Severe hypovitaminosis D is widespread and more common in non-diabetics than diabetics in Saudi adults

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ABSTRACT

الأهداف: مقارنة بين حدوث نقص فيتامين د في كلا المجموعتين المصابة وغير المصابة بالسكري من البالغين السعوديين، وتحديد الارتباطات مع عوامل الخطر المختلفة.

الطريقة: أجريت دراسة مقطعية في برنامج أبحاث المؤشرات الحيوية، جامعة الملك سعود، الرياض، المملكة العربية السعودية خلال الفترة من مارس حتى أغسطس 2009م، اشتملت الدراسة على 341 حالة (177 غير مصاب بالسكري، و164 مصاب بالسكري من النوع الثاني T2DM). وقد كانت هذه الحالات من البالغين السعوديين ضمن برنامج تقصي المؤشرات الحيوية بالرياض. وقد تم أخذ قياسات الجسم وعينات الدم عند الصيام، وتقدير كل من الجلوكوز، ومستويات الدهون. كما تم التقدير الكمي لكل من هيدروكسي-25 فيتامين د، وهرمون الغدة الدرقية (PTH) باستخدام اختبار تقييم المناعة المرتبطة. وقد تم تعريف النقص الحاد لفيتامين د عندما يكون مستواه في الدم أقل من 12.5 نانومول/لتر.

النتائج: كان العمر أهم مؤشر معنوي مرتبط بفيتامين د في كلا المجموعتين، حيث كان موضحاً في 25% قيمة إحصائية (p=0.0005) و 16% قيمة إحصائية (p=0.0005) من الاختلافات. وبضبط تعريف العمر وأخذ نسبة الخصر، ومستوى ضغط الدم، ومؤشر كتلة الجسم كمؤشرات معنوية لمستوى هيدروكسي-25 فيتامين د في غير المصابين بالسكري، وقد أسهم ذلك في توضيح 21% من الاختلافات بقيمة إحصائية (p=0.039). كما أن مستوى هرمون الغدة الدرقية (PTH) أعلى في كل من الرجال والنساء غير المصابين بالسكري.

خاتمة: ينتشر حدوث النقص الحاد لفيتامين د في كل من المصابين وغير المصابين بالسكري في السعوديين، إلا أنه يعتبر شائع بدرجة أكبر في الأعمار الصغيرة والمتوسطة من غير المصابين بالسكري. تؤكد الدراسات العديدة إلى الحاجة إلى إضافة فيتامين د إلى الغذاء السعودي، وتعزيز مكملات فيتامين د في كلا المجموعتين.

Objectives: To compare the incidence of hypovitaminosis D in subjects, with and without type 2 diabetes mellitus (T2DM), and determine its association to various risk factors.

Methods: Three hundred and forty-one (177 non-diabetic, and 164 T2DM) Saudi adults were included in this cross-sectional study conducted at the Biomarkers Research Program (BRP) of King Saud University, Riyadh, Kingdom of Saudi Arabia from March to August 2009. Anthropometrics and fasting blood samples were obtained. Fasting glucose (FG) and lipid profiles were determined. Serum 25-hydroxy vitamin D (25[OH]D) and parathyroid hormone (PTH) were quantified using enzyme-linked immunosorbent assay. Severe hypovitaminosis D was defined as serum 25(OH)D with levels <12.5 nmol/l.

Results: Age was the most significant predictor of 25(OH)D in both groups, explaining 25% (p=0.0005) and 16% of variances (p=0.0005). Waist-hip ratio, systolic blood pressure and body mass index were significant predictors of 25(OH)D among non-diabetics after age adjustment, explaining 21% of variance perceived (p=0.039). Serum PTH levels were higher in non-diabetic men and women.

Conclusion: Severe hypovitaminosis D is prevalent in both non-diabetic and diabetic Saudis, but was more common in the young and middle-aged non-diabetics. The study further underscores the need for vitamin D fortification of the Saudi diet, and the promotion of vitamin D supplementation in both groups.

