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Prevalence of Cardio-metabolic Risk Factors among Young Saudi Women with Vitamin D Deficiency

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Authors' contributions

This work was carried out in collaboration between both authors. Author HAK Conception and design of the study; data collection; data analysis, interpretation and writing of results, critical revision of the final report; and final approval of the version to be published. Author EA Interpretation of the results, drafting the final report and final approval of the version to be published. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: The aim of this study was to determine the prevalence of cardio-metabolic risk factors in apparently healthy Saudi women with vitamin D deficiency.
Study Design: A retrospective chart review.
Place and Duration of Study: This study was conducted in the Center of Excellence for Osteoporosis Research (CEOR), King Abdulaziz University, Jeddah, Saudi Arabia, between June 2015 to October 2015.
Methodology: Healthy women 20–40 years old, with no history of previous illnesses and not on any medications were included in this study. Data on anthropometric measurements as well as blood pressure (BP) were obtained. Body mass index (BMI) was calculated. Laboratory results including fasting blood glucose (FBG), fasting lipid profile, 25-hydroxyvitamin D3 (25(OH)D3) and parathyroid hormone (PTH) were also obtained. Vitamin D deficiency was defined as 25(OH)D3

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concentration <50 nmol/l. Modified NCEP:ATPIII criteria were used to define cardio-metabolic risk factor cutoff points.

Results: A total of 305 women were included in the current analysis. Mean (± S.D.) age of the study group was 28.4±6.1 years and median (IQR) 25(OH)D3 was 17.8 (11.9–28.2) nmol/l. Almost 97% of the study participants were vitamin D deficient and 70% had values below 25 nmol/l. 25(OH)D3 was significantly inversely associated with waist circumference, systolic and diastolic BP and PTH (P=0.011, <0.0001, <0.0001, <0.0001, respectively). Prevalence of cardio-metabolic risk factors were higher among participants who fell in the lowest tertile of 25(OH)D3 except total cholesterol and low density lipoprotein cholesterol, however only higher PTH was statistically significant (P=0.022).

Conclusion: The results of the present study confirm the high prevalence of vitamin D deficiency among otherwise healthy Saudi women. The results also suggest that the prevalence of selected cardio-metabolic risk factors is higher among those with low vitamin D status. Prospective studies are needed to determine whether such deficiency will be of clinical significance with advancing age in this population, and whether vitamin D supplementation has beneficial effects.

Keywords: Vitamin D deficiency; cardio-metabolic; risk factors; Saudi.

1. INTRODUCTION

Cardiovascular disease (CVD) is a major cause of morbidity and mortality globally. It is defined as a group of non-communicable diseases, encompassing ischemic heart disease, coronary artery disease, myocardial infarction, and stroke as well as its associated risk factors such as hypertension, type 2 diabetes mellitus and dyslipidemia that further contribute to high mortality rates from CVD [1]. Thus, the interest in identifying potential cardiovascular biomarkers continue in the context of early detection of CVD leading to improved healthcare plans and overall survival rates.

It has been long hypothesized that reduction in CVD mortality during summer season might be due to a cardio-protective action of vitamin D [2]. More attention is given to the role of vitamin D deficiency in extra-skeletal diseases including CVD. Recently, many studies are addressing the association of low vitamin D serum levels with hypertension, diabetes, atherosclerosis, myocardial infarction and stroke, with greater concern over the concomitant rise in vitamin D deficiency prevalence worldwide [3]. Reasons for this widespread deficiency remain unclear but are partly related to lifestyle factors such as low dietary vitamin D intake, decreased outdoor activity, air pollution, urbanization, sunscreen use, as well as reduced cutaneous production of vitamin D with aging [3]. Elderly people in particular are at higher risk of developing vitamin D deficiency because of reduced ability to synthesize vitamin D through skin with advancing age, which is usually accompanied by limited outdoor physical activities, low dietary vitamin D intake and inadequate sunlight exposure [4]. In countries with plenty of sunshine like Saudi Arabia, it would be expected to find adequate vitamin D levels in most of the population. Nevertheless, vitamin D deficiency is considered a major public health problem among all age groups in Saudi Arabia [5] and several other countries in the Middle East [6].

