

Mini-Review

Calcium and Vitamin D Status in the Adolescent: Key Roles for Bone, Body Weight, Glucose Tolerance, and Estrogen Biosynthesis

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Abstract. This review paper highlights a number of important public health issues related to calcium and vitamin D status in adolescents. Dietary calcium intake has declined dramatically over the past several decades among adolescents, and inadequate serum vitamin D levels have been documented in up to 54% of teens. A recent trend of decreasing consumption of dairy foods, especially milk, has contributed to this problem. Calcium and vitamin D are critically important for bone mineral accrual during adolescence, and altered calcium homeostasis can impact optimal bone acquisition. Serum and cellular calcium concentrations are controlled, in part, by the actions of vitamin D. Newer research seeks to clarify the potential functions of calcium and vitamin D in the regulation of body weight, glucose tolerance, and ovarian function. Numerous observational studies have noted an inverse association between body weight, percent body fat, and dietary calcium intake; however, clinical trials evaluating the affect of increased calcium on weight loss have been mixed. There is a reduced incidence of insulin resistance syndrome with increasing dairy intake in overweight individuals, and serum 25 hydroxyvitamin D levels are positively correlated with insulin sensitivity. Vitamin D receptor is expressed in all calcium-regulated tissues, including the ovary; thus, calcium and vitamin D appear to be necessary for full ovarian function. This review paper will examine the important role of vitamin D and calcium in the regulation of bone, weight, glucose tolerance, and estrogen biosynthesis.

Key Words. Calcium—Vitamin D—Adolescents—Bone—Obesity—Insulin Resistance—Ovary—Weight loss

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Introduction

There is mounting evidence that adolescents are at risk for poor calcium and vitamin D nutritional status. Since calcium and vitamin D are critical for optimal bone mineral accrual in the developing skeleton, poor nutritional status in adolescence is a matter for concern. The human skeleton has an abundant supply of calcium and finely tuned mechanisms for release of calcium as needed. When either calcium intake or vitamin D status is low, calcium homeostasis is maintained, through the regulation of the parathyroid gland and kidneys, at the expense of bone. In a growing child or adolescent, lack of calcium accumulation in the skeleton can have negative consequences for achievement of peak bone mass.^{1–3}

Calcium and vitamin D are also necessary for many cellular processes. In fact, the primary role of calcium is to serve as a second messenger in virtually all cells. Ionized calcium is the most common signal transduction element in cells due to its ability to reversibly bind to proteins. Vitamin D receptors have been identified in most body cells, including the small intestine, colon, brain, heart, skin, prostate, gonads, breast, lymphocytes, osteoblasts, β -islet cells, and mononuclear cells.⁴ Intracellularly, 1,25-dihydroxyvitamin D interacts with vitamin D receptor and retinoic acid X receptor to enhance or inhibit the transcription of vitamin D-responsive genes, including calcium-binding protein. 1,25-dihydroxyvitamin D has been shown to promote stimulation of many noncalcemic physiological functions including insulin production, thyroid hormone secretion, and activated T and B lymphocyte function.⁴

Despite evidence indicating the crucial role of calcium and vitamin D in many physiological functions, maintaining adequate calcium and vitamin D status in adolescents is challenging in today's food

and living environment. The goal of this review is to highlight new research on calcium and vitamin D in the adolescent, focusing on current public health issues related to these nutritional deficiencies.

Trends in Calcium Dietary Intake

In the USA, dairy products are the major source of dietary calcium, contributing greater than 50% of daily calcium.⁵ However, calcium intake among female adolescents in the USA is considerably lower than the dietary reference intake (DRI) recommendation of 1300 mg/d. Mean calcium intake, from the National Health and Nutrition Examination Survey (NHANES; 1999–2000), for females 12–19 years was 793 mg/d.⁶ Contributing to this low dietary intake is a marked decrease in the consumption of milk, a good source of calcium and vitamin D among children and adolescents, with a concomitant increase in soft drink and juice consumption. Nationally, from 1977–1978 to 1994–1998, milk intake decreased by 36% among female adolescents.⁷ During the same period, carbonated beverage use increased by 127% among younger adolescent girls (11–13 years of age) and by 93% among older adolescent girls (14–17 years of age).⁸ Approximately 25% of adolescents drank more than 26 oz of soft drinks per day.⁹

