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Original Article

Obstetrics and Gynecology Section

Vitamin D Status and Cardio-Metabolic Risk in Indian Postmenopausal Women

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ABSTRACT

Introduction: The prevalence of chronic and non-communicable health disorders like cardiovascular diseases and metabolic syndrome is increasing worldwide including in India. The various risk factors for these health issues need to be addressed. The role of vitamin D deficiency in the causation of all these abnormal health conditions among postmenopausal women is a matter of debate now-a-days.

Aim: To determine the correlation of serum vitamin D levels with various cardio-metabolic risk factors and metabolic syndrome (MetS) in postmenopausal women (PMW).

Materials and Methods: Total of 64 PMW were included in this cross-sectional study. Clinical (waist circumference, body mass index, blood pressure) and biochemical (fasting plasma glucose, lipid profile and serum 25-hydroxyl vitamin D levels) parameters were measured. MetS was defined using modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) guidelines. Serum 25-hydroxyl vitamin D levels <50 nmol/l, between 52.5-72.5 nmol/l and ≥75 nmol/l were classified as deficient, insufficient and sufficient, respectively.

Results: MetS was prevalent in 33 (52%) subjects. There were no differences in serum vitamin D levels or proportion of vitamin D deficient individuals in those with and without MetS. 33 women (52%) had vitamin D deficiency. Cardio-metabolic risk profile was similar in both vitamin D deficient and replete women.

Conclusion: Despite a high prevalence of vitamin D deficiency and MetS in Indian PMW, serum vitamin D concentrations do not correlate with the cardio-metabolic risk factors or MetS.

Keywords: Dyslipidemia, Hypertension, Obesity

INTRODUCTION

Vitamin D Deficiency (VDD) is a pandemic, affecting populations across the globe [1]. Despite its favourable tropical location and perennial ample sunshine, India is not immune to this public health menace [2]. VDD is more likely to occur in women and elderly [3]. In particular, VDD is exacerbated in Post-Menopausal Women (PMW) owing to the loss of estrogen and age-related changes in the vitamin D receptor and vitamin D synthesis. No wonder, prevalence of VDD ranges from 50% to 90% in PMW in western world [4,5]. Similar results have been found in few studies from India as well [6-8].

Hypovitaminosis D is increasingly being recognized as a potential novel cardiovascular risk factor. Low levels predispose to conventional cardiovascular risk factors like hypertension (HTN), adiposity, dyslipidaemia and diabetes [9-12]. Epidemiological studies also provide speculation over a possible inverse association between vitamin D status and metabolic syndrome (MetS) [13-15]. However, there is limited evidence regarding this relationship in Asian populations, who are at risk for cardiovascular diseases (CVDs) at lower body mass index (BMI) [16-20]. Additionally, prevalence of CVD risk factors has been reported to be increased after menopause owing to the risk of central obesity resulting from estrogen deficiency [21,22]. Yet, studies investigating the association between vitamin D levels and cardio-metabolic risk factors including MetS in Asian Indian PMW are scarce [6,7].

AIM

The objective of our study was to determine the correlation of vitamin D levels with conventional cardiovascular risk factors like obesity, HTN, hyperglycaemia and dyslipidaemia in PMW. It also aimed to investigate the association between vitamin D status and MetS.

MATERIALS AND METHODS

This cross-sectional study was carried out at a teaching hospital over one year from January 2014 to December 2014. The study was approved by the ethical committee of the institute. All subjects gave their informed consent before participating in the study. Total of 64 PMW attending the outpatient clinic of Gynaecology department as well as Menopause clinic were recruited. Postmenopausal status was defined as cessation of menstruation for at least 1 year. Hysterectomised women were included if aged 45–52 years, provided they had elevated serum follicular stimulating hormone (> 40 IU/L). None of our patients were taking hormone replacement therapy. Exclusion criteria were chronic liver or kidney disease, previous or current cancer, malabsorption, sunlight allergies, endocrine disorders like Cushing syndrome, hyperthyroidism, hypothyroidism and primary hyperparathyroidism, those on drugs like oral contraceptives, statins, anti-epileptics, rifampicin, vitamin D or calcium supplementations, current or past treatment with glucocorticoids > 6 months, addiction to alcohol or drugs and those who were diagnosed to have PCOS previously.