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Hypovitaminosis D is a widespread phenomenon worldwide, and is most common in South Asia and the Middle East.[1] Existing evidence indicates that low levels of vitamin D, coupled with other known risk factors increase predisposition to cardiovascular disease.[2] This is probably because circulating levels of vitamin D specifically 1,25-dihydroxyvitamin D affects cardiac muscle directly, controls parathyroid secretion, regulates the renin-angiotensin-aldosterone system, and modulates the immune response.[3] Moreover, observational data strongly suggests a pathogenic role for vitamin D deficiency in the progression of type 2 diabetes mellitus (T2DM).[4] Vitamin D appears to act directly on the beta cells of the pancreatic islets, on mediators of inflammation, and parathyroid hormone (PTH) secretion.[5] The presence of vitamin D receptors (VDRs) and vitamin D binding proteins (DBP) in the pancreatic tissue, and the association between certain allelic variants in the VDR and DBP genes with glucose tolerance and insulin secretion further strengthens this theory.[6] Recently, the uncarboxylated fraction of osteocalcin, whose secretion by osteoblasts is regulated by vitamin D was implicated as a mediator in the metabolic change in vitamin D. The Middle East and the North African region in general have very high prevalence of hypovitaminosis D, which appears to be most prominent in women of varying ages.[7] Several studies in the Kingdom of Saudi Arabia (KSA) also point to decreased levels of vitamin D, even in the normal asymptomatic population.[8,9] Furthermore, vitamin D deficiency, the most common cause of rickets is very prevalent in KSA.[10] However, no study has been conducted as to the differences in the serum 25-hydroxy vitamin D (25[OH]D) levels between non-diabetic adults and those with T2DM, and as to whether these variations translate to different associations between 25(OH)D levels and metabolic risk factors in the 2 groups. In this study, serum levels of 25(OH)D were quantified in a cohort of both non-diabetic and diabetic Saudi adults to compare the incidence of hypovitaminosis D in the 2 groups. Furthermore, this study aimed to determine associations of 25(OH)D to various risk factors in both non-diabetic and diabetic subjects.

Methods. A total of 341 male and female Saudi adults, aged 18-80 years old were randomly selected from the existing Biomarkers Screening in Riyadh Program (Riyadh Cohort), a capital-wide study composed of randomly selected subjects aged 1-80 years from different Primary Health Care Centers (PHCCs) in Riyadh, KSA. The study proper was carried out at the Biomarkers Research Program (BRP), King Saud University, Riyadh, KSA from March to August 2009. They were subdivided into: those with T2DM, and those without T2DM. A generalized questionnaire was given to all participating subjects aimed to seek demographic information, and past medical history. Those with diabetic complications, poorly controlled glycemic status (glycosylated hemoglobin [HBA1c] >11.0 based from recent medical records), and with acute co-morbidities that needed immediate medical attention were excluded from the study. Furthermore, subjects who were morbidly obese (body mass index [BMI] >40 kg/m^2), with known hepatic and/or renal dysfunction, and those who declared taking vitamin D supplements were also excluded. Written consent was obtained after orientation for the study. Ethical approval was granted by the Ethics Committee of the College of Science Research Center, King Saud University, Riyadh, KSA.

Anthropometric data and blood collection. Participating subjects were requested to return to their respective PHCCs in an overnight fasted state (>10 hours) for anthropometric measurements, and blood withdrawal by the assigned research nurse and physician. Anthropometric data included height (cm), weight (kg), waist (cm), hips (cm), and mean systolic and diastolic blood pressure (mm Hg [average of 2 readings]). The BMI was calculated as weight divided by height in squared meters. Waist-to-hip-ratio (WHR) was defined as the quotient between waist and hip circumference. Venous blood was extracted once in the left ante-cubital vein, unless otherwise specified. Blood (approximately 10 cc) was transferred immediately to a non-heparinized tube for centrifugation. Collected serum was then transferred to a pre-labeled plain tube, stored in ice, and delivered to the Diabetes and Endocrinology Research Center in King Saud University on the same day.

Sample analyses. Delivered fasting serum samples were stored in a -20°C freezer prior to analysis. Fasting glucose (FG) and lipid profile were measured using a chemical analyzer (Konelab, Vantaa, Finland). Serum 25(OH)D and intact PTH were measured by enzyme linked immunosorbent assays (ELISA) (IDS Ltd, Boldon Colliery, Tyne & Wear, UK). The ELISA inter-assay was 5.3%, and intra-assay variability was 4.6% for 25(OH)D. For serum intact PTH, ELISA inter-assay was 4.4%, and intra-assay variability was 4.7%. For this study, mild vitamin D deficiency was defined as serum 25(OH)D level of 12.5-24.9 nmol/l, and severe deficiency at <12.5 nmol/l).[11]

The Statistical Package for Social Sciences version 11.5 (SPSS Inc, Chicago, IL, USA) was used for data analysis. Variables were presented as mean ± standard deviation. Group comparisons were carried out using independent student t-tests, and Mann-Whitney U-tests

for non-normally distributed variables (triglycerides and intact PTH). Spearman correlation and linear regression analyses were carried out to determine cross-sectional associations between variables of interest. Significance was set at $p<0.05$.