Studies have confirmed an inverse relationship between consumption of soft drinks and milk.^{10,11} Among adolescents, those consuming 26 oz of soft drinks per day were four times more likely to consume less than 8 oz of milk per day when compared to non-consumers of soft drinks. Higher dairy intake is associated with significantly increased intake of essential vitamins and minerals, including calcium, magnesium, potassium, zinc, iron, vitamin A, riboflavin, and folate.⁵ In addition, dairy consumption was positively associated with whole grain, fruit, and vegetable intake in the CARDIA study (Coronary Artery Development in Young Adults).¹² Thus, low consumption of milk and high consumption of soft drinks contribute to inadequate vitamin and mineral status.

Calcium and Bone Growth

Adolescence is a critical time for bone mass accumulation, with up to 50% of adult total bone mass achieved during this period of life.^{13–15} Bone formation is the predominant activity with numerous factors influencing bone formation and modeling, including calcium availability and vitamin D status.¹⁶ Nutritional rickets and osteomalacia can be caused by inadequate calcium or vitamin D. In either case, there is insufficient calcium to promote bone mineral accrual and bone growth failure occurs.

It has been confirmed that increasing dietary calcium to optimal levels of 1200–1600 mg/d has a positive affect on bone in adolescents.^{17–20} In children 7–17 years of age, increased calcium resulted in a higher bone density over 2 years, with gains of 1.6–5.1%, compared with that in controls.²¹ Recently, in a co-twin randomized, placebo-controlled trial of calcium supplementation, Cameron et al²¹ demonstrated that, after 24 months of a high calcium diet (diet + supplement totaling 1631 mg/d) vs. a lower calcium diet (718 mg/d), there was a significant within-pair difference in adjusted total body bone mineral content of 3.7% ($P < 0.05$) in girls (age 8–17 years). Many short-term and long-term studies have supported the efficacy of increased dietary calcium, as a positive influence on bone mineral acquisition during adolescence.^{18,22–26}

Thus, sustained avoidance of milk in the diet during growth years can lead to poor calcium accrual in bone tissue and increased fracture risk. For example, milk intake positively correlates with bone mineral density (BMD) of the total body, radius, and spine ($P < 0.05$) in adolescent girls.^{27,28} Children who avoid milk suffer from more fractures than children who consumed milk (16 observed vs. 6 expected, $\chi^2 = 31$, $P < 0.001$).²⁹ Moreover, an inverse relationship has been demonstrated between carbonated soft drink consumption and bone mineral content accrual and dominant heel BMD in girls (12 and 15 years of age; $P < 0.05$), and a non-significant inverse relationship for forearm BMD.^{11,30}

Calcium is considered a “threshold” nutrient, which means that bone mass increases as calcium intake increases up to a threshold level.³¹ If calcium intake exceeds the threshold, then the excess is excreted and not stored. Bone does not uptake calcium limitlessly, but makes bone with calcium as needed. The body maintains bone mass based on mechanical load and growth needs and will make bone as needed to provide for the current level of work or growth. Numerous studies have documented the synergistic relationship between mechanical load, through physical activity, and bone calcium accumulation.^{32–34} However, it is important to note that physical activity has a positive effect on BMD only at high calcium intakes, with no effect at calcium intakes < 1000 mg/d.³³

Trends of Vitamin D Intake

Similar to reports on calcium, female adolescents are not meeting the DRI recommendation for vitamin D (200 IU/d or 5 μ g/d). Only 50% of girls (age 9–13 years), 32% of girls (age 14–18 years) and 25% of women (age 19–30 years) are meeting the DRI.³⁵ Dietary sources of vitamin D are limited with fortified

products (milk, orange juice, and breakfast cereals) providing most dietary vitamin D. More than 90% of the vitamin D requirement for most people comes from passive sunlight exposure, which results in synthesis of 25-hydroxyvitamin D, or [25(OH)D], by cutaneous conversion of 7-dehydrocholesterol. Environmental factors, skin pigmentation, sunscreen use, northern latitude, and lifestyle can limit sunlight exposure.

