Adolescent growth and maturation in zinc-deprived rhesus monkeys1–4

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ABSTRACT Growth retardation has been associated with zinc deficiency in adolescent human populations, but animal models were not available previously to explore this syndrome. Moderate dietary zinc deprivation (2 µg Zn/g diet) was introduced in female rhesus monkeys (Macaca mulatta; n = 10) from the beginning of pubertal through menarche. Subgroups of animals (n = 4) continued to be fed the zinc-deficient diet through 45 mo of age (sexual maturity). Reduced weight gain and linear growth and lower plasma zinc concentrations (11.8 ± 0.6 and 9.2 ± 0.8 µmol/L in control and zinc-deficient monkeys, respectively) were evident during the premenarcheal growth spurt. Slower skeletal growth, maturation, and mineralization were recorded in the postmenarcheal period and some indicators of sexual maturation were delayed. Food intake was slightly higher in the zinc-deficient group than in controls. These data confirm that adolescent growth and maturation are vulnerable to disruption by moderate dietary zinc deprivation in nonhuman primates. Am J Clin Nutr 1996;64:274–82.

KEY WORDS Zinc deficiency, diet, female rhesus monkeys, adolescence, skeletal maturation, bone mineralization, puberty

INTRODUCTION

The essentiality of zinc in humans was noted dramatically in the 1960s by a syndrome of growth retardation and arrested sexual maturation in adolescent boys in the Middle East, which could be reversed by dietary supplements including zinc (1–4). A similar syndrome that responded to zinc supplementation was described in two female subjects (5). Subsequently, it has been recognized that periods of rapid growth, such as the third trimester of pregnancy, infancy, and adolescence are particularly vulnerable to dietary zinc deprivation. However, no animal model has been developed to firmly identify a causative role for dietary zinc deprivation in this adolescent syndrome and to explore its relevance to human health at the degrees of zinc deficiency that are common in human populations.

Recent data indicate that 81% of adolescent girls consume less than the recommended dietary allowance (RDA) for zinc and 59% consume < 77% of the RDA (6). Zinc deficiency can be further exacerbated by pregnancy in adolescent girls. The implications of suboptimal zinc intake in adolescence are not well understood but it could affect growth and bone maturation during the time when mature body size and proportions are attained and the larger part of bone mineralization takes place in girls (7). In addition, the normal course of sexual maturation could be delayed or altered.

Rhesus monkeys have provided a useful animal model for the study of many aspects of female puberty and adolescence, including growth and sexual maturation (8–11). Studies in nonhuman primate species are particularly valuable in understanding the relation between nutrition and pubertal growth because nonhuman primates, like humans, show a pubertal growth spurt before sexual maturation and epiphyseal closure (12, 13). The growth spurt makes heavy demands on anabolic metabolism and presumably on tissue zinc pools. Zinc deficiency may also affect growth hormone (GH) physiology and growth factor biology (14). Sexual maturation could be affected secondary to growth suppression or through direct actions on gonadal hormone regulation. Similarly, growth retardation could be secondary to hypogonadism (15).

Studies by our group of developmental zinc deficiency in nonhuman primates were extended recently to the adolescent period. The current report describes the effects of zinc deprivation on growth and skeletal and sexual maturation in zinc-deprived female rhesus monkeys. The period of evaluation began at the onset of puberty (18 mo of age) and continued through the adolescent growth spurt (27–33 mo of age) and menarche (30–33 mo of age) and, for a subsample of animals, through the postmenarcheal period to the age of full reproductive maturity (34–45 mo of age).

METHODS

Animals and evaluation schedule

Healthy prepubertal female monkeys (Macaca mulatta) were obtained from the colony at the California Regional Primate

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Research Center (CRPRC) and enrolled in the study at 18.33 ± 0.25 mo of age (based on a 30-d mo). Monkeys were assigned to treatment groups to balance age and size (body weight). They were housed in pairs in light- and temperature-regulated indoor colony rooms (48 animals per room) (16). A double cage with a partition (120 × 65 × 79 cm) allowed separation of pairs for urine collection and food intake determinations, while permitting socialization at other times. Before initiation of treatments, monkeys were acclimated to caging and purified diets over a 3-mo period, followed by baseline morphometric examinations and blood sampling.