A growing body of evidence suggests that vitamin D may play a role in modifying risk of cardio-metabolic outcomes, including diabetes mellitus type 2, hypertension, dyslipidemia and metabolic syndrome [7]. As recently reviewed, low vitamin D status is associated with other cardio-metabolic risk factors and events, such as obesity, carotid atherosclerosis, myocardial infarction and stroke [8]. In spite of these numerous studies, findings from different studies that addressed the relation of serum 25-hydroxy vitamin D3 (25(OH) D3) to the individual cardio-metabolic risk factors in observational settings havebeen inconsistent [9,10]. Additionally, underlying mechanisms behind these relations remain poorly understood.

Apart from a few local studies [11-14], information about vitamin D status and its association with prevalent cardio-metabolic risk factors among healthy Saudi females is still scarce. Hence, we aimed to determine the prevalence of cardio-metabolic risk factors in otherwise healthy young Saudi women with vitamin D deficiency.

2. METHODOLOGY

This cross-sectional study was conducted retrospectively to review medical charts of 305 Saudi women, aged 20-40 years, who attended

the Center of Excellence for Osteoporosis Research (CEOR), King Abdulaziz University, Jeddah, Saudi Arabia between June 2015 toOctober 2015. Informed written consents were obtained from all participants and the study was approved by the Ethics Committee at CEOR.

Inclusion criteria of study participants were: having standardized blood pressure readings, normal renal and liver function tests. Exclusion from the study involved pregnant women, women aged above 40 years, those with any chronic illness, receiving any medications, calcium and vitamin D supplementation and/or missing serum 25(OH)D3 results.

Blood pressure was measured in all participants while sitting with an automated blood pressure monitor (BpTRU, VSM Med Tech Ltd, Coquitlam, Canada). Three readings were taken after 5 minutes rest. The average of the last two readings was used for analysis [15].

Body height was measured by a wall mounted stadiometer and body weight was measured by a balance beam scale with participants wearing light clothes and barefooted. Body mass index (BMI) was calculated as body weight (kilograms) ÷ body height (meters^2) and classified according to the World Health Organization guidelines. Obesity was defined as BMI ≥ 30 kg/m^2 [16]. Waist circumference (WC) was measured at the umbilical level in standing position using a non-stretchable measuring tape.

Blood samples were collected after 12 hr fasting for subsequent analysis of fasting lipid profile, fasting blood glucose (FBG), parathyroid hormone (PTH) and 25(OH)D3. Blood samples were withdrawn from an antecubital vein, placed into appropriate tubes that were centrifuged at 3000 x g for 10 minutes. The collected serum and plasma were stored at -80°C until the time of analysis, with the exception of glucose which was determined immediately after blood was drawn.

All biochemical analytes measurements were determined using Vitros 250 Chemistry Auto analyzer (Ortho-Clinical Diagnostics- Johnson & Johnson Co., USA). Low density lipoprotein-cholesterol (LDL-C) concentration was calculated using the Friedewald's equation [17], except for those with triglycerides exceeding 4.5mmol/L. The atherogenic index was calculated by dividing total cholesterol (TC) by high density lipoprotein-cholesterol (HDL-C).

Serum 25(OH)D3 analysis was performed by chemiluminescence immunoassay using a LIASON auto analyzer (DiaSorin Inc., Stillwater, MN, USA). Vitamin D deficiency was defined as serum 25OHD < 50 nmol/l according to Lips criteria [18].

The modified "National Cholesterol Education Program Adult Treatment Panel III" Criteria were used to define the cut-off values of the following cardio-metabolic risk factor [19]. Central obesity was defined at WC of 80 cm in women. Hypertension was defined as a systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥85 mmHg. FBG ≥ 5.6 mmol/L was used to define dysglycemia. Dyslipidemias were defined by the following: TC ≥5.2 mmol/L, TG ≥1.7 mmol/L, HDL-C <1.30 mmol/L for women, LDL-C ≥ 3.36 mmol/L and TC/HDL ratio ≥ 5 [20].

2.1 Statistical Analysis

Data were checked for normality using Shapiro-Wilk test. Results are reported as mean±SD or median (interquartile range) for continuous variables while categorical variables were presented as frequency (%). Study participants were grouped according to tertile values of serum 25(OH)D3. All measured variables were compared between the lower and upper 2 tertiles of 25(OH)D3 using Student-t test and Chi-square test for numeric and categorical variables, respectively. Relationships between 25(OH)D3 and selected cardio-metabolic risk factors were sought by Pearson or Spearman's correlation coefficient according to distribution. Data analysis was performed with the SPSS statistical program (version 20, SPSS Inc, Chicago, Illinois). A *P* value less than 0.05 was considered significant.