Detailed history was elicited with respect to symptoms of VDD. Clinical and anthropometric data were recorded such as age, years of menopause, height, weight, BMI, waist circumference (WC) and blood pressure (BP). Height and weight were measured with subjects wearing light clothing but without shoes, using stadiometers and calibrated digital weighing scales respectively. BMI was calculated by dividing the weight in kilograms by the height in meters squared. As per WHO BMI range for Asians,

normal, overweight and obesity was defined as BMI of 18.5-22.9 kg/m^2, 23.0 to 26.9 kg/m^2 and ≥ 27 kg/m^2 respectively [23]. WC was measured at the midpoint between the lower costal margin and iliac crest at the end of normal expiration using an inch tape as per National Institute of Health (NIH) guidelines [24]. BP was measured in the sitting position after resting for 10 min, twice with 5-min intervals, using a mercury sphygmomanometer, and the average value in mmHg was used. MetS was defined according to the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) criteria [25], which requires any three or more of the following: (a) Fasting plasma glucose (FPG) ≥ 5.6 mmol/l (or receiving drug therapy for hyperglycaemia); (b) Systolic blood pressure (SBP) ≥ 130mmHg and diastolic blood pressure (DBP) ≥ 85mmHg (or taking drugs for the treatment of hypertension); (c) WC ≥ 80cm in women or ≥ 90 cm in men; (d) Fasting serum triglyceride (TG) ≥ 1.69 mmol/l (or receiving treatment for elevated TG); (e) High density lipoprotein cholesterol (HDL-C) ≤ 1.03 mmol/l in men or ≤ 1.29 mmol/l in women (or taking drug therapy for low HDL-C). All the biochemical measurements (FPG, lipid profile & 25-hydroxyl vitamin D {25-(OH) vitamin D}) were done in the morning after an overnight fast of 8-12 hours. FPG, TG and total cholesterol (TC) were measured by glucose oxidase-peroxidase, glycerol oxidase-peroxidase and cholesterol oxidase-peroxidase methods, respectively. Direct estimation was done for low density lipoprotein cholesterol (LDL-C) and HDL-C. Serum 25-(OH) vitamin D was estimated by chemiluminescence method (Access 2 immunoassay systems, Beckman Coulter, California USA). The intra-assay and inter-assay coefficients of variation were 2.2% and 7.2%, respectively. Serum 25-(OH) vitamin D levels <50 nmol/l, between 52.5-72.5 nmol/l and ≥75 nmol/l were classified as deficient, insufficient and sufficient, respectively, as per Endocrine Society 2011 guidelines [26].

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS software version 17. All continuous normally distributed data were summarized as mean & standard deviation (SD). Data not normally distributed were presented as median with inter-quartile ranges (IQR). The categorical data were expressed as frequency (as percentages), which were compared using Chi-Square test. Correlation between components of MetS and serum vitamin D levels was calculated using Spearman's correlation co-efficient. To compare between the subjects of different groups, unpaired t-test, Mann-Whitney test, one-way analysis of variance (ANOVA) & Kruskal-Wallis test were used. p-value <0.05 was considered significant.

RESULTS

The baseline parameters are depicted in [Table/Fig-1]. The median BMI was 27kg/m^2 and mean WC was 98cm. The median serum 25-OH vitamin D level was 48.75 nmol/l for the entire cohort. The median of post-menopausal status duration was 6 years. [Table/Fig-2] compares the parameters between MetS and non-MetS group. The prevalence of MetS was quite high (52%). As expected, those with MetS had significantly higher weight, BMI, WC, SBP, DBP, FPG and TG and lower HDL-C compared to those without MetS, despite similar cholesterol levels. Overweight/obesity and central adiposity were highly prevalent in both groups (85% & 87% in MetS, 61% & 69% in non-MetS respectively). Interestingly, the proportion of vitamin D deficient subjects or median serum concentrations of vitamin D did not differ between these two groups [Table/Fig-2]. Among the 64 PMW, the proportion of vitamin D deficient, insufficient and sufficient individuals were 52% (n=33), 23% (n=15) and 25% (n=16) respectively [Table/Fig-3]. Apart from serum vitamin D levels, women in these 3 groups were comparable in all other variables. Despite the high prevalence of VDD and MetS, there was no correlation between vitamin D levels and components of MetS, as evident in [Table/Fig-4].

