Original Article

Vitamin D and insulin resistance in postmenopausal Indian women

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ABSTRACT

Purpose: The purpose of this study is to investigate the association of the serum 25-hydroxyvitamin D (25-OHD) level with markers of insulin resistance (IR) in postmenopausal Indian women. **Materials and Methods:** This was a cross-sectional study, conducted at a Tertiary Care Hospital in New Delhi, India. Seventy one postmenopausal women (mean age 56.3 ± 7.6 years) were enrolled. Exclusion criteria were known or newly detected diabetics, subjects with chronic renal failure, chronic liver disease or any other chronic inflammatory condition, chronic smokers and chronic alcoholics. Serum calcium (and albumin for calculating corrected calcium), phosphorus, alkaline phosphatase and 25-OHD were measured as parameters of calcium homeostasis. Fasting blood glucose (FBG), systolic and diastolic blood pressures, body mass index (BMI), fasting serum insulin, calculated glucose insulin ratio (GIR), and homeostatic model assessment of insulin resistance (HOMA-IR) were studied as parameters of IR. Data was then analyzed for statistical significance. **Results:** The mean serum 25-OHD level was 12.73 ± 7.63 ng/ml. The mean BMI was 27.78 ± 5.37 kg/m^2. The mean calculated GIR was 13.14 ± 9.39 and HOMA-IR was 2.31 ± 1.70. Serum 25-OHD was inversely correlated with BMI (correlation coefficient –0.234, *P* value 0.050) and with HOMA-IR (correlation coefficient –0.237, *P* value 0.047). However, when 25-OHD was adjusted for BMI the correlation between 25-OHD and HOMA-IR lost its significance. No correlation was found between serum 25-OHD and any other parameters of IR studied. **Conclusions:** There is a significant negative linear correlation between 25-OHD and BMI. The significant negative linear correlation between 25-OHD and HOMA-IR was confounded by BMI. There is no correlation between 25-OHD and parameters of IR.

Key words: Body mass index, homeostatic model assessment of insulin resistance, postmenopausal women, 25-hydroxy vitamin D3

Introduction

As early as 1989, Lind *et al.*[1] showed in a small cohort that there was a positive relationship between the tissue insulin sensitivity and the serum concentrations of 25-hydroxyvitamin D (25-OHD). Later, several epidemiologic studies have suggested that 25-OHD status is inversely associated with metabolic syndrome in Western populations.[1-9] Nevertheless, evidence from the Asian population is limited. Because of ethnic differences in vitamin D metabolism and its nutritional status as indicated by previous studies,[2,10] it is not clear whether the findings from Western populations could be extrapolated directly to Asian individuals.

This study was thus intended to evaluate the association of insulin resistance (IR) with vitamin D status in postmenopausal Indian women.

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Materials and Methods

We conducted a cross-sectional study at a Tertiary Care Hospital at New Delhi, India (Latitude 28°38'N and longitude 77°17'E).

Ethics

Ethical Committee approval was sought from the institutional review board.

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Study design

Selection and description of participants

A total of 71 postmenopausal women (mean age 56.3 ± 7.6 years) were enrolled. Subjects with chronic renal failure, chronic liver disease or any other chronic inflammatory condition, chronic smokers and chronic alcoholics were not included as they could potentially alter the IR. Subjects who were known diabetics or who were found to have fasting blood glucose (FBG) in the diabetic range were also excluded. Samples were drawn in the months of October or November. All subjects enrolled underwent detailed history and physical examination including body mass index (BMI) calculation. Serum calcium (and albumin for calculating corrected serum calcium), phosphorus, alkaline phosphatase and 25-OHD were measured as parameters of calcium homeostasis. FBG and fasting serum insulin were measured at induction. FBG, systolic and diastolic blood pressures, BMI, fasting serum insulin, calculated glucose insulin ratio (GIR) and homeostatic model of assessment of Insulin resistance (HOMA-IR) were studied as parameters of IR.

Technical information

Peripheral venous blood was drawn in the fasting state without a tourniquet. Serum calcium, albumin, phosphorus, alkaline phosphatase, blood glucose and serum insulin were measured using automated analyzer at an accredited local laboratory. Samples for 25-OHD were stored at −20°C and were transported to a central academic laboratory after 3 months for analysis. All samples were evaluated in duplicate and mean of the values taken for statistical analysis. 25-OHD was measured using DiaSorin Inc, Stillwater, MN 55082-0285, kit, manufactured in USA and imported by collaborating academic institute, normal range 9.3-37.9 ng/ml. The sensitivity of this assay is 1.5 ng/ml, within-run coefficient of variation (CV) is 10.5% and the total imprecision CV is 8.2% at 22.7 ng/ml.