3. RESULTS AND DISCUSSION

A total of 305 women were included in the current analysis. Mean (±SD) age of the study participants was 28.4 ± 6.1 years and median (IQR) 25(OH)D3 was 17.8 (11.9-28.2) nmol/L. Fig. 1 illustrates that almost all of the study participants were considered vitamin D deficient (97%) with 70% had serum levels below 25 nmol/L.

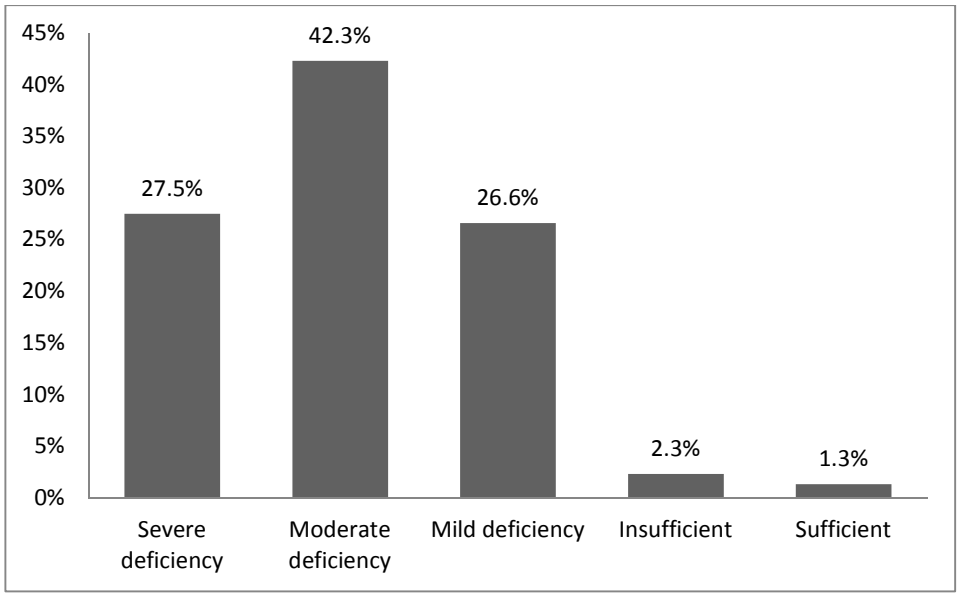

Fig. 1.Categorization of vitamin D status among the study participants (n=305)

Severe deficiency: 25(OH)D3 <12.5 nmol/L, moderate: 12.5-<25 nmol/L, mild: 25-<50 nmol/L, insufficient: 50-<75 nmol/L, sufficient ≥ 75 nmol/L

Table 1. Mean age, anthropometric, blood pressure and biochemical characteristics of the study participants in the lowest and highest 25(OH)D3 tertiles

Variable	Lowest tertile(n=99)	Highest tertile(n=206)	*P*-value
Age (years)	28.1 ± 6.1	28.6 ± 6.2	0.506
BMI (kg/m^2)	27.1 ± 6.5	25.9 ± 6.2	0.099
WC (cm)	78.5 ± 16.2	75.3 ± 12.7	0.061
SBP (mmHg)	104.3 ± 8.8	100.8± 7.9	0.001
DBP (mmHg)	67.5 ± 7.7	65.0± 6.6	0.006
25(OH)D3 (nmol/L)	9.2 ± 2.7	26.8 ± 13.5	<0.0001
PTH (pmol/L)	13.0 ± 8.0	9.4 ± 4.1	<0.0001
FBG (mmol/L)	4.6 ± 0.57	4.4± 0.45	0.012
TC (mmol/L)	4.86±0.86	4.80±0.96	0.607
TG (mmol/L)	1.08±0.49	0.96±0.36	0.081
HDL (mmol/L)	1.43± 0.34	1.44±0.38	0.805
LDL (mmol/L)	3.07± 0.75	2.99± 0.83	0.539
TC:HDL ratio	3.57±0.94	3.60± 1.35	0.860

Values are expressed as mean ± SD. Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; 25(OH)D3, 25-dihydroxyvitamin D3; PTH, parathyroid hormone; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC:HDL ratio, total cholesterol: high-density lipoprotein ratio.