After initiation of treatment, food intake was measured five times per week, animals were weighed and urine collected at monthly intervals, morphometric examinations and limb X-rays were made, and blood samples were collected at 3-mo intervals (quarterly). The monkeys were anesthetized with ketamine (10 mg/kg body wt) for the examinations conducted at 3-mo intervals. All animals were also involved in behavioral testing during the study period (not reported here). A daily morning health check included examination for perineal bleeding, which was recorded as menses.

The study period was subdivided relative to maturational landmarks and the annual breeding season (Figure 1). For spring-born rhesus females similar to those used in this study, menarche typically occurs during the breeding season of the 3rd year of life (30–36 mo of age) and is preceded by an adolescent growth spurt. Full sexual maturation and first pregnancy usually occur during the breeding season of the 4th year of life (42–47 mo of age). The premenarcheal period was considered to extend from 18 to 33 mo and included early puberty (18–27 mo), the growth spurt (27–33 mo), and the onset of menses (30–33 mo). The postmenarcheal period extended from 36 to 45 mo of age, through the breeding season when first pregnancy would be anticipated to occur.

All procedures conformed to the guidelines of the Animal Welfare Act and the guidelines for the care and use of laboratory animals of the National Research Council. The CRPRC is fully accredited by American Association for Accreditation of Laboratory Animal Care. Individual protocols were approved for use before implementation by the campus veterinarian under the auspices of the Animal Use and Care Administrative Advisory Committee of the University of California, Davis.

**Diet and diet administration**

Monkeys were fed a pelleted purified diet containing National Research Council recommended amounts of macro- and micronutrients (17). Preweighed 75-g portions were provided twice a day. Deionized water was available ad libitum via an automatic watering system. The zinc-adequate diet contained 50 μg (30.6 nmol) Zn/g diet as zinc carbonate, whereas the zinc-deficient diet contained 2 μg (1.5 nmol) Zn/g diet, a dietary zinc content that has been determined to produce moderate deficiency during pregnancy (17).

**Monthly weights and food intake**

Body weight was measured monthly by placing each monkey, conscious, in a transport cage on a tared scale accurate to 0.01 kg. Food intake was recorded on weekdays by counting the number of pellets remaining at the end of the day in the food hopper or drop pan (monkeys were fed at 0900 and 1600). The percentage of partially eaten pellets remaining was estimated. Food intake was summarized monthly as g/d and as g · kg body wt⁻¹ · d⁻¹ by using body weight at the beginning of the month.

**Somatic growth measures**

Body weight (to the nearest 0.01 kg), crown-rump length, arm and thigh circumferences, and skinfold thicknesses were measured as described previously (18). Crown-rump length was measured on anesthetized animals by using a thermaplastic platform with a built-in scale accurate to 0.1 cm and sliding pieces to identify the farthest points. This measurement was conducted with the animal in its natural curved trunk position. Limb circumferences were obtained with nylon thread and a ruler at the center of the triceps and thigh. Skinfold thicknesses were measured at preidentified triceps, thigh, subscapular, and suprailiac sites by using a Harpenden caliper (Quinton Instruments, Seattle).

