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Vitamin D deficiency and secondary hyperparathyroidism in pediatric obesity

Abstract

Obesity is one of the health problems in the developing and developed countries. Obesity subjects the individuals with metabolic and endocrine disorders. It is obvious that vitamin D deficiency or insufficiency may lead to secondary hyperparathyroidism. Thus, obesity increases the risk of vitamin D deficiency. Considering the high prevalence of vitamin D deficiency in children and adolescents with overweight or obesity, it seems logical to have treatment and prevention from vitamin D deficiency. This is similar to a study in adult vitamin D deficiency related with adiposity which also demonstrates the importance of vitamin D deficiency screening in children and adolescent obesity. Vitamin D replacement can reduce many complications in childhood (skeletal disorder, secondary hyperparathyroidism) and decreases metabolic disorder and cardiovascular disease incidence in later childhood. On the other hand, calcium has a key role in weight regulation, useful in replacement therapy, but there is a need for a further study to reveal exactly the effects in children obesity or overweight.

Key words: Vitamin D Deficiency, Pediatric Obesity, Secondary hyperparathyroidism.

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Pediatric obesity is one of the most pressing health problems children and adolescents face today (1). According to National US surveys, the high prevalence of overweight and obesity during childhood and adolescence increased in the past few decades (2). Around 250 million people, about 7% of the current world population, are obese. Two to three times more people are overweight. In one of the most extreme examples, the prevalence of overweight is doubled among children age 6–11 and tripled in 12–17 years old (3). The prevalence of overweight or obesity in developing countries increased from 8.7% to 13.5% in boys, and from 11.8% to 18.6% in girls from 1998 to 2004 (4). The prevalence of overweight and obesity in Portuguese children age 7–9, 20.3% are overweight and 11.3% are obese children (5). According to Mercedes de Onis and Monika Blössner, the study of the global prevalence of overweight was 3.3%, but some countries and regions had considerably higher rates, and overweight was shown to increase in 16 of 38 countries with trend data. Countries with the highest prevalence of overweight are located mainly in the Middle East, North Africa, and Latin America (6). Other cross-sectional survey indicated high prevalence of overweight and obesity in school-aged youth. Therefore, adolescent obesity epidemic is a global issue (7,8). Obesity imposed costs to Health Care System. The proportion of discharges with obesity-associated diseases has increased dramatically in the past 20 years. This increase has led to a significant growth in economic costs (9). Incidence of childhood obesity has been accompanied with many complications such as obstructive sleep apnea, orthopedic problems, hyperandrogenism, and cardiovascular disease. These complications can be a threat to children's health, thus increasing both their medical burden on society and their risk for early morbidity and mortality (10,11). Obesity has a close relationship with increased risk of impaired glucose tolerance and insulin resistance in children and adolescents (12).

Concentrations of biochemical markers of nutritional status have been also associated with an increase in body mass index (BMI) and other measures of adiposity (13-15). Among the obese, vitamin D has been shown to have decreased bioavailability from cutaneous and dietary sources and possibly sequestered by adipose tissue (16). In general, the severity of obesity and age at onset affects the likelihood of the persistence of obesity into adulthood. Although childhood onset obesity that persists into adulthood may be associated with more severe adult diseases (17).

Vit D physiology, function and deficiency definition:

Vitamin D is synthesized in the skin under the influence of ultraviolet light of the sun, or it is obtained from food, especially fatty fish. After hydroxylation in the liver into 25-hydroxyvitamin D (25-OH-D) and kidney into 1,25-dihydroxyvitamin D (1,25-OH-2D), the active metabolite can enter the cell, bind to the vitamin D-receptor and subsequently to a responsive gene such as calcium binding protein (18,19). After transcription and translation, the protein is formed, e.g. osteocalcin or calcium binding protein. The calcium binding protein mediates calcium absorption from the gut. The production of 1, 25(OH)2D is stimulated by parathyroid hormone (PTH) and decreased by calcium. The parathyroid hormone (PTH) is the most important regulator of calcium metabolism (17,20). It is a polypeptide consisting of 84 amino acids and is secreted by the chief cells of the parathyroid glands in response to hypocalcemia and hyperphosphatemia (21).