Significant differences in mean BP (both systolic and diastolic), PTH and FBG values were observed among participants who fell in the lower tertile of 25(OH)D3 versus those in the highest tertile (Table 1).

Overall, obesity was prevalent among 25% of the study participants (n=305). However, prevalence of cardio-metabolic risk factors among the study groups is shown in Fig. 2. Although nonsignificant (*P*>0.05), the prevalence of cardio-metabolic risk factors was higher among participants who fell in the lowest tertile of 25(OH)D3 versus those in the highest 25(OH)D3 tertile (except for TC and LDL).

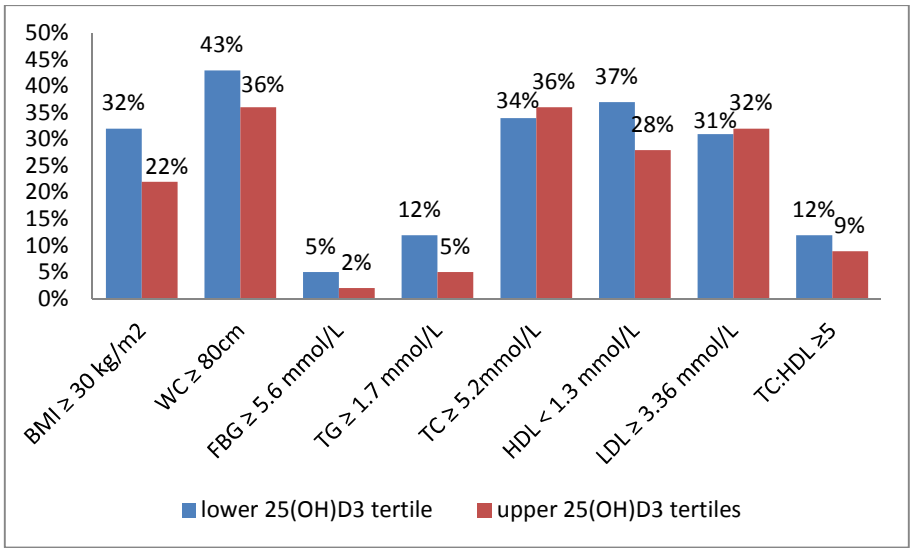

Fig. 2. Prevalence of cardio-metabolic risk factors among those in the lower 25(OH)D3 tertile (n=99) as compared to those in the upper 25(OH)D3 tertile (n=206). Categorical data are compared by Chi-square test

Fig. 3 (a-d) depicts that 25(OH)D3 had negative correlation with waist circumference (r= -0.146, *P*=0.011), PTH (r= -0.333,*P*<0.0001) and blood pressure readings (r= -0.215, *P*<0.0001 and r= -0.203, *P*<0.0001).

3.1 Discussion

Small increases in blood pressure, BMI, plasma lipids, or blood glucose can be an early indication of a developing cardio-metabolic disorder [21]. Efforts to detect these subtle changes are cost effective in young adults so that preventive measures, to abort or delay the development of cardiovascular events, can be implemented at an early stage.

This study confirmed the high prevalence of vitamin D deficiency among otherwise healthy young women as reported by other local observational studies [5,22,23]. The prevalence of selected cardio-metabolic risk factors was higher in women with 25(OH)D3 values that fell in the lower tertile. This is in agreement with several studies that considered the association between vitamin D status and cardio-metabolic risk factors [24,25].

Vitamin D receptors were found to be present in many organs and extra-skeletal physiological effects of vitamin D are well documented [26]. Therefore, it is not surprising that vitamin D deficiency has been implicated in the pathogenesis of several chronic diseases including cardio-metabolic disorders e.g. hypertension, diabetes and obesity [27-29]. The association between hypertension and hypovitaminosis D was supported by the finding that vitamin D is “a negative regulator of the renin-angiotensin system” (RAS) [30]. When stimulated, the RAS ultimately increases salt and water retention in addition to vasoconstriction mediated by angiotensin II, which together brings an increase in blood pressure. Studies on vitamin D deficient subjects also reported high renin activity which correlated with the higher blood pressure readings [31]. However, clinical trials studying the hypotensive effects of vitamin D supplementation in hypertensive subjects were inconclusive with few showing a positive effect [32]. This could be explained by the low dosage of vitamin D given in many of the trials, the short duration of the study, or the baseline vitamin D level which may be deficient but not severely so. Therefore, long-term clinical trials with a short dose interval and a high bioavailable vitamin D supplementation may be needed to reverse the adverse impact.