**Bone growth and maturation**

Radiographs of left upper and lower limbs were taken at 3-mo intervals beginning at 18 mo of age. The upper limb radiographs included the shoulder through the fingertips filmed with the arm elevated over the head, the elbow extended, and the forearm and hand supinated. The lower limb was filmed in frontal projection from hip to toes with the foot plantarflexed at the ankle and the foot thereby imaged in frontal projection as well. Nonscreen medical X-ray film was used and radiographic exposure factors varied according to the part examined and the size of the animal. Long bone (femur, humerus, tibia, ulna, and radius) lengths were measured from distal to proximal epiphyses in radiographs of the left limbs. Bone widths were also measured at some ages at the calculated midshaft point. Skeletal maturation was determined from radiographs by

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**FIGURE 1.** Stages of adolescent development and changes in plasma zinc during the study period. x ± SEM; n = 10/group through 33 mo of age and n = 4/group thereafter. *Significant group differences at time point. P < 0.05.
using a modification of a human system (19) adapted for rhesus monkeys (20). Specifically, the carpal bones were omitted because of differences in size and appearance from available human standards. Additionally, because of the morphologic differences between monkey and human bones, the small size of the bones being studied, and the omission of the carpal bones, intermediate categories were added for some bones (G/H for the distal radius and F/G for the first metacarpal and proximal phalanges). The left hand and wrist bones (minus the distal phalanx of the thumb and the carpal bones) were evaluated by using diagrams, descriptions, and the weighting system developed by Tanner et al (19) to obtain total scores. In children these scores are compared with normative data to produce a "bone age". Although normative data are not available for monkeys, relative maturity of skeletal development could be compared between groups by using the scores.

Films were rated for the presence of fusion of the following ossification centers: capitellum, radial head, olecranon process, acetabulum (triradiate cartilage), femoral head, greater trochanter, distal tibia, and distal fibula. These centers were expected to fuse during the study period (21) and were visible in the single view radiographs obtained. The small bones of the hands and feet were not included in this part of the study.

Dual energy X-ray absorptiometry (DXA; model QDR-2000; Hologic Instruments, Waltham, MA) scans were conducted on monkeys anesthetized with ketamine (10 mg/kg). This method has been verified to produce an accurate reflection of mineral density in monkeys (22). Bone scans were obtained at 27 mo (n = 6/group), 39 mo (n = 4/group), and 45 mo (n = 4/group). Whole-body scans were conducted first, which provided regional information for limbs, ribs, pelvis, head, and thoracic and lumbar spine as well as whole-body totals. Instrument routines for human diagnostic scans were used after adjustment of the scan area for the smaller body size. The line spacing was 1.303 cm and the resolution was 0.102 cm. In addition, individualized scans of lumbar vertebra (L2, L3, and L4) and a femoral head were conducted by using single-beam methodology for greater accuracy. Bone mineral densities (g/cm²) were calculated for the selected areas by the appropriate Hologic software.

Sexual maturation

Nipple length and width were measured in anesthetized animals at the quarterly exams and used to compute a nipple volume measure (23). Occurrence of perineal bleeding was noted daily at the morning health check conducted by animal care personnel, categorized as light or heavy, and entered into a computer database. Printouts of menses occurrence on monthly calendars were provided by software and were examined to determine menarche (first incidence of perineal bleeding) and monthly menses (any occurrence of ≥ 2 d of menses in a 4-d period). At 39 mo of age animals were anesthetized for an ultrasound examination of the uterus. This included measurement of uterine length and uterine body length, width, and height, and ratings for maturity of appearance (shape, position, texture, and contours).

At 42–45 mo of age, urine was collected on alternate days from control and zinc-deprived groups for 60 d. When possible, urine collection was scheduled to correspond with the end of a menses period. Urine was analyzed for estradiol and pregnanediol conjugates by using monoclonal antibodies to human estrone-1-glucuronide and pregnanediol glucuronide (24). Values were indexed to creatinine. Follicular and luteal activities were determined from examination of peak conjugate values in monthly plots.

Statistical analysis

Repeated-measures analysis of variance (ANOVA) was conducted for each endpoint using dietary zinc and exam time point as the independent variables, with repeated measures on the exam time point. Separate ANOVAs were also conducted at each time point by using dietary zinc (control or zinc-deprived) as the independent variable. The ANOVA used a general linear model with type III error (SAS; SAS Institute, Inc, Cary, NC). Separate ANOVAs were conducted for the premenarcheal and postmenarcheal periods because of the different group sizes. The probability level of P < 0.05 was used to indicate statistical significance.