Results. The general characteristics and gender-specific comparisons between non-diabetic and T2DM patients are presented in **Table 1**. Patients with T2DM were significantly older with higher BMI, systolic and diastolic blood pressure, and waist and WHR than those without T2DM. As expected, the T2DM group had significantly higher levels of serum FG and triglycerides. The non-diabetic group on the other hand, had significantly higher levels of serum low density lipoprotein (LDL)-cholesterol and intact PTH, with lower levels of 25(OH)D and high-density lipoprotein (HDL)-cholesterol than the T2DM group. Spearman correlation using 25(OH)D as a dependent variable for all groups revealed significant positive associations with age, WHR, systolic and diastolic blood pressure, and circulating HDL-cholesterol and FG concentrations. A negative correlation was elicited with LDL-cholesterol. In the non-diabetic group, 25(OH)D was significantly associated with age, WHR, and systolic blood pressure. Age was also significantly associated with 25(OH)D levels in the T2DM group with significant negative associations with BMI, and circulating LDL-cholesterol, total cholesterol, and triglyceride concentrations. The rest of the associations are shown in **Table 2**. Worthy to note was that BMI had a significant negative association with 25(OH)D levels (coefficient [R]: -0.20, $p=0.023$), and no associations in the non-diabetic group after excluding all patients with severe hypovitaminosis D (not shown in **Table 2**). Intact PTH was not significantly correlated with serum 25(OH)D. Prevalence of hypovitaminosis D was present in both groups, with severe hypovitaminosis D more evident in the non-diabetic group (**Figure 1**). Linear regression analysis revealed that in both group age, HDL-cholesterol, and systolic and diastolic blood pressure, all had significant associations with 25(OH)D (**Figure 2**). Stepwise linear regression analysis using 25(OH)D as a dependent variable, and the rest of the parameters as independent variables showed that age was the most significant predictor of 25(OH)D in both the non-diabetic and T2DM groups, explaining 25% ($p=0.005$), and 16% of the variance ($p=0.0005$). Adjusting for age however, revealed that WHR, systolic blood pressure, and BMI were the significant predictors of 25(OH)D among the non-diabetic group with 21% of variance ($p=0.039$), while no significant predictors were elicited in the T2DM group (not shown in **Table 2**).

Table 1 - General characteristics and gender-specific comparisons between non-diabetic and T2DM patients.