Systolic and diastolic blood pressures were found to be higher among participants with vitamin D levels that fell in the lower tertile (although readings did not reach the hypertensive range). This is in agreement with most studies that addressed the correlation between 25(OH) vitamin D levels and high blood pressure [33-35].

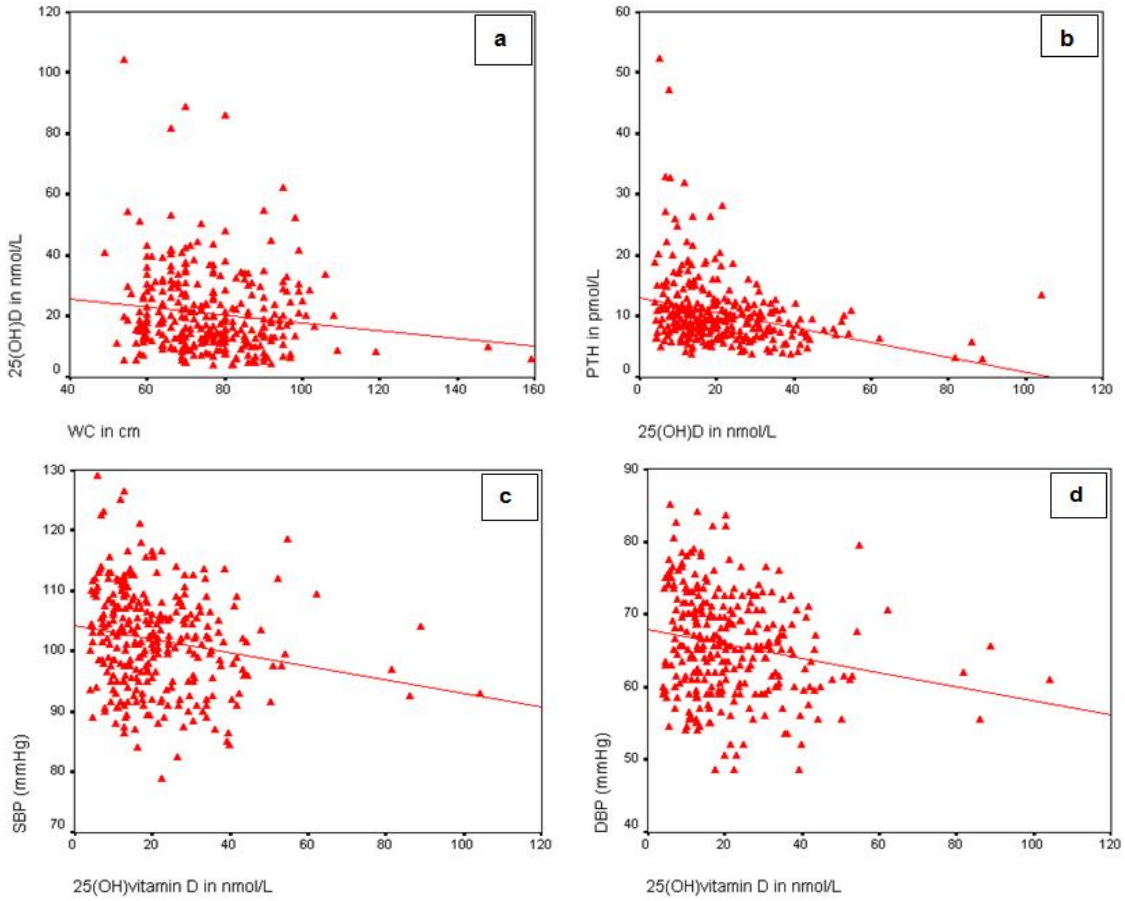

Fig. 3. Scatter plots showing the correlation between 25(OH)D3 and (a) WC(r= -0.146, *P*=0.011), (b) PTH (r= -0.333, *P*<0.0001), (c) systolic blood pressure (r= -0.215, *P*<0.0001) and (d) diastolic blood pressure (r= -0.203, *P*<0.0001)