Parameters	Mean/ Median	Standard Deviation (SD)/ Inter-quartile range (IQR)
Age (y)	51	7.75
*Height (cm)	151.23	5.71
*Weight (kg)	62.64	13.04
BMI (kg/m^2)	27	7.90
*WC (cm)	98	13.43
SBP (mm Hg)	130	20
DBP (mm Hg)	80	11
Post-menopausal status (yrs)	6	9
*Total Cholesterol (mmol/l)	4.97	1.08
Triglyceride (mmol/l)	1.42	0.72
HDL Cholesterol (mmol/l)	1.16	0.28
LDL Cholesterol (mmol/l)	2.69	1.14
VLDL Cholesterol (mmol/l)	0.65	0.31
FPG (mmol/l)	5.44	1.33
Serum 25-OH vitamin D level (nmol/l)	48.75	47.3

[Table/Fig-1]: Baseline Parameters.
BMI-body mass index; WC- waist circumference; SBP-systolic blood pressure; DBP-diastolic blood pressure; HDL- high density lipoprotein; LDL- low density lipoprotein; VLDL – very low density lipoprotein; FPG – fasting plasma glucose.
* Expressed as mean with standard deviation. Others are expressed as median with inter-quartile range

Parameters	MS (N=33)	Non-MS (N= 31)	p-value
Age (y)	54 (11)	50 (09)	0.012
Height (m)^	1.51 (0.06)	1.50 (0.05)	0.627
Weight (kg)^	66 (13)	58 (11)	0.013
BMI (kg/m^2)	29 (07)	24 (07)	0.018
Overweight/Obese (BMI ≥23.0 kg/m^2) *	28 (85%)	19 (61%)	0.0001
WC (cm)^	101 (13)	94 (12)	0.040
Central Obesity (WC ≥ 80 cm)*	29 (87%)	23 (69%)	0.0001
SBP (mm Hg)	130 (23)	120 (21)	0.010
DBP (mm Hg)	87 (10)	80 (10)	0.002
Post-menopausal status (yrs)	08 (11)	04 (07)	0.050
Total Cholesterol (mmol/l)^	4.94 (0.98)	5.02 (1.21)	0.840
Triglyceride (mmol/l)	1.70 (0.75)	1.24 (0.53)	0.024
HDL Cholesterol (mmol/l)	1.08 (0.20)	1.34 (0.36)	0.001
LDL Cholesterol (mmol/l)	2.72 (0.69)	2.72 (1.06)	0.973
VLDL Cholesterol (mmol/l)	0.77 (0.38)	0.57 (0.26)	0.039
FPG (mmol/l)	5.83 (02)	5.16 (0.66)	0.002
25-OH Vitamin D (nmol/l)	52.5 (47.5)	45 (47.5)	0.904
Vitamin D deficiency* (serum 25-OH vitamin D < 50 nmol/l)	16 (48%)	17 (55%)	0.16

[Table/Fig-2]: Patients with/without metabolic syndrome.
BMI-body mass index; WC- waist circumference; SBP-systolic blood pressure; DBP-diastolic blood pressure; HDL- high density lipoprotein; LDL- low density lipoprotein; VLDL – very low density lipoprotein; FPG – fasting plasma glucose.
*Expressed as number with percentages
^Expressed as mean with standard deviation
Rest parameters are expressed as median with inter-quartile range.