RESULTS

Indicators of zinc status

As shown in Figure 1, there was a circannual pattern of plasma zinc concentrations with peaks during the breeding season, as described previously (25). Plasma zinc was generally lower in the zinc-deficient group than in controls after 27 mo of age (beginning of the growth spurt) although group differences were significant only at 39 mo of age (P < 0.001) and marginally significant at 30 mo of age (P = 0.049). A comparison of plasma zinc averages during different adolescent periods showed that, values were similar in the two groups before the growth spur (12.29 ± 0.4 and 11.67 ± 0.5 μmol/L, for control and zinc-deficient groups, respectively, at the 21-, 24-, and 27-mo exams) but were lower in the zinc-deficient group than in controls during the growth spur (11.77 ± 0.59 and 9.23 ± 0.85 μmol/L, for control and zinc-deficient groups, respectively, at the 30- and 33-mo exams, P = 0.024) and also in the postmenarcheal period (12.77 ± 0.5 and 9.09 ± 0.736 μmol/L, respectively, at the 39-, 42-, and 45-mo exams, P = 0.007). Statistical analysis showed that alkaline phosphatase activity did not decrease significantly from baseline values at any time during the study in the zinc-deficient group. Reduced taste sensitivity (quinine acceptance) was noted at two biweekly sessions during the growth spur (tests 20 and 27; P = 0.009 and P = 0.024, respectively).

Animals in all groups showed a scattered incidence of alopecia and dermatitis. The two most severely growth-retarded monkeys in the zinc-deficient group consistently had alopecia at all exams after 27 mo of age (these two animals were followed through 45 mo of age). There was no consistent pattern of dermatitis seen in the quarterly exams. The dermatitis characteristic of zinc deficiency was transiently noted in zinc-deficient animals at other times.

Food intake

Mean food intake (g/d) of the zinc-deficient group was consistently higher than that of controls in the premenarcheal period (Figure 2), with significant group differences at 21–24 mo (P = 0.005). There was a decline in food intake of both groups before the growth spurt (25–27 mo) followed by an increase beyond previous amounts. The zinc-deficient group...
indicated that growth retardation was not symmetrical and weight gain was more affected than linear growth.

Subcutaneous fat (skinfold thicknesses) decreased dramatically before the growth spurt and also appeared to show a seasonal pattern with increases before the breeding season. Muscle mass (limb circumference) increased substantially in the postmenarcheal period. Few significant group differences were recorded for limb circumferences and skinfold thicknesses, although means for controls were generally above those of zinc-deficient monkeys. At 30 mo of age, the peak of the adolescent growth spurt, zinc-deficient monkeys had smaller triceps skinfold thicknesses ($P = 0.009$) and thigh circumferences ($P = 0.043$) than controls. At 36 mo of age, the sum of all skinfold thicknesses was lower in the zinc-deficient group than in controls ($P = 0.018$).

### Sexual maturation

Nipple volume (Figure 4) increased several-fold from 18 mo of age through the end of the growth spurt ($P < 0.001$), with a rapid rate of growth just before menarche (24-, 27-, and 30-mo exams). There were no diet group differences during this time period. In the postmenarcheal period, nipple volume continued to increase, showing very rapid growth at the time of the 4th year breeding season. Zinc-deficient monkeys did not show this seasonal increase and their nipple volumes were significantly lower than those of controls at 42 mo of age ($P = 0.036$). Individual data indicated that one zinc-deficient monkey did not show a maturational pattern of nipple growth during the study period.

All animals reached menarche at 29–34 mo of age, except for one zinc-deficient monkey (menarche at 36 mo of age). Uterine size and maturity as determined by ultrasound at 39 mo of age were similar in the two diet groups. The cumulative number of months with menses over the study period is shown in Figure 4. Zinc-deficient animals had fewer months with menses ($P = 0.05$) by the end of the breeding season during which they had reached menarche (April, 34 mo of age). One zinc-deficient monkey had only one instance of menses during the second breeding season, resulting in high variability in the zinc-deficient group in data collected from 42 to 45 mo.