Parameters	Non-diabetic		All non-diabetics	T2DM		All T2DM	*P*-value
Gender	Males	Females		Males	Females		
Number	71	106	177	88	76	164	
Age (years)	34.7 ± 14.9	39.4 ± 15.3†	37.5 ± 15.3	51.7 ± 11.0	49.4 ± 8.9	50.6 ± 10.1	0.0005
BMI (kg/m²)	29.2 ± 6.2	29.2 ± 6.5	29.2 ± 6.3	28.4 ± 4.3	34.0 ± 4.7†	31.0 ± 5.3	0.02
Systolic BP (mm Hg)	115.7 ± 11.8	121.1 ± 17.0†	119.1 ± 15.4	122.8 ± 19.4	130.8 ± 22.9†	127.1 ± 19.3	0.0005
Diastolic BP (mm Hg)	75.4 ± 7.5	77.8 ± 9.4	76.9 ± 8.8	86.4 ± 13.0†	79.9 ± 10.4	83.5 ± 12.3	0.0005
Waist circumference (cm)	87.7 ± 18.3	89.6 ± 17.3	88.9 ± 17.7	109.8 ± 24.8†	101.6 ± 14.9	105.2 ± 20.5	0.0005
Hip circumference (cm)	104.4 ± 19.2	101.8 ± 16.4	102.8 ± 17.5	93.7 ± 14.8	108.7 ± 10.7†	102.1 ± 14.7	0.72
WHR	0.8 ± 0.1	0.9 ± 0.1†	0.87 ± 0.1	1.2 ± 0.3†	0.9 ± 0.1	1.05 ± 0.3	0.0005
Glucose (mmol/l)	5.2 ± 0.7	5.4 ± 0.7	5.3 ± 0.7	8.4 ± 3.3	10.5 ± 4.1†	9.3 ± 3.8	0.0005
Triglycerides (mmol/l)*	1.3 ± 0.8	1.6 ± 1.0	1.4 ± 1.0	2.0 ± 1.8	2.0 ± 1.2	2.0 ± 1.6	0.0005
Total cholesterol (mmol/l)	4.7 ± 1.0	5.0 ± 1.2†	4.8 ± 1.1	4.8 ± 1.1	5.2 ± 1.1†	5.0 ± 1.1	0.34
LDL-cholesterol (mmol/l)	3.4 ± 0.9	3.5 ± 1.0	3.4 ± 1.0	2.9 ± 0.8	3.1 ± 0.9	3.0 ± 0.9	0.0005
HDL-cholesterol (mmol/l)	0.7 ± 0.2	0.8 ± 0.3†	0.8 ± 0.2	0.9 ± 0.3	1.1 ± 0.4†	1.0 ± 0.4	0.0005
25-Hydroxyvitamin D (nmol/l)	18.0 ± 8.3	17.9 ± 7.3	17.9 ± 7.7	30.0 ± 12.3†	23.4 ± 9.8	26.9 ± 11.7	0.0005
Intact PTH (pmol/l)*	1.6 ± 1.0	1.5 ± 1.4	1.5 ± 1.2	1.3 ± 0.9†	0.5 ± 0.4	0.9 ± 0.8	0.001

Data are presented as mean ± standard deviation. T2DM - type 2 diabetes mellitus, BMI - body mass index, BP - blood pressure, WHR - waist to hip ratio, LDL - low-density lipoprotein, HDL - high density lipoprotein, PTH - parathyroid hormone. *Mann-Whitney U test was carried out for comparison, significance was set at $p<0.05$, †denotes significantly higher difference compared to the opposite gender

Discussion. The prevalence of hypovitaminosis D was high in adult Saudi men and women, regardless of the presence of DM. Lower vitamin D levels were earlier documented in diabetic patients types 1 and 2 than their non-diabetic counterparts.[12,13] Interestingly however in our study, the prevalence of severe hypovitaminosis D was higher in the non-diabetic than the T2DM group. Moderate to severe hypovitaminosis D was reported as quite common in young, normal Saudi adults in 1981.[9] Back then however, severe hypovitaminosis D was more common among the elderly in contrast to the findings in our study, in which serum 25(OH)D was strongly correlated with age, that is similar to the findings of Hashemipour et al,[14] in a cohort of 1210 Iranians adult. The strong correlation of 25(OH)D to age is also in agreement with a study carried out in the US, where severe hypovitaminosis D was found to be more common among the young, and less common among the elderly.[15]

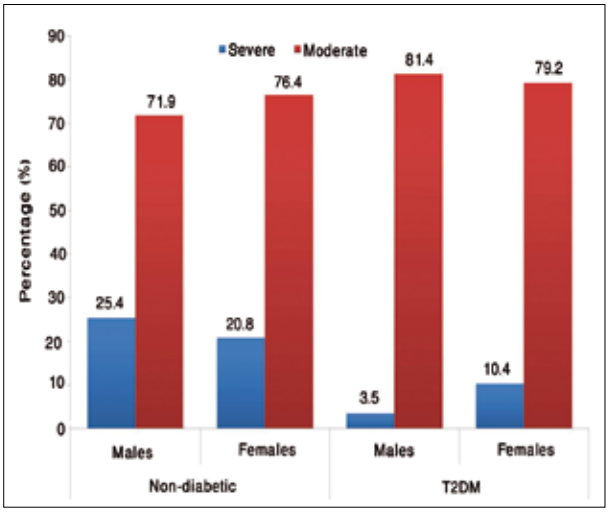

Figure 1 - Prevalence of hypovitaminosis D in non-diabetics versus type 2 diabetes mellitus (T2DM) subjects.