DISCUSSION

The high prevalence of VDD in PMW observed in our study is in accordance to most studies [4-8]. But the prevalence of MetS in our study is strikingly higher than other studies conducted in PMW including from Asia [27-29]. However, the study by Alissa et al., reported a prevalence rate of 57% [30]. Asian Indians tend to have disproportionately higher total body fat at any given BMI compared with those of the other ethnicities that might predispose them to increased risk of MetS and CVD [20]. Additionally, false

Parameters	Deficiency (N=33)	Insufficiency (N=15)	Sufficiency (N=16)	p-value
Age (y)	51 (9)	54 (07)	51 (12)	0.496
Height (m)^	1.50 (0.06)	1.53 (0.05)	1.49 (0.04)	0.087
Weight (kg)^	64 (13)	63 (14)	59 (10)	0.530
WC (cm)^	99 (15)	96 (11)	96 (11)	0.737
BMI (kg/m^2)	29 (09)	26 (08)	26 (05)	0.738
SBP (mm Hg)	130 (20)	120 (10)	125 (14)	0.445
DBP (mm Hg)	80 (10)	80 (18)	80 (15)	0.305
Post-menopausal status (yrs)	05 (09)	10 (10)	06 (11)	0.181
Total Cholesterol (mmol/l)^	4.92 (1.11)	5.23 (1.08)	4.89 (1.03)	0.684
Triglyceride (mmol/l)	1.42 (0.72)	1.47(0.82)	1.47 (0.82)	0.722
HDL Cholesterol (mmol/l)	1.21 (0.31)	1.08 (0.28)	1.11 (0.33)	0.229
LDL Cholesterol (mmol/l)	2.64 (0.88)	2.87 (0.98)	2.77 (0.72)	0.773
VLDL Cholesterol (mmol/l)	0.64 (0.31)	0.57 (0.44)	0.67 (0.38)	0.750
FPG (mmol/l)	5.44 (1.05)	5.33 (1.44)	6 (2.61)	0.305
Metabolic Syndrome*	16 (48%)	09 (60%)	08 (50%)	0.753
25-OH Vitamin D (nmol/l)	30 (20)	57.5 (12.5)	97.5 (65)	<0.0001

[Table/Fig-3]: Patients with vitamin D deficiency, insufficiency & sufficiency.
BMI-body mass index; WC- waist circumference; SBP-systolic blood pressure; DBP-diastolic blood pressure; HDL- high density lipoprotein; LDL- low density lipoprotein; VLDL – very low density lipoprotein; FPG – fasting plasma glucose.
*Expressed as number with percentages
^Expressed as mean with standard deviation
Rest parameters are expressed as median with inter-quartile range.

Parameters	Spearman's correlation coefficient	p-value
Age (yrs)	0.107	0.40
Height (m)	-0.005	0.972
Weight (kg)	-0.101	0.433
WC (cm)	-0.051	0.699
BMI (kg/m^2)	-0.064	0.623
SBP (mm Hg)	-0.155	0.228
DBP (mm Hg)	-0.178	0.167
Post-menopausal status (yrs)	0.157	0.220
Total Cholesterol (mmol/l)	0.086	0.549
Triglyceride (mmol/l)	0.092	0.525
HDL Cholesterol (mmol/l)	-0.290	0.051
LDL Cholesterol (mmol/l)	0.119	0.43
VLDL Cholesterol (mmol/l)	0.084	0.583
FPG (mmol/l)	0.135	0.320
Metabolic Syndrome	0.015	0.905

[Table/Fig-4]: Correlation of serum 25-OH vitamin D level with different parameters.
BMI-body mass index; WC- waist circumference; SBP-systolic blood pressure; DBP-diastolic blood pressure; HDL- high density lipoprotein; LDL- low density lipoprotein; VLDL – very low density lipoprotein; FPG – fasting plasma glucose.

characterization of individuals as vitamin D deficient, based on their serum estimates, can occur owing to sequestration of the fat soluble vitamin D in the large pool of body fat. The high proportion of individuals with overweight/obesity (73%) with high mean WC (98cm) may explain the high prevalence of both vitamin D inadequacy and MetS in this study. Our finding of high prevalence of overweight/obesity and central adiposity in both MetS and non-MetS groups is supported by another study in Saudi Arabian PMW [30], underscoring the alarming burden of obesity in PMW and its associated cardiovascular implications among Asians. Despite high prevalence of VDD as well as MetS, we could not demonstrate any differences in the frequency of VDD or Median serum level of 25-OH vitamin D between individuals with and without MetS. This is in agreement with few studies [30] but contrary to others [17,31].