Every-other-day urine sampling for ovarian hormone metabolites was conducted for 60 d (data not shown). Urine samples with creatinine concentrations below the detection limit were not included in the analysis. Three of the four control animals were judged to show follicular activity (estrone-1-glucuronide values $> 50 \mu g/g$ creatinine for 3 of 4 consecutive days), whereas the fourth monkey had marginal follicular activity. In the zinc-deficient group one monkey had an estrogen profile that was consistent with definite ovarian follicular activity. One other zinc-deficient monkey had an estrogen profile that was consistent with marginal ovarian follicular activity. The remaining two animals in the zinc-deficient group had no indications of ovarian follicular activity. None of these urinary hormone profiles contained evidence of coordinated follicular and luteal activity indicative of ovulatory menstrual cycles.

### Bone growth

The femur, tibia, and ulna were similar to each other in length (114–117 cm) at 18 mo of age and grew $\sim 20$ cm by the end of the premenarcheal period in controls (Figure 5). Growth

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**Figure 2.** Food intake in control and zinc-deprived rhesus monkeys during adolescence. $\bar{x}$ ± SEM; $n = 10$/group through 33 mo of age and $n = 4$/group thereafter. *Significant group differences at time point, $P < 0.05$.**

Body weight, length, and composition measures at quarterly exams

Weight and body length growth are shown in Figure 3. Diet group differences in these measures were seen during and immediately after the growth spurt: weight at 30, 33, and 36 mo ($P = 0.015, P = 0.007$, and $P = 0.013$), and body length (crown-rump + tibia length) at 33, 36, and 39 mo ($P = 0.029, P = 0.029$, and $P = 0.041$). The ponderal index (weight/ crown-rump length) appeared to diverge from control values early in the pubertal period (21 mo) but group values were significantly different only at 30, 33, and 36 mo ($P = 0.006, P = 0.013$, and $P = 0.015$). The values for the ponderal index

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**Figure 3.** Food intake in control and zinc-deprived rhesus monkeys during adolescence. $\bar{x}$ ± SEM; $n = 10$/group through 33 mo of age and $n = 4$/group thereafter. *Significant group differences at time point, $P < 0.05$.**
FIGURE 3. Somatic growth in control and zinc-deprived rhesus monkeys during adolescence. \( \bar{x} \pm \text{SEM}; n = 10/\text{group} \) in the premenarcheal period and \( n = 4/\text{group} \) in the postmenarcheal period. *Significant group differences at time point, \( P < 0.05 \).
curves of zinc-deficient monkeys for these bones began to fall behind those of controls at the 24- and 27-mo exams, but group differences were not significant in the premenarchal period (for the tibia at the 33-mo exam). Two shorter bones, the humerus (100 cm) and radius (104 cm) also grew ~20 cm between 18 and 33 mo but were not apparently affected by zinc deficiency in the premenarchal period.

In the postmenarchal period, diet group differences in bone length for the femur, tibia, and ulna were measured at several of the quarterly exams. [For the radius, marginal group differences were seen at the 36-, 39-, and 42-mo exams (P = 0.07, 0.08).] No significant group differences were recorded for any bone length at the end of the study period (45 mo of age), although group means were still lower in the zinc-deficient group. Overall gain in bone length from 18 to 45 mo was significantly lower in the zinc-deficient group than in controls for the tibia (P = 0.031) and ulna (P = 0.021) but not for other bones.

Bone widths at midshaft were compared at 18, 33, and 45 mo of age (femur and humerus only). No significant group differences were found at any time point or in the growth between time points.

