CLINICAL VIGNETTE

Vitamin D Deficiency and Obesity at a Tertiary Care Center

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Introduction

Obesity has reached epidemic proportions in the United States. Recent studies report that third of the US adults are clinically obese, defined by a body mass index of 30 or greater with the cumulative incidence of overweight and obesity approaching 70%[1]. Obesity may be considered a state of over-nutrition but despite excess caloric intake, nutritional deficiencies are common[2]. The causes of such deficiencies are not entirely known, but may stem from intake of caloric dense, poor quality foods. These contribute to increased adipose tissue formation, which may influence the metabolism and storage of certain nutrients, such as vitamin D.

Vitamin D has numerous roles in the human body and most actions of vitamin D are mediated through the vitamin D receptor, which closely mimics the vitamin A receptor. Together, these receptors regulate the expression of over 50 genes in humans[3]. The impact of vitamin D is profound and is known to have significant effects on bone health, muscle function, cancer, immunity, and the cardiovascular system. Vitamin D impacts bone health by stimulating the production of calbindin, which allows for absorption of calcium through the digestive tract, and mediates the deposition of calcium into bones and the blood stream via parathyroid hormone[3]. Vitamin D receptors have been found in a number of cancers including breast, colon, prostate, bone and melanoma. Current research is looking at the influence of vitamin D in the treatment of breast, prostate, and colon cancer[3].

Moderate-to-severe vitamin D deficiency has been associated with increased incidence of cardiovascular disease in 1739 patients from the Framingham Offspring Study. Subjects with 25-hydroxy vitamin D (25OHD) < 15ng/ml had twice the risk of myocardial infarction, congestive heart failure, and cerebral vascular accident[4]. Low vitamin D levels defined as <30 ng/ml and hypertension were associated with twice the risk of heart disease five years[4]. Another study of 4,818 patients found 25OHD < 20ng/ml was associated with heart failure and peripheral artery disease after adjustment for other risk factors[5]. Small clinical trials have also shown that vitamin D supplementation can help lower incidence of cumulative cardiovascular events in patients with chronic kidney disease, reduce blood pressure, and decrease triglyceride levels[5].

Many studies have found higher prevalence of vitamin D deficiency in the obese population[6]. Recently, a cross-sectional prospective cohort study involving over 25,000 subjects found an inverse relationship between vitamin D level and incidence of obesity after 11 years of follow-up[6]. In this paper, we explore the association between vitamin D and body mass index (BMI) at a tertiary care center of excellence for weight loss in Los Angeles.

Subjects and Methods

After obtaining approval from the Cedars-Sinai Institutional Review board, we reviewed charts of patients who presented to the Cedars-Sinai weight loss program seeking medical and/or surgical weight loss treatment between June 2009 and July 2010. Sequential patients were identified from a clinical tracking spreadsheet. Demographics, clinical and laboratory data were abstracted from clinical charts. Data included age, weight, BMI and 25OHD level. BMI was categorized into: BMI $\leq$ 30, 30-40, 40-50, 50-60, and $\geq$60 kg/m2. Serum 25OHD values were categorized into normal >30 mcg/dl, insufficiency between 20 -29.9mcg/dl or deficiency <20mcg/dl[7]. All analyses were performed using the SAS software (version 9.2, SAS Institute, Cary NC) and statistical significance was defined as $p<0.05$. Means and standard deviations were reported for continuous

variables and Chi-square analysis was used to test for association between categorical variables, and analysis for variance was used to analyze continuous variables by categories.

Results

Of the 288 patients seen for initial consult, 168 (58%) had returned for follow up and had complete medical record data to review. The mean age was 45.5 ± 12.5 years, mean BMI was 43.3 ± 10.5 kg/m2 and mean weight was 270.7 + 78.0 lbs. There were 138 patients (48%) with a BMI < 30; 59 patients (20%) with a BMI 30-40, 48 patients (17%) with a BMI 40-50, 34 patients (12%) with a BMI 50-60, and 9 patients (3%) with a BMI ≥60. 132 patients of the 168 (79%) had vitamin D levels measured with the mean vitamin D level of 21.8 ± 10.2mcg/dl. One third (30%) of the patients were vitamin D insufficient (values 20-29.9 mcg/dl) while half (49%) were vitamin D deficient (levels <20 mcg/dl). There was a statistically significant association between Vitamin D deficiency category and BMI category (p=0.003). There was also a significant difference in mean vitamin D levels across BMI categories (p<0.001) with the lowest vitamin D levels seen in the patients with BMI 50-60 and >60 kg/m2 (15.6 ± 8.1 and 15.3 ± 7.0, respectively, see figure).