Many investigators have found an unfavourable cardio-metabolic risk profile in VDD individuals such as higher weight, BMI, WC, BP, TG, cholesterol, FPG, fasting insulin and homeostatic model assessment-insulin resistance (HOMA-IR) and lower HDL-C compared to vitamin D sufficient and insufficient individuals [16,17,31,32]. Our results, however, are in sharp contrast to these studies. Also, the prevalence of MetS did not differ between subjects with different categories of vitamin D adequacy, a finding corroborated by few studies [17] but disagreeing with others [31].

Studies investigating the association between hypovitaminosis D and MetS have yielded conflicting results. Most studies have found an inverse association between prevalent/incident MetS and serum vitamin D levels [13-19], but only few of them controlled for adiposity. Other studies [29], including ours, refute this observation. While some studies have found association with all components of MetS [15], few have found association only with anthropometric parameters [33] and some with individual parameters like TG [28,30] FPG [30] and BP [28,30]. Chon et al., in a study of more than 4000 Korean PMW, observed that although there was no significant association between serum vitamin D levels and prevalence of MetS, the adjusted odds ratio (OR) for elevated BP, elevated TG, and reduced HDL-C showed tendency to decrease sequentially as tertiles of serum 25(OH)D levels increased [29]. Conversely, Moy et al., noted that there were higher metabolic risk scores and higher odds of MetS in vitamin D deficient subjects but no significant association with individual components [16]. These varied results and inconsistencies in literature are possibly due to the proposed inconsequential metabolic effects of vitamin D in some populations, differences in vitamin D metabolism in different ethnicities resulting in different optimum concentrations, differences in baseline concentrations of serum 25-(OH) vitamin D, different definitions for vitamin D adequacy and MetS and different assay methodologies employed in different studies or varying control of measures of adiposity.

Contrary to existing evidence, our findings did not show significant correlation between serum vitamin D levels and the conventional cardiovascular risk factors. The high prevalence of MetS observed in our cohort may have obscured the impact of other coronary risk factors including VDD. Cross-sectional design and small sample size restricted to only PMW may also be another reason, unlike other studies which were largely epidemiological with large sample size and inclusive of both sexes and all age-groups. It can also be because of the fact that majority of our study sample was comprised of subjects with hypovitaminosis D (serum 25-OH vitamin D < 75 nmol/l). Owing to this reduced variability in the serum 25-(OH) vitamin D levels, the protective effects of higher vitamin D levels could have been compromised and hence, no association could be established between the studied parameters.

LIMITATION

Our study had some limitations. Firstly, this study was based on a single measurement of serum 25-(OH) vitamin D as an indicator of vitamin D status. Secondly, the results cannot be generalized to the entire nation as our participants were PMW and universally indoor-bound. Thirdly, other factors associated with low vitamin D status such as dietary survey or physical activity pattern were not assessed. Additionally, insulin resistance, risk of which is known to be increased by hypovitaminosis D in MetS, was not evaluated, which could have provided better insights into the possible link between high prevalence of VDD and MetS. Lastly, being a cross-sectional study with small sample size, it has its own limitations.

CONCLUSION

Indian PMW have high prevalence of VDD as well as MetS, although no correlation exists between serum vitamin D levels and cardio-metabolic risk factors. Our study suggests that there is no association between vitamin D status and MetS. Nevertheless, the high prevalence of obesity, especially central adiposity, as well as MetS in this vulnerable group and the growing experimental and epidemiological evidence for the novel cardio-metabolic effects of vitamin D warrants large-scale randomized studies adequately powered to study CVD outcomes.

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