Skeletal maturation

Skeletal maturation was scored at baseline and at 30, 33, 36, and 42 mo of age. Data shown in Figure 6 indicate that the zinc-deficient group had significantly lower scores than controls at 33 (P = 0.019), 36 (P < 0.0001), and 42 (P = 0.034) mo. Group differences appeared to be smaller at the last time point; maturity scores were only 90% of adult values at the last time point, and catch-up would still be possible. Delayed maturation was recorded mainly in phalanges, which had achieved a fully mature score by the end of the experiment in controls; scores for the long-bone epiphyses (radius and ulna) were similar in the two groups at the last time point. Epiphyseal closure was not yet achieved in the distal radius and ulna of controls by the end of the study period as indicated by the scoring system.

Fusion of the epiphyses at other sites occurred at ages similar to those described previously (21). Fusion of the capitellum and acetabulum was achieved by 34 mo of age and fusion of the radial and femoral head was achieved by 45 mo of age in all animals. There were no diet-group differences in age at fusion. Epiphyseal closure of the olecranon was complete in six of eight animals at the end of the study, but fusion of the greater trochanter, distal tibia, and distal fibula was seen in only a few or no animals at that time.

Bone mineralization

No significant diet-group differences were found for bone mineralization at 27 mo of age. Whole-body mineralization (excluding the head) differed for the two groups at 39 (P = 0.040) and 45 (P = 0.033) mo (Figure 6). Regional differences were recorded at 39 mo for left ribs (P = 0.0157), lumbar spine (P = 0.038), and pelvis (P = 0.006), and at 45 mo for thoracic spine (P = 0.042). Individual vertebral scans showed significant group differences at 39 but not at 45 mo for L2 (P = 0.001), L3 (P = 0.051), and L4 (P = 0.010). No group differences in bone mineralization in the hip area (femoral head) were noted at any age.

Individual patterns

The high variability in indexes of growth and sexual maturation from the 39-, 42-, and 45-mo exams was due to markedly different responses of the four animals in the zinc-deficient group. One animal had values outside the range of controls on measures of sexual maturation at 45 mo, one animal had values well within the control range, and two had values at the borderline of the control range. Plots of body weight and ponderal index showed that the most affected animals in terms of sexual differential were not necessarily the most growth-retarded.

DISCUSSION

Normal patterns of adolescent growth and sexual maturation in rhesus monkeys were observed under the conditions of the study. Data from the control group in this study were very similar to previous detailed information for rhesus females provided by Wilson et al (10, 11), and Terasawa et al (9).

This study indicates that dietary zinc can be a limiting factor in growth during adolescence, that growth restriction occurs without a decrease in food intake, and that growth begins to slow before the appearance of reduced plasma zinc concentration. Although zinc has frequently been identified as the limiting factor in linear growth in infants and children, this conclusion was based primarily on nutritional rehabilitation studies rather than on an association with dietary zinc intake at the time of growth restriction. It was interesting to note that anorexia, which is frequently reported in zinc-deprived laboratory rodents, did not appear in these monkeys. Also, although plasma zinc was lower in the zinc-deficient group than in controls, the concentrations in the zinc-deficient group did not fall outside the normal range. Thus, it is doubtful that a growth- and maturation-retarding adolescent zinc deficiency similar to that
produced in this experiment could be detected in a human population by plasma zinc measurement.

The zinc deprivation used here (2 μg Zn/g diet) has been termed moderate because clear signs of zinc deficiency only appeared in association with rapid growth [late pregnancy (17) and adolescence]. In a previous experiment with male rhesus monkeys, a marginal dietary zinc content of 4 μg Zn/g was fed from conception through adolescence and a transient delay in adolescent growth was noted without other signs of zinc deficiency (26). This shows the narrow range between marginal and moderate deprivation in nonhuman primates.

The dietary zinc content used in this experiment cannot form a basis for estimating adequate zinc intakes for human adolescents. The use of zinc as zinc carbonate in a purified diet maximizes gastrointestinal absorption. In comparison, zinc in foods is bound to protein and cell constituents, and zinc ion released during digestion can be complexed to other natural ligands in the gut. A much higher dietary zinc content than 2 μg/g dry weight in natural
foods might still be inadequate to support adolescent growth and maturation in humans. The current RDA for adolescent girls is 12 mg/d or ~24 μg Zn/g dry weight of food.