Statistical methods

Data was analyzed for the statistical significance using Pearson's correlation, considering it significant at the $P < 0.05$.

Results

The mean ± standard deviation (SD) levels of the parameters studied are shown in Table 1. In the study cohort, only 5.6% subjects (4/71) had normal 25-OHD level (taken as being >30 ng/ml) and 7.0% (5/71) had vitamin D insufficiency (25-OHD levels between 20 and 30 ng/ml) while 87.3% (62/71) were vitamin D deficient (<20 ng/ml).[11]

Table 1: Mean±SD of the various parameters studied

Parameter (unit)	Mean±SD
Corrected serum calcium (mg/dl)	8.72±0.59
Phosphorus (mg/dl)	3.76±0.51
25-OHD (ng/ml)	12.73±7.63
BMI (kg/m^2)	27.78±5.37
FBG (mg/dl)	92.46±10.91
Fasting insulin (μIU/ml)	10.19±8.38
GIR	13.14±9.39
HOMA-IR	2.31±1.70

25-OHD: 25-hydroxyvitamin D, BMI: Body mass index, FBG: Fasting blood glucose, GIR: Glucose insulin ratio, HOMA-IR: Homeostatic model assessment of insulin resistance, SD: Standard deviation

Interestingly, more than 81% (58/71) of the study subjects were overweight (BMI ≥23 kg/m^2) according to the WHO criteria for Asians.[12] Four were pre-obese (BMI 23-24.9 kg/m^2), 31 had obesity grade I (BMI 25-29.9 kg/m^2), 23 had obesity grade II (BMI >30 kg/m^2).

25-OHD was found to have significant negative linear correlation with BMI [correlation coefficient −0.234 and *P* value 00.050, Figure 1] and HOMA-IR [correlation coefficient −0.237 and *P* value 0.047, Figure 2]. When the correlation was studied after removal of one outlier value of HOMA-IR and adjustment of 25-OHD for BMI, this significant correlation was lost.

25-OHD was not found to be correlated with any of the other parameters of IR studied including GIR.

Discussion

Key findings

The very high prevalence of vitamin D deficiency (87.3%) is consistent with previous reports of very prevalent vitamin D deficiency in India.[13-19] 25-OHD was not found to have significant correlation with parameters of IR.

Strengths and limitations

Our study demonstrated point prevalence of vitamin D deficiency and its association with obesity in postmenopausal women. However, it was limited by the small number of subjects. The parameters studied were limited due to logistic constraints. Also, only patients who were known diabetics or who were diagnosed as having diabetes on the basis of FBG were excluded. The cohort could have included individuals with impaired glucose tolerance with possible abnormalities in insulin secretion.

Interpretation and implications and future research directions

The fact that in our study, more than 81% (58/71) of the study subjects were overweight (BMI ≥25 kg/m^2) probably reflects that menopause is associated with metabolic

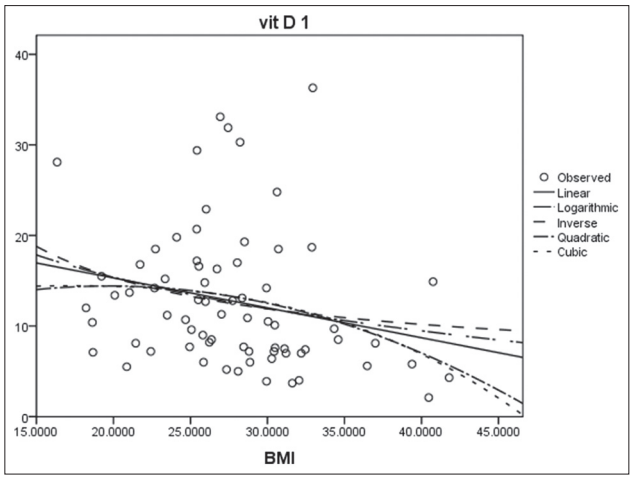

Figure 1: Correlation between 25-hydroxyvitamin D and body mass index

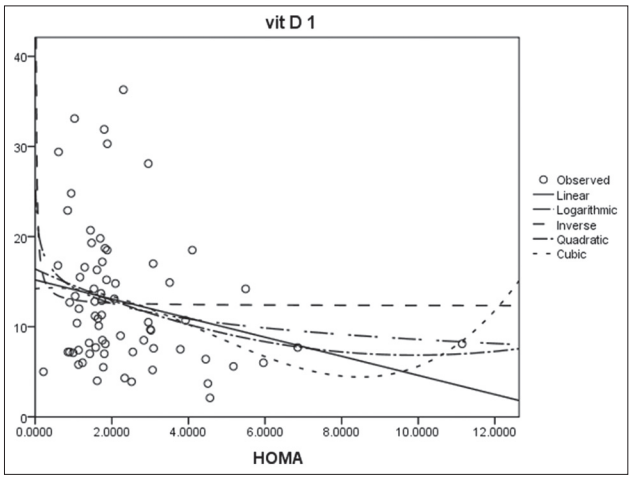

Figure 2: Correlation between 25-hydroxyvitamin D and homeostatic model assessment of insulin resistance

changes contributing to increased cardiovascular risk. Weight gain frequently occurs in perimenopausal women not receiving hormone replacement therapy. This is mainly attributed to an increase in body fat, which is concentrated in the abdomen (android) rather than peripherally (gynoid). Increased BMI tends to reduce the insulin sensitivity and increase systolic blood pressure.[20,21]