Vitamin D has also been linked to diabetes mellitus. Vitamin D receptors were found on beta cells of the pancreas, the stimulation of which stimulates calcium influx into the beta cells and enhances insulin release [9]. Moreover, a positive correlation of serum vitamin D concentration with insulin sensitivity as well as a negative effect of low vitamin D on pancreatic beta cell function was reported [36]. In this study, higher FBG levels were found in women with vitamin D level that fell in the lower tertile, which is in favour of a hypoglycaemic role of vitamin D. Our findings were compatible with the confirmation of an inverse and significant association between circulating 25(OH)D3 levels and risk of type 2 diabetes in a number of systematic reviews and meta-analyses [28,29]. Nevertheless, inconsistency between observational and interventional evidence still stands in supporting the benefits of vitamin D therapy in diabetic patients [36].

Optimum vitamin D levels suppress parathyroid hormone, which reduces lipolysis [37]. Vitamin D is also known to increase lipoprotein lipase enzyme activity in adipocytes, which reduces triglycerides level [38]. An inverse relationship between serum vitamin D levels and important cardio-metabolic risk factors, including hypertriglyceridemia was previously demonstrated [39]. This could explain the higher TG level in those women who have low vitamin D levels in this study, which is consistent with other studies [40]. One study showed that low 1,25(OH)D levels were associated with low HDL-C levels while low 25(OH)D levels were associated with high levels of TC, LDL-C and TG [41]. Moreover, vitamin D deficiency was found to be associated with lower HDL-C, higher TG, TC as well as apolipoprotein E levels [42]. Although observational studies unequivocally confirm an association between sufficient vitamin D status and a favorable lipid profile [43], the effect of

vitamin D supplementation upon optimal serum lipid profile in hypovitaminosis D patients remains unclear. Noteworthy, vitamin D and blood lipids relationship might be confounded by vitamin D and obesity link.

More obese women were found to have lower vitamin D levels in this study. The higher prevalence of obesity among vitamin D deficient subjects, irrespective of age, ethnicity or geographic location, has been well documented [44]. Of all cardio-metabolic risk factors, obesity has a clear association with vitamin D deficiency as both are implicated to be risk factors for cardio-metabolic disorders [45]. As a fat-soluble vitamin, its deposition in adipose tissue reduces its bioavailability in the circulation [46]. Additionally, the role of traditional Saudi diet in providing adequate vitamin D intake levels is highly suspected, given the fact that fortification measures in Saudi Arabia are limited to some extent [47]. This can be a major public health concern, especially among high-risk groups who are not taking vitamin D supplementation. Furthermore, vitamin D metabolism and 25-OH vitamin D synthesis might be impaired due to the development of hepatic steatosis in obese individuals[48].Obese people are more likely to have a sedentary lifestyle; consequently, exposure to sunlight and endogenous synthesis of vitamin D is decreased among them.

3.2 Strengths and Limitations

The studied group of women were young and apparently healthy with no history of chronic diseases. They were not on regular medications which eliminates the effects of several confounding factors. However, some limitations need to be addressed. These include the cross-sectional design of the study which precludes the cause-effect relationship between the different cardio-metabolic risk factors and low vitamin D status. Presence of unmeasured confounding factors that may have biased the association between vitamin D deficiency and cardio-metabolic risk factors cannot be ruled out. Moreover, genetic variations that were not addressed in this study may influence the correlations reported in the study.

4. CONCLUSION

Our results indicated high prevalence of vitamin D deficiency in apparently healthy young Saudi women living in Jeddah. The higher prevalence of cardio-metabolic risk factors among those subjects with hypovitaminosis D suggests an association between poor vitamin D status and a detrimental cardio-metabolic profile. Whether vitamin D deficiency is indeed a cardio-metabolic risk factor or is just a reflection of health characteristics that are usually encountered in subjects with cardio-metabolic risk is yet to be confirmed.

Large-scale intervention studies are needed to further investigate whether vitamin D supplementation, improving or optimizing vitamin D status in severely deficient subjects, has an independent role in the prevention and/or management of cardio-metabolic risk in young adults who are otherwise healthy. Other novel biomarkers of cardio-metabolic risk and inflammatory markers can be investigated in future studies.

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DISCLAIMER

The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge.

CONSENT

All participants received information on the study and provided written informed consent to participate.

ETHICAL APPROVAL

Ethical approval for conducting the study was obtained from the Ethics committee at CEOR.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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