditure is normal in GH-deficient patients, when data are corrected for age, gender, and FFM (398, 548). Nonetheless, GH replacement therapy in hyposomatotropic patients and obese individuals elevates the basal metabolic rate significantly by within-subject comparison (393, 398, 549, 550). GH administration in hyposomatotropic adults is associated with: 1) increased expression of mitochrondrial UCPs (551); 2) early stimulation and delayed suppression of leptin concentrations (387, 525, 552); 3) accrual of lean-body tissue and recession of intraabdominal FM (387, 398, 550, 553); and 4) enhanced conversion of T_4 to T_3 by 3′-monodeiodination in peripheral tissues (549, 553, 554). At present, the impact of rh IGF-I on energy expenditure is not well studied. In one investigation, acute infusion of this growth factor did not stimulate energy expenditure in the parenterally fed rat.

TABLE 4. Illustrative unresolved issues in mechanisms of pubertal activation of somatotropic and gonadotropic axis

- Molecular factors that mediate populational diversity
- Cellular factors that govern the timing and progress of puberty
- Basis for decline in GH/IGF-I production postpubertally
- Interactive control by ghrelin, GHRH, and somatostatin
- Mediators of ethnic diversity in GH/IGF-I and GnRH/LH secretion
- Biological impact of species distinctions in control of somatotropic and gonadotropic axes

V. Summary

Body composition adapts across the *in utero*, neonatal, pubertal, and adult lifetime in an ethnicity- and gender-related fashion. The present review highlights these developmental adaptations and illustrates how signals from the gonadotropic and somatotropic axes singly and jointly govern accrual and depletion of muscle, fat, and bone mass. These emerging concepts should enlarge the platform of critical clinical and basic-science investigations of this developmental theme.

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