In our study, 25-OHD did not correlate significantly with any of the other parameters of IR studied including. The initial significant correlation between 25-OHD and HOMA-IR was probably because it is a fat soluble vitamin and obesity was a confounder. This correlation was lost after adjustment for BMI.

The current literature supports an inverse relationship between 25-OHD and components of the metabolic syndrome, including high blood glucose concentration, IR, dyslipidemia, elevated blood pressure, abdominal obesity[22] and a positive correlation with insulin sensitivity with a negative effect of hypovitaminosis D on β-cell function.[2] In a study conducted among the Hispanic and African Americans as part of the Insulin Resistance Atherosclerosis family study, vitamin D levels were inversely associated with baseline BMI and adipose tissue (subcutaneous and visceral) in both the populations.[23] In a similar study, BMI was found to be negatively related to 25-OHD, the prevalence of 25-OHD deficiency (defined by the authors as 25-OHD <8.8 ng/ml) increased from 8.8% in subjects with BMI <30 kg/m^2 to 15.0% in subjects with BMI >30 kg/m^2.[9] This relationship between 25-OHD and percentage body fat (measured by dual energy X-ray absorptiometry) persisted significantly after adjusting for race, age, season and dietary vitamin D intake.[8]

Some of such data comes from Asian population. In a study conducted among middle aged and elderly Chinese adults, 25-OHD was negatively associated with fasting insulin and HOMA-IR and the associations were stronger among overweight and obese subjects.[5]

However, all the available literature is not in unison. Data from the Women's Health Study suggested that neither total nor supplemental vitamin D was significantly associated with metabolic syndrome. Dietary vitamin D was inversely associated with the prevalence of metabolic syndrome, but was not independent of total calcium intake. Strong relations between intakes of dairy products and metabolic syndrome were also observed.[24] Similarly, contradicting results were found from data from the Rancho Bernardo study.[6] Neither Parathormone (PTH) in women nor 25-OHD levels in either sex were related to the metabolic syndrome. There was a significant trend of increasing adjusted odds for metabolic syndrome with increasing PTH concentrations. 25-OHD levels are significantly inversely associated with blood pressure in Hispanic and African Americans. However, this association was not significant after adjustment for BMI.[6]

It is interesting to note however that supplementation with vitamin D improves insulin sensitivity as observed in some studies. However, some studies also showed that supplementation with calcium and/or vitamin D did not reduce the risk of developing diabetes nor reduced blood pressure or the risk of developing hypertension.[24,25]

Obesity is associated with alterations in the vitamin D physiology as seen from our and some previous studies.[5] There is not enough data to establish a cause and effect relationship between obesity and vitamin D levels or IR and vitamin D. Lower levels of serum 25-OHD in obese individuals may be secondary to an alteration in tissue distribution resulting from an increase in adipose mass.

Vitamin D being fat soluble gets accumulated in the adipose tissue and less is bioavailable for action at other sites. Therefore, it is difficult to conclude that the serum levels of 25-OHD actually reflect the true circulating levels in the obese. Also, morbidly obese individuals are expected to need higher doses of vitamin D supplementation than the general population. Further studies will be required in this direction. Furthermore, it needs to be established whether it is the dietary calcium and/or vitamin D or its total circulating level, which is affected as seen in some studies.[4]

It is believed that other important factors determining serum 25-OHD vitamin D level are race and ethnicity. In this regard, there is a higher prevalence of hypovitaminosis D in ethnic populations such as African-Americans, Hispanics, etc., who are at greater risk of IR, obesity, type 2 diabetes and cardiovascular diseases than Caucasians.[26] National Health and Nutrition Examination Survey III data did not show any significant association between 25-OHD and IR (homeostasis model of assessment for IR) in African-Americans, but showed significant association in Caucasians and Hispanic-Americans.[26]

Given the fact that 25-OHD levels are related to vitamin D polymorphism,[27] it may be postulated that the differences among race and ethnicity and variability of results may be due to Vitamin D receptor polymorphism.

Conclusion

Data from our study suggest that the correlations between 25-OHD and HOMA-IR are secondary to increased adiposity.

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