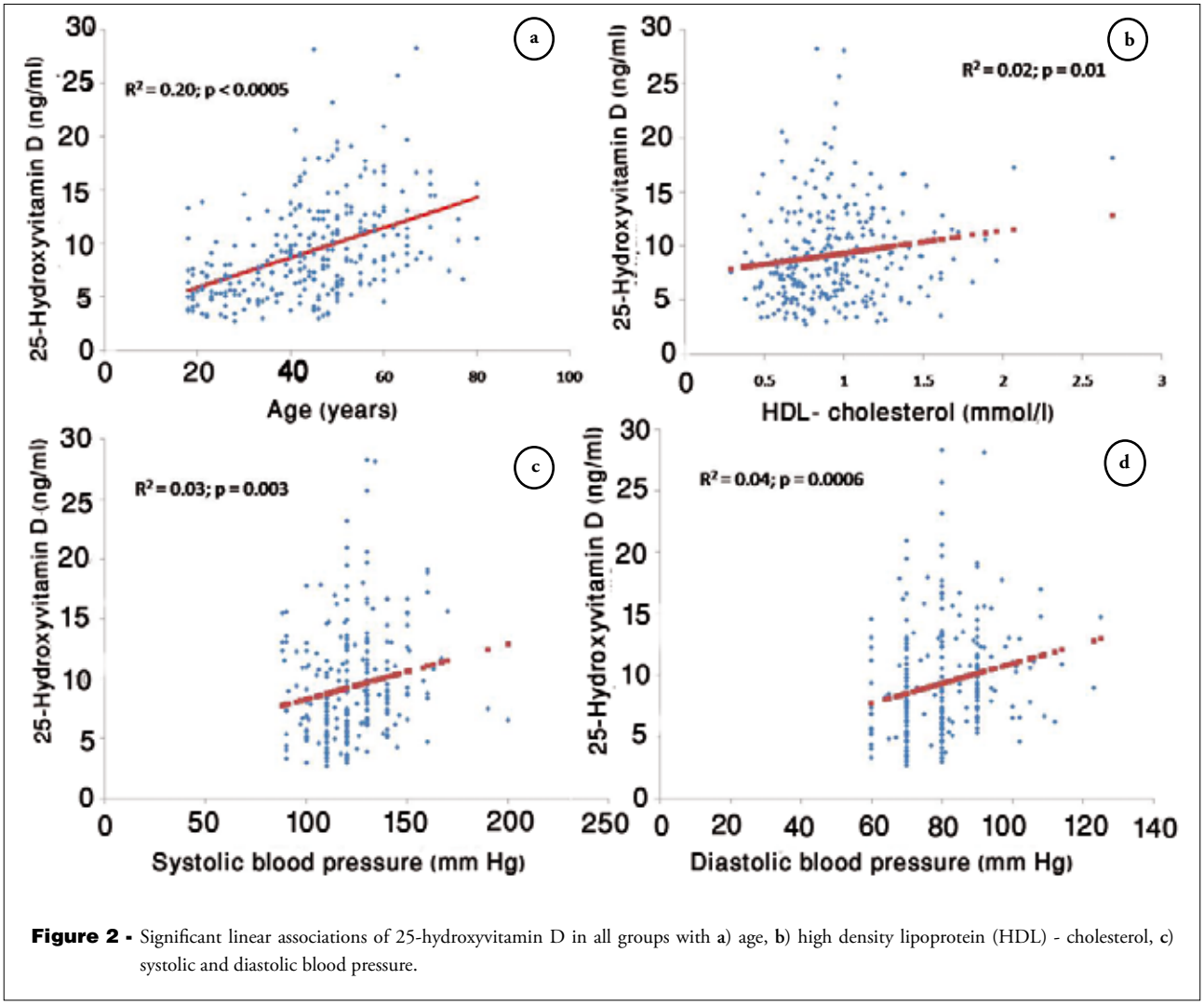

Figure 2 - Significant linear associations of 25-hydroxyvitamin D in all groups with **a**) age, **b**) high density lipoprotein (HDL) - cholesterol, **c**) systolic and diastolic blood pressure.