Prevalence of Vitamin D Deficiency in Adolescents

Several recent reports have raised concerns about vitamin D status in adolescence.^{36–38} Traditionally, vitamin D deficiency in children and adolescents has been defined as a serum 25(OH)D concentration < 27.5 nmol/L (11 ng/ml) to prevent bone abnormalities and rickets. Vitamin D deficiency leads to decreased dietary calcium absorption, altered formation of the growth plate, and defective mineralization of the skeleton, resulting in rickets.^{4,39,40} More recently, it has been determined that subclinical vitamin D deficiency may also result in secondary hyperparathyroidism, lower serum calcium, increased serum alkaline phosphatase, and increased risk of bone abnormalities.^{41–43} For example, Harkness and Cromer⁴⁴ determined that a rise in parathyroid hormone (PTH) occurred when serum levels of 25(OH)D were < 90 nmol/L (36 ng/ml). Increased production of PTH mobilizes calcium from bone, thereby compromising bone development in the adolescent. Other groups have also reported a significant inverse relationship between 25(OH)D and PTH in adolescents.^{37,44–46} As a result, in addition to the traditional diagnosis of vitamin D deficiency, vitamin D insufficiency has been defined as a serum 25(OH)D levels between 20–80 nmol/L (8–32 ng/ml) depending on subject population.^{41–43}

In Cleveland, Harkness and Cromer³⁶ found that 17% of adolescent girls (n = 400; age 12–18 years) were vitamin D deficient, while 54% were identified as vitamin D insufficient: serum 25(OH)D ≤ 50 nmol/l. Similarly, in Boston, Gordon et al³⁷ documented that 24% of male and female adolescents (n = 307; age 11–18 years) were vitamin D deficient while 42% were vitamin D insufficient. In both studies, African American adolescents had significantly higher rates of deficiency and insufficiency as compared to white subjects ($P < 0.001$). In addition, low levels of vitamin D were more prevalent during the winter compared to the summer in all racial/ethnic groups ($P < 0.001$).^{36,37}

Vitamin D and Bone Growth

A positive correlation between BMD and 25(OH)D levels in previous studies supports the important role of vitamin D in protecting adolescent bone.^{45,47,48} For example, Outila et al⁴⁵ found that with serum 25(OH)D levels ≤ 40 nmol/L, mean forearm BMD at both the radial and ulnar sites in adolescent girls was lower ($P = 0.04$) than those measured in girls with 25(OH)D levels > 40 nmol/L. In young men (age 18–20.6 years), Valimaki et al⁴⁷ demonstrated a positive correlation between serum 25(OH)D and bone mineral content at lumbar spine, femoral neck, trochanter, and total hip ($P = 0.06$). Lastly, Cheng et al⁴⁹ reported significantly higher concentrations of the bone resorption marker, tartrate-resistant acid phosphatase, in vitamin D deficient girls (age 10–12 years; $P = 0.015$) compared to vitamin D sufficient girls. Using peripheral quantitative computed tomography, Cheng et al⁴⁹ found that the girls with vitamin D deficiency had significantly lower cortical volumetric bone mineral density at the distal radius ($P = 0.001$) than girls with adequate vitamin D levels.