Vitamin D is an essential factor in the regulation of calcium and phosphorus balance (21,22). Vitamin D is important for calcium absorption and bone growth and accretion in childhood and adolescence who are in growing period (23,24). In addition to skeletal effects, including maintenance of normal bone turnover, mineralization during adulthood, and prevention of rickets in children, vitamin D may confer protection against health problems such as type 1 diabetes mellitus, hypertension, multiple sclerosis, and cancer(8). Among infants and young children, both the Institute of Medicine (IOM) and the American Academy of Pediatrics (AAP) have defined vitamin D deficiency as a

serum 25 –OH-D level below 11 ng/mL (27.5 nmol/L). In children, studies have shown that vitamin D deficiency is associated with higher PTH levels (25,26).

Obesity and prevalence of Vit D deficiency: There are some data about pediatric obesity and vitamin D deficiency. As study in adult obesity revealed high prevalence of Vitamin D deficiency in them (27-31). Prevalence of childhood overweight and its metabolic consequences in countries are still grappling with the public health effects of malnutrition and micronutrient deficiencies (32). Prevalence on vitamin D deficiency in developed countries is higher. More than 78% of all Turkish nationals who migrated to Germany had 25(OH)D levels of less than 50 nmol/l (33) also, the prevalence of vitamin D deficiency among healthy Saudi men is between 28% to 37% among the young and middle aged Saudi Arabian (34). Ali Rabbani et al. reported that the prevalence of vitamin D deficiency was 53.6% in girls and 11.3% in boys. Vitamin D deficiency in female students was about five times more common than males (35). In the 1980s, small case-control studies showed that serum 25(OH) D levels were lower in obese subjects compared with non - obese individuals with higher serum PTH levels (36).

In the study of Rajakumar et al. vitamin D deficiency occurred in 57% of obese children and 40% versus the non - obese children. There was no significant difference in the non-obese 6–10 year old African American children but the treatment response effects were different between the obese and the non-obese. Treatment was effective in the non-obese with basal 25(OH)D <30 ng/ml and in the obese with basal 25(OH)D ≤20 ng/m. This study concludes that therapeutic doses of vitamin D in the study population is inadequate (37). In the study of Alemzadeh et al. in obese children approximately 59% of them were 25(OH)D insufficient (≤29 ng/ml), and 41% were sufficient (≥30 ng/ml). In their study, strong negative relationships were present between serum 25-OH-D and computed tomography measures of visceral and subcutaneous fat but no changes in peak bone mass.

In this study, it revealed that hypovitaminosis D was in 74% in 127 children and adolescents (age, 6.0-17.9 years)

who met the criteria for obesity body mass index (BMI) >95 percentile for age, whereas vitamin D deficiency was observed in about one third (32.3%) of obese children and adolescents, 41.7% met the definition of vitamin D insufficiency, but only 26% of the subjects had sufficient vitamin D levels (38).

Tangorra et al. determined the prevalence of vitamin D insufficiency and markers of metabolic syndrome in an obese pediatric population. In their study, more than half of the obese children had vitamin D levels <20 ng/ml with equal gender distribution. Vitamin D insufficiency was associated with increased age, BMI, and SBP (39). This study in pediatric is in concordance with the study in adult because BMI, waist circumference, and sum of skin folds were statistically significant and was positively associated with serum PTH (40,41).

Cizmecioglu et al. reported the prevalence of hypovitaminosis D in a highly industrialized city in the Marmara region of Turkey where obesity is on the rise of 65% in all of the students (12% deficiency and 53% insufficiency). Vitamin D deficiency in female students was about 2 times more common than in males. Although the girls appeared to have higher BMI values than the boys (42,43).

Effects of obesity on Vit D: Previous studies indicated the association between vitamin D and obesity, and the serum levels of 25-hydroxyvitamin D (25(OH)D) reduced in obese subjects (44,45).

In the cross-sectional study of a national representative sample of American adults, the odds of low vitamin D levels increased with increasing BMI among women were found. The association of adiposity with serum 25(OH)D and serum PTH levels showed exactly the measured total body fat which is inversely associated with 25(OH)D levels and is positively associated with PTH levels in adults (46). Also, in adult with morbid obesity vitamin D had low level and iPTH was significantly higher (47,48). BMI was inversely correlated to 25-OH-D levels. A high BMI is related to lower 25(OH)D values, possibly by storing lipid-soluble vitamin D in fat tissue therefore reducing serum levels (49). On the

other hand, significant weight reduction in overweight and obese subjects is unlikely to occur with cholecalciferol supplementation (50).