The improved but still deficient levels of 25(OH)D levels among the elderly diabetic group can be possibly attributed to 3 reasons: first is the issue of supplementation. It was noted that multivitamins were prescribed on a routine basis for patients with T2DM in KSA.[16] Multivitamins normally contain 400 IU of vitamin D, and this entirely explains the 10 nmol/L difference between the 2 groups. Although patients were excluded if they were on vitamin D supplements alone, those who were on multivitamins were included, and the long half-life of vitamin D and the chronicity of multivitamin intake could have explained the difference,[17,18] especially in elderly women who would have been on vitamin D therapy for either prophylactic, or adjuvant treatment for osteoporosis. Although the dietary habits were not noted in this study, it was already documented among Saudi males that total dietary protein intake increased with age with subsequent decrease in energy and carbohydrate intake.[19] This improved diet could have somehow favored increased 25(OH)D levels especially in diabetic males, but probably not enough to achieve adequate levels. Third, the improved lipid profile of the T2DM subjects strengthens the notion that this group were more likely to be on lipid-lowering drugs. Statins (rosuvastatin) were shown to increase the levels of 25(OH)D and 1,25 dihydroxyvitamin D in a cohort of hyperlipidemic patients.[4]

Another significant finding in this study was the lack of correlation between 25(OH)D levels and intact PTH. Physiological deficiency is defined by 25(OH)D concentrations, below which PTH levels increase.[15] The lack of correlation despite the big percentage of patients with severe hypovitaminosis D suggests that the threshold cut-off in this cohort might be inappropriate for diagnostic use. True enough, there is still no consensus on what defines hypovitaminosis D.[20] Furthermore, the large numbers of patients with severe hypovitaminosis D in both the control and T2DM groups led to many significant positive associations in variables that should have otherwise demonstrated inverse relations, such as BMI,[21] systolic and diastolic blood pressure,[22] and fasting plasma glucose.[23] All these associations were lost and an inverse association was elicited as expected (such as, inverse association with BMI in the T2DM group) after excluding patients with severe hypovitaminosis D. These findings should be further explored.

This study has several limitations. The non-consensus definition of hypovitaminosis D used in this study and the cut-off point used might may have given bias as to the true prevalence of hypovitaminosis D. The cross-sectional nature of the study prevented the findings from defining causality. The lack of detailed information in the supplementation intake, and the lack of dietary data from the subjects led to evidence-based assumptions. Finally, the general questionnaire employed in this study might have created a recall bias.

In conclusion, severe hypovitaminosis D is prevalent in both non-diabetic and diabetic Saudi adults, and is more common among the young and the middle-aged non-diabetics. The results of this study further strengthen the need to propose recommendations of fortifying the Saudi diet with vitamin D, and the promotion of vitamin D supplementation in all groups, especially those at risk. It has been documented that insulin resistance can be improved by 60% if levels

Table 2 - Spearman correlations using 25-Hydroxyvitamin D as a dependent variable.

Parameters	Non-diabetic			T2DM			Both non-diabetics and T2DM
	Males	Females	All non-diabetics	Males	Females	All T2DM	
Age	0.38†	0.18	0.26†	0.28†	0.27*	0.29†	0.42†
BMI	-0.03	-0.15	-0.06	-0.14	0.05	-0.22*	-0.05
WHR	0.30*	0.05	0.16 *	-0.06	-0.11	0.04	0.27†
SBP	0.19	0.22*	0.22 *	-0.01	0.20	0.007	0.20†
DBP	0.10	0.17	0.16	-0.04	0.04	0.06	0.22†
FG	0.16	-0.10	-0.01	0.09	-0.18	-0.12	0.26†
TG	0.36*	-0.08	0.10	-0.09	-0.17	-0.17*	0.09
TC	0.23*	0.005	0.11	-0.20	-0.09	-0.20*	-0.01
LDL-C	0.22	0.03	0.11	-0.13	-0.14	-0.17*	-0.13*
HDL-C	-0.28*	0.06	-0.07	0.08	0.08	0.03	0.18*
PTH	0.19	-0.08	0.08	0.18	-0.04	0.17	0.007

Data presented as coefficient (R). *denotes significance at 0.05 level, †denotes significance at 0.01 level. BMI - body mass index, WHR - Waist-hip ratio, SBP - systolic blood pressure, DBP - diastolic blood pressure, FG - fasting glucose, TG - triglycerides, TC - total cholesterol, LDL-C - low-density lipoprotein-cholesterol, HDL-C - high-density lipoprotein-cholesterol, PTH - parathyroid hormone

of 25(OH)D levels are increased from 25-75 nmol.[24] Further clinical trials should be conducted to determine the best supplemental dose to achieve vitamin D levels of ≥75 nmol/l.

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