Calcium, Vitamin D, and Obesity

Obesity is a major health problem among children and adolescents. Interestingly, a number of studies have supported the potential role that dietary calcium, vitamin D, and dairy products may have in the modulation of obesity, energy metabolism, and insulin resistance.^{50–53} In individuals of all ages, authors of observational studies have reported that weight and percent body fat are negatively related to dietary calcium intake.^{50,51,54,55} For example, Novotny et al⁵¹ found an inverse association between iliac skinfold thickness and both total calcium and dairy calcium intakes in girls (age 9–14 years; $P < 0.01$). In addition, Novotny et al⁵¹ noted that calcium intake accounted for 57% of the variability in weight ($P = 0.001$). In a 2-year exercise intervention program, Lin et al⁵³ demonstrated that in young women (age 18–31 years), there was a negative correlation between calcium intake and change in body weight ($r = -0.35$) and body fat ($r = -0.34$; $P < 0.05$). Similarly, Skinner et al⁵⁰ reported dietary calcium was negatively related to body fat ($P = 0.02$) in 8 year old children, and Drapeau et al⁵⁶ found an inverse association between intake of skim and partly skim milk with changes in body weight, percent body fat, and waist circumference in adults over a 6-year period.

Recently, utilizing five previously completed clinical trials from the Osteoporosis Research Center at Creighton University, Davies et al⁵⁵ conducted a re-evaluation of the study data to examine body weight.

The original aims of the five clinical studies were to determine the effect of calcium on the skeleton. In the re-evaluation of the subject data ($n = 780$), a significant negative association between calcium intake and weight was found for all age groups (women in the 3rd, 5th, and 8th decades; $P < 0.02$). For the younger women, the odds ratio of having a body mass index (BMI) > 26 was 2.25 when calcium intake was below the median. In women with BMI > 30 , there were seven obese subjects in the lower half of calcium intakes and only one in the upper half. In one of the re-evaluated clinical trials, subjects who received calcium supplements for 4 years experienced a weight change of -0.67 kg/yr compared to -0.33 kg/yr in the control group ($P < 0.025$).⁵⁵

Potential mechanisms for the relationship between adiposity and calcium were elucidated by Zemel et al in animal models.^{52,54} In a series of experiments using Agouti mice, Zemel et al⁵⁴ demonstrated that altering adipocyte intracellular calcium concentrations could change fatty acid metabolism. Animal models given high calcium diets experienced a 51% inhibition of adipocyte fatty acid synthase expression and activity ($P < 0.002$) while lipolysis was increased by 3.4 to 5.2 fold ($P < 0.015$).⁵⁴ Thus high dietary calcium suppressed fat storage while stimulating fat breakdown. It is hypothesized that this occurs through a mechanism that is governed by serum calcium concentrations. For example, when dietary calcium is inadequate, leading to marked changes in serum calcium concentrations, vitamin D hydroxylation to the active form of the vitamin (1,25 dihydroxyvitamin D) is stimulated. This increase in circulating 1,25 dihydroxyvitamin D causes increased flux of calcium across the adipocyte membrane. When intracellular calcium levels rise, lipogenesis is stimulated and lipolysis is inhibited. High calcium diets could potentially suppress this response.⁵²

Weight Loss and Dietary Calcium

Clinical trials on the effect of high calcium diets on weight loss have yielded mixed results. In one recent trial that yielded no significant results, Shapses et al⁵⁷ gave 1000 mg/d of supplemental calcium to obese women on a weight loss program for 6 months. There was no significant difference between the calcium supplemented and the placebo groups for body weight or fat mass changes.⁵⁷ A small, non-significant, effect was observed relative to greater loss of fat mass with the calcium supplementation (1.0 kg more fat mass lost). Conversely, Zemel et al⁵⁸ reported that a diet containing high amounts of dairy foods or supplemental calcium resulted in higher rates of weight loss compared to a standard weight loss diet in 32 obese

adults after 24 weeks. In this study, all subjects were provided with a standard lower kilocalorie weight loss diet, which provided 400–500 mg/d of calcium. Subjects were randomized to three study arms; high dairy (+1200 mg/d calcium), supplementation with calcium (+800 mg/d) or control (no additional calcium). Subjects in the high dairy group lost $10.9 \pm 1.6\%$ of body weight compared to $8.6 \pm 1.1\%$ in the calcium supplemented group and to $6.4 \pm 2.5\%$ loss in the standard control. In addition, fat loss was significantly more on the higher calcium diets (38% more on the calcium supplemented diet and 64% on high dairy foods diet). Of particular interest was that the subjects on the higher calcium and high dairy foods lost more adipose tissue from the truncal region.