The association between serum 25(OH)D and obesity can be explained by an increased storage of 25(OH)D in adipose tissue in obese subjects. Several lines of evidence have suggested a role for 1,25-(OH)₂-D in obesity (40). Vitamin D receptor gene polymorphism is associated with susceptibility to obesity in patients with early onset type II diabetes (51) and circulating 1,25-(OH)₂-D levels are elevated in obese individuals (52). In a recent study by Wortsman et al. the capacity of the skin to produce vitamin D was not altered in obesity. However, the increase in serum vitamin D₃ after sun exposure was 57% less in obese compared with non-obese subjects. The increase in serum vitamin D₃ after oral supplementation was similar in obese and non-obese subjects. This supports the hypothesis of a decreased release of endogenously produced vitamin D into the circulation due to more storage in subcutaneous fat in obese subjects. In the UV-B irradiation study, basal concentrations of vitamin D were not significantly different between the obese and non-obese control groups (50). Obese subjects had significantly lower basal 25-hydroxyvitamin D concentrations and higher parathyroid hormone concentration. The main mechanism of vitamin D insufficiency is likely due to the decreased bioavailability of vitamin D₃ from cutaneous and dietary sources because of its deposition in body fat compartments (51).

Thomas et al. showed PTH levels that were positive and 25(OH) D concentrations were negatively related to weight status. Since these alterations normalized after weight loss, these changes are consequences rather than causes of overweight (52). The low levels of 25(OH) D in obese children are in concordance with most studies in adults (53). A good vitamin D status has been postulated to prevent obesity (54,55). Since 25(OH) D concentrations increased after reduction of overweight, these finding points towards a consequence rather than a cause of overweight (27). PTH concentrations were elevated in obese children (39). PTH decreased after weight loss occurred in obese adults (56).

Pediatric obesity and vitamin D deficiency relation with other diseases: Obesity is one of the many factors contributing in metabolic syndrome. On one hand, previous studies linking low 25(OH)D showed an increased prevalence of metabolic syndrome (57,58) which is closely related to disorders, including insulin resistance/hyperinsulinemia, hypertension, and cardiac hypertrophy (59). These diseases are integrated into metabolic syndrome and also observed as an increased risk of metabolic syndrome with elevated PTH levels in older men but with no effect of 25(OH) D concentrations (60). Vitamin D status may influence glucose metabolism. In a cohort study, it revealed Serum 25(OH) D level decreased and A1C increased with increasing BMI. Body size with a strong determinant for 25(OH) D, with concentrations being suboptimal in most obese participants (61). Also, in other studies the reported association between vitamin D and glucose metabolism may depend on body size (62,63). Interestingly, these data suggested that the decrease in A1C with increasing 25(OH)D was the steepest in levels <65 nmol/l, with some small decrease with further increase (64).

Chiu et al. observed a positive relationship between vitamin D status and insulin sensitivity index in adults. In addition, they showed that vitamin D levels were negatively correlated with both first-and second phase insulin responses during a hyperglycemic clamp and glucose levels during oral glucose tolerance test. Thus, they suggested that subjects with hypovitaminosis D not only displayed impaired β -cell function causing impaired glucose homeostasis, but also were at increased risk of developing insulin resistance and metabolic syndrome compared with vitamin D-sufficient adults (57). Hypovitaminosis D subjects had decreased insulin sensitivity compared with the vitamin D-sufficient subjects, corresponding to significantly higher BMI and FM in the hypovitaminosis D. Moreover, serum 25(OH) D levels were inversely correlated with HbA1c independent of body fat, implying higher ambient glucose concentrations in children with lower vitamin D concentrations (65) In Alemzadeha et al. study which was similar to a previous study, serum 25(OH) D was positively correlated with

insulin sensitivity, but negatively correlated with HbA1c, implying that obese children and adolescents with low vitamin D status may be at increased risk of developing impaired glucose metabolism independent of body adiposity. Mean fasting serum glucose levels were considered obese with the vitamin D deficient and had higher HbA1c and serum insulin levels (38).

Obesity, calcium and Vit D: BMI and calcium intake were positively related in men who had negative and significant associations between the intake of vitamin D and BMI in both sexes (62).