Zinc deprivation did not prevent puberty, although one zinc-deficient animal failed to reach menarche at the expected age, and follicular activity comparable with that of controls was not apparent in two other zinc-deficient monkeys at the end of the study period. Thus, although sexual maturation was influenced by the zinc deprivation, a syndrome of arrested sexual maturation similar to that described for humans was not produced. It is not clear what proportion of zinc-deprived individuals in these human populations may have experienced arrested sexual development but the present study suggests that this could occur in a sensitive subset of the population at moderate zinc deprivation. It is not known whether the zinc-deprived monkeys in this experiment with incomplete sexual maturation would be fertile, or whether fertility problems would occur in the other zinc-deprived animals despite apparently normal signs of sexual maturation.

Reduced bone mineralization is an important finding of the study. Bone mineralization has not been widely studied in connection with zinc-deficiency syndromes. In vitro, zinc can interact with other factors to modify activity of the zinc-dependent enzyme alkaline phosphatase (27, 28), but in vivo effects of zinc deficiency have not been studied. The regulatory role of zinc in bone mineralization at the level of the matrix vesicle was elucidated by Wu et al. (29). However, it is as yet unknown whether zinc deficiency affects mineralization at this level.

Information about bone mineralization in the zinc-deprived adolescent monkeys may be most relevant to long-term health concerns. Peak bone mass is attained during adolescence and the extent of increase in bone density during this time is inversely related to the occurrence of osteoporosis later in life (30). In girls, peak bone mass is reached 2 years after menarche (equivalent to 39 mo of age in monkeys) and bone mineralization slows dramatically thereafter (7, 31). Our data show less bone mineralization in zinc-deficient monkeys in the postmenarcheal period than in controls, with substantial differences recorded in the lumbar spine. If the pattern in monkeys is similar to that in humans, it is unlikely that full catch-up growth will occur at later ages.

The mechanisms underlying retarded growth because of zinc deprivation are not known. The decrease in linear growth did not require severe weight loss and it was not secondary to delayed sexual maturation. The appearance of a delay in linear growth at the same time as a delay in weight gain suggests down-regulation of the GH system. Three potential sites for this adjustment are decreased sensitivity of GH releasing hormone (GHRH) receptors in the pituitary, decreased availability of circulating GH or insulin-like growth factor 1 (IGF-1) through alterations in GH binding protein (GHBP) or IGFBP profiles, and changes in GH receptor numbers, binding affinity, or signal transduction at the tissue level. Recently, decreases in GH production, circulating IGF-1, GHBP profiles, and hepatic GH receptors were found in zinc-deficient weanling rats (32-35). Confirmation of a causal relation with zinc deficiency is complicated by concurrent anorexia in the weanling rat model; similar (although sometimes less extensive) effects appear in matched, food-restricted groups. Food restriction is known to decrease activity in the GH system (36). The occurrence of growth retardation without decreased food consumption in the present experiment offers an opportunity to more precisely examine the role of the GH system in zinc deficiency–induced linear growth retardation in a model that resembles childhood growth retardation.

The inability of the monkeys to compensate for inadequate dietary zinc during the postmenarcheal period of rapid growth and bone mineralization emphasizes the risk incurred by adolescent pregnancy. In addition, the continued laying down of muscle mass suggests an inability to route bioavailable zinc away from this process even when linear growth is compromised. A recent study failed to detect zinc deficiency in pregnant adolescents in Ontario although pregnancy outcome was better in girls who had higher plasma zinc concentrations (37). Although competition for nutrients between the pregnant adolescent and her fetus has been difficult to document (38), dietary zinc may be one factor contributing to low birth weight and adverse outcome as described recently in teenage pregnancy (39).

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**FIGURE 6.** Skeletal maturation and bone mineralization in control and zinc-deprived rhesus monkeys during adolescence. *Significant group differences at time point, P < 0.05.
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