Insulin Resistance and Glucose Tolerance

Altered serum calcium and low serum 25(OH)D concentrations may be risk factors for abnormalities of glucose homeostasis. A number of researchers have demonstrated that dietary calcium, dairy foods, and vitamin D play a role in glucose tolerance. In the CARDIA study, there were inverse associations between dietary intake of dairy and the development of obesity and abnormal glucose tolerance in overweight young adults.¹² In addition, there was a substantial reduction in odds ratio of the incidence of insulin resistance syndrome over a 10-year period with increasing category of dairy intake.¹² The reduction in odds ratio was 71% for the highest category of dairy intake compared to the lowest category ($P < 0.001$) in individuals who were overweight or obese.

An inverse association between vitamin D status and elevated fasting glucose and insulin levels was found in an analysis of NHANES III (1988–1994) data.⁵⁹ In individuals with impaired glucose tolerance, such as type 2 diabetes, lower serum 25(OH)D levels have been documented.^{60,61} Type 2 diabetic women have a significantly higher prevalence of vitamin D deficiency compared to controls (39 vs 25%).⁶⁰ In addition, vitamin D receptor gene polymorphism is associated with risk of obesity in type 2 diabetics.⁶² To test the interaction between 25(OH)D concentrations and insulin sensitivity, Chiu et al⁶³ performed hyperglycemic clamp studies on subjects with normal glucose tolerance and determined that serum 25(OH)D was positively correlated with insulin sensitivity index ($P = 0.0007$) and negatively correlated with plasma glucose concentrations ($P < 0.001$). Moreover, among the study subjects, Chiu⁶³ identified 14/47 subjects with hypovitaminosis D who were at risk for metabolic syndrome compared to 9/79 subjects with adequate levels of vitamin D. Thus, low

levels of vitamin D may be associated with type 2 diabetes and metabolic syndrome.

Vitamin D Receptor in the Ovary: Effect of Vitamin D Deficiency

Vitamin D receptor (VDR) is expressed in calcium-regulated tissues, including the ovary, and appears to be necessary for full ovarian function. In female rats, vitamin D deficiency results in reduced fertility and litter size compared to vitamin D replete animals.⁶⁴ Uterine hypoplasia and impaired folliculogenesis have been found, as well as low levels of circulating estradiol and elevated levels of luteinizing hormone and follicle stimulating hormone, in female VDR-null mice.^{65,66} In addition, gene expression of aromatase is reduced resulting in decreased aromatase activity in VDR-null mutant mice.⁶⁶ Supplementation with estrogen leads to increased uterine weight and normalized histological abnormalities in these mice. When VDR-null mutant mice were given high calcium diets to correct low serum levels, the activity of aromatase cytochrome P450 in the ovary increased to 60% of that in wild-type mice and the expression of CYP19 (gene encoding for P450 aromatase) recovered to 20% of that of the wild-type.⁶⁶ These studies indicate that vitamin D plays a key role in estrogen biosynthesis potentially via maintenance of extracellular calcium concentrations and by direct regulation of aromatase gene expression.

Summary

Evidence indicates that calcium and vitamin D play crucial roles in many physiological processes. Among adolescents, calcium intake has decreased dramatically over the past several decades, and inadequate levels of vitamin D have been identified in up to 54% of youth. Negative consequences of low calcium and vitamin D status on adolescent bone growth are well documented. Furthermore, data suggests that calcium and vitamin D play critical roles in glucose tolerance, adipocyte metabolism, and estrogen biosynthesis. Low calcium and vitamin D levels may be risk factors for both obesity and insulin resistance. Health providers need to be aware of the high prevalence of calcium and vitamin D insufficiency in the adolescent age group, and make assessment and management of calcium and Vitamin D nutritional status a component of routine adolescent health care.

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