Discussion

Our results indicate that vitamin D insufficiency and deficiency is common in obese patients. We also found that vitamin D deficiency was greater in patients in the highest BMI > 50 kg/m2. While the exact mechanism for why obesity is a risk factor for vitamin D deficiency is still unclear, this information is important for clinicians to be aware of and screen. Our results add to the growing body of literature that vitamin D deficiency and obesity are related. Studies in the past have suggested that low levels of vitamin D in obese people can be explained by decreased bioavailability of this hormone after controlling for potentially confounding variables such as age, sex, race, sunlight exposure, vitamin D supplementation, and renal function[8]. Vitamin D is fat-soluble and in the obese person more vitamin D is stored in the adipose tissue therefore decreasing the level of circulating vitamin D for other tissues to utilize. Furthermore, in one study when subjects were exposed to sunlight or given an oral dose of 50,000 IU of vitamin D2, the obese subjects were only able to raise their vitamin D levels by no more than 50% compared to the non-obese subjects[7]. Moreover, there were no significant differences in the content of vitamin D precursors in the skin of obese and non-obese persons after irradiation, which implies that obese and non-obese individuals produce the same amount of vitamin D after sun exposure. Our study corroborates with the explanation that low vitamin D levels in obese people does not lay in production, but rather in bioavailability when fat sequesters this hormone and suggests that obese people require more vitamin D supplementation than non-obese people to treat vitamin D deficiency[8]. Recent guidelines recommend that obese adults need at least two to three times more vitamin D (at least 6000–10,000 IU/d) to treat and prevent vitamin D deficiency[7].

Vitamin D has a wide range of biological actions, so deficiency in this hormone may have many significant health implications, especially in the obese population. Patients with low vitamin D level have increased insulin resistance and components of metabolic syndrome such as increased waist circumference, adiposity, blood pressure and triglycerides[9, 10, 11]. The relationship between vitamin D and metabolic syndrome may be mediated by IL-6 and CRP; elevated levels are seen in patients with metabolic syndrome and vitamin D deficiency[10]. The role of vitamin D in the pathogenesis of metabolic syndrome and diabetes is still unclear. However, supplementation with vitamin D over one year in one prospective study of subjects with vitamin D deficiency and metabolic syndrome found improvement in metabolic syndrome features such as decrease plasma glucose, triglycerides, hypertension, obesity and increase in HDL[11]. The pathophysiology of vitamin D in improvement of dyslipidemia may involve elevation of serum apolipoprotein A-1 concentrations, which results in improvement of cholesterol transportation[12]. Apolipoprotein A-1 is linked to vitamin D and the gene expression of apolipoprotein A-1 is regulated by vitamin D receptor modulators[12-14]. Vitamin D may exert its beneficial effect on diabetes by stimulating the expression of insulin receptors which improves glucose transport and mediates the calcium influx, which is important for the insulin mediated intracellular process in insulin responsive tissues[15]. Furthermore, adipose tissue can promote insulin resistance through the release of fatty acids, and vitamin D has been shown to lessen this effect[16].

In conclusion, our study is consistent with current literature and shows vitamin D deficiency and insufficiency is more prevalent in the morbidly obese population. Vitamin D deficiency is associated with many important extra-skeletal manifestations including metabolic syndrome and cardiovascular health. Just as checking hemoglobin A1C and lipid panel is part of routine health maintenance, it may be

important to include vitamin D levels in obese patients at high risk for vitamin D deficiency. Screening for vitamin D deficiency should measure serum 25OHD level, which has a half-life of 2-3 weeks and is the best indicator of vitamin D status[7]. It is important to educate patients who are vitamin D deficient to increase vitamin D intake by increasing vitamin D fortified foods and by vitamin D supplementation. However, despite the relationship between vitamin D deficiency to metabolic syndrome and cardiovascular health, there have not been any randomized controlled trials that show causation or the clinical impact of raising vitamin D levels on cardiovascular outcomes including myocardial infarction, stroke, dyslipidemia, hypertension and diabetes. Future studies are needed in the obese population.

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Figure: Vitamin D levels by BMI