Intracellular Ca²⁺ plays a key role in the metabolic disorders associated with obesity and insulin resistance (66). Recombinant agouti protein, an obesity gene product, stimulates Ca²⁺ influx in a variety of cells (67,68). Agouti also stimulates the expression and activity of fatty acid synthase, a key enzyme in de novo lipogenesis, and inhibits basal and agonist-stimulated lipolysis in human and murine adipocytes via a Ca-dependent mechanism (68).

Increasing adipocyte Ca²⁺ appears to promote triglyceride accumulation in adipocytes by exerting a coordinated control over stimulation of lipogenesis and inhibition of lipolysis (66). Antagonism of Ca²⁺ by either blocking Ca²⁺ channels or inhibiting Ca²⁺ agonists is an attractive and logical approach for the development of therapeutic intervention in obesity. Indeed, calcium channel blockade has been proven to reduce body weight and fat pad mass effectively in several animal models. Consequently, increasing dietary calcium resulted in increased adipocyte lipolysis and suppression of lipogenesis (66).

High calcium diets reduced lipogenesis by 51% and stimulated lipolysis three- to five folds (69). The induced 26% to 39% reductions in body weight and adipose tissue mass (70) dietary calcium does not only attenuates diet-induced obesity but also accelerates weight loss and fat-mass reduction secondary to caloric restriction in established obesity (67). The second proposed mechanism by which calcium may have impact on body weight is that, increased dietary calcium seems to bind more fatty acids in the colon, thereby inhibiting fat absorption. Zemel et al. reported

increasing dietary calcium suppresses adipocyte intracellular Ca and thereby modulates energy metabolism and attenuates obesity risk. Suppressing 1,25-(OH)₂-D levels by increasing dietary calcium is predicted to inhibit adiposity and promote weight loss (70).

The regulation of serum calcium by parathyroid hormone (PTH) and 1,25 dihydroxyvitamin D (1,25(OH)₂D) induced by changes in dietary calcium has been proposed as a mechanism that mediates the effects of dietary calcium on fat mass (71). High dietary calcium loads can acutely suppress concentrations of serum PTH (72). The results of Gunther et al. study suggested that a chronic diet high in dairy calcium increases whole-body fat oxidation from a meal, and increases fasting serum PTH that relates to decrease in postprandial whole-body fat oxidation (73). There were significant differences in changes to markers of bone turnover with vitamin D supplementation, between obese and non-obese children. The anticipated compensatory increase in PTH in response to vitamin D deficiency and insufficiency was observed only among the non-obese suggesting that the innate PTH response to vitamin D deficiency/insufficiency may be blunted in the obese state (74). In addition, the post-supplementation OC (marker of bone formation) and urinary NTX (marker of bone resorption) were significantly lower in obese children compared to non-obese children therefore, suggesting lower rates of bone turnover in obese children (37).

Resistance that forces higher PTH secretion and leads to more efficient utilization of dietary calcium (73) to prolong energy restriction may play an important role in the different endocrine responses and ultimate effect on Ca and bone metabolism. For example, it is possible that less fat tissue after energy restriction in lean compared with obese rats may have contributed to greater reduction in serum estrogen and lower final 25(OH)D concentrations (74).

The roles of vitamin D and parathyroid hormone (PTH) are discussed controversially in obesity, and studies of these hormones in obese children are limited. Reinehr et al. reported obese children had significantly higher PTH and lower 25-OH Vit D concentrations compared with non-obese

children, while calcium, phosphate, Alkaline Phosphatase and 1,25-OH vit D did not differ significantly. PTH concentrations elevate in obese children. It has been postulated that increased PTH levels contribute towards obesity. While in weight loss, PTH can decrease to optimal range (52).

Discussion

Obese children are at high risk for vitamin D deficiency and secondary hyperparathyroidism. Body mass index appears to be an important and risk factor for vitamin D deficiency hypovitaminosis. Like in adult study, vitamin D deficiency is related with adiposity. It also demonstrates the importance of vitamin D deficiency screening in children and adolescent obesity. Vitamin D replacement can reduce many complications in childhood and decreased metabolic disorder incidence in the future. On the other hand, calcium has a key role in weight regulation and is useful in replacement therapy but there is a need to a further study to reveal the exact effects of obesity or overweight in children.

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