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## Modest reversal of metabolic syndrome manifestations with vitamin D status correction: a 12-month prospective study

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### ABSTRACT

Numerous cross-sectional studies have noted significant negative associations between circulating levels of 25-hydroxyvitamin D and cardiometabolic risk factors, highlighting potential extraskeletal functions of this sterol hormone. Prospective studies, however, have been limited; and hence, no cause-and-effect relations can be inferred. This study aims to determine whether vitamin D status correction can reverse already established manifestations of the metabolic syndrome (MetS). A total of 59 adult nondiabetic, overweight, and obese Saudis (31 male, 28 female) were prospectively enrolled in this 1-year interventional study. Anthropometry and biochemical evaluation were performed, including determination of serum 25-hydroxyvitamin D, calcium, and phosphorous concentrations, as well as fasting blood glucose and lipid profile. Subjects were advised to regularly expose themselves to sunlight and increase intake of vitamin D-rich foods. All measurements were repeated 6 and 12 months later. At the initial baseline visit, the prevalence of both low high-density lipoprotein cholesterol and hypertension was significantly increased among patients with 25-vitamin D deficiency ( $P < .05$ ), even after adjusting for sex and body mass index. Overall prevalence of MetS patients by the modified National Health and Nutrition Examination Survey Adult Treatment Panel III definition decreased from 25.2% to 13.0%;

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and this was largely due to a parallel decrease in the prevalence of low high-density lipoprotein cholesterol, triglycerides, and hypertension. Optimization of vitamin D status through sun exposure and increased intake of a vitamin D-rich diet can lead to an improved cardiometabolic profile, offering a promising nonpharmacologic approach in the prevention of MetS manifestations.

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## 1. Introduction

Populations with a relatively high percentage of elderly citizens due to an increased life expectancy tend to exhibit increased prevalence of age-related metabolic abnormalities, such as visceral fat accumulation, sarcopenia, osteoporosis, and diabetes mellitus type 2 (DMT2) [1-3]. However, aside from nonmodifiable risk factors, such as age and sex, several other significant factors, such as depressed vitamin D status, which were previously unrecognized have recently gained the spotlight in the fight against the global burden of chronic noncommunicable diseases.

Vitamin D deficiency is common among the elderly population [4]. Because of its numerous extraskeletal functions, its deficiency cannot be underestimated, especially in a group in which predisposition to a vast variety of chronic noncommunicable diseases is already heightened. Hypertension, for instance, was observed to be more prevalent among elderly men with vitamin D deficiency [5]. The same observation was also noted among other cardiometabolic risk factors, such as degree of adiposity and dyslipidemia [6,7]. Furthermore, the metabolic syndrome (MetS), a cluster of known cardiovascular risk factors (obesity, hypertension, dyslipidemia, and insulin resistance) that harbors an increased risk for adverse cardiovascular events and DMT2, was also associated with vitamin D deficiency in several cross-sectional studies involving middle-aged East Asians and Europeans [8-10]. The same association, however, was not observed among study populations recruited from multicultural environments, such as the United States and New Zealand [11,12]. Whether this discrepancy lies in the homogeneity of the cohort or the study design used remains to be shown.

Despite the significant cross-sectional associations of low 25-hydroxyvitamin D (25[OH]D) concentrations with the components of MetS of which most confer cardioprotective effects, there have been limited longitudinal data available on whether correction of 25(OH)D deficiency can translate to cardiometabolic benefits among patients with MetS manifestations. A recent report by the Institute of Medicine of the National Academies of the United States emphasized the lack of concrete documentation on the use of 25(OH)D for extraskeletal manifestations (<http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx>). Furthermore, no longitudinal study has been conducted so far, more so in the Gulf region, where the prevalence of both vitamin D deficiency and the MetS is significantly higher than in other regions [13,14]. This prospective longitudinal study aims to determine whether there is an improvement in the baseline prevalence of MetS and its components in a

cohort of overweight and obese adult Arab men and women through vitamin D status correction by increased sun exposure and prescription of a vitamin D-rich diet.

## 2. Materials and methods

A total of 59 (31 male; 28 female) adult (aged 18 to 65 years) nondiabetic Saudis with varying body mass indexes (BMIs) were included in this prospective study. Patients with diabetes mellitus (types 1 and 2), morbid obesity, or complicated comorbidities and those taking vitamin D supplementation were excluded from the study. Written and informed consents were taken before inclusion. Ethics approval was granted by the Ethics Committee of the College of Science, King Saud University, Riyadh, Kingdom of Saudi Arabia (KSA). Participating subjects were recruited and enrolled longitudinally in 4 primary health care centers (PHCCs) within the Riyadh Central Region during the summer months (April-July 2009). They were asked to complete a generalized questionnaire, which contains demographic information including past and present medical history, and to return after fasting for more than 10 hours for anthropometry and blood withdrawal. They were also seen 6 and 12 months later for another anthropometry and metabolic assessments.

### 2.1. Anthropometry and blood collection

Subjects were requested to visit their respective PHCCs in an overnight fasted state (>10 hours) for anthropometry and blood withdrawal by the PHCC nurse and physician on duty, respectively. Anthropometry included height (rounded off to the nearest 0.5 cm), weight (rounded off to the nearest 0.1 kg), waist and hip circumference (centimeters), and mean systolic and diastolic blood pressure (millimeters of Hg) (average of 2 readings). Body mass index was calculated as weight in kilograms divided by height in square meters. *Overweight* was defined as having a BMI of 25 to 29.9 kg/m<sup>2</sup>; *obesity*, at least 30 up to 34.9; and *morbid obesity*, at least 35. Fasting blood samples were collected and transferred immediately to a non-heparinized tube for centrifugation. Collected serum was then transferred to prelabeled plain tubes; stored in ice; and delivered to the Biomarkers Research Program (BRP) in King Saud University, Riyadh, KSA, for immediate storage at -20°C.

### 2.2. Sample analyses

Fasting glucose, lipid profile, calcium, and phosphorous were measured using a chemical analyzer (Konelab, Espoo,

Finland). Serum 25(OH)D was measured by a specific enzyme-linked immunosorbent assay (IDS, Tyne and Wear, UK). The inter- and intraassay variability of this assay was 5.3% and 4.6%, respectively. Caution was exercised in the interpretation of results, as significant variability between different assays and laboratories has been reported [15]. It is noted that although the BRP laboratory did not participate in the Vitamin D External Quality Assessment Scheme, Quality Assurance (QA) standards are maintained by ISO 9000 and 17025, whereas the QA department audits the BRP laboratory at regular intervals.

### 2.3. Definitions

Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III; 3 or more of the following criteria had to be fulfilled: fasting blood glucose level of at least 5.6 mmol/L; blood pressure of at least 130/85 mm Hg; triglycerides of at least 1.7 mmol/L; high-density lipoprotein cholesterol (HDL-C) less than 1.03 mmol/L for men and less than 1.29 mmol/L for women; and waist circumference greater than 102 cm and greater than 88 cm for men and women, respectively [16]. Hypovitaminosis D was defined as those having less than 25 nmol/L 25(OH)D [17,18].

### 2.4. Sunlight exposure and vitamin D-rich diet

Subjects were given verbal advice to expose themselves to sunlight for 5 to 30 minutes twice a week either before 10:00 AM and/or after 3:00 PM. The time for sun exposure was based on a previous study done by Hannan and colleagues [19] in Riyadh, KSA, detailing the hours of daylight during which ultraviolet radiation levels are considered carcinogenic and thus should be avoided. They were also regularly encouraged every week through Short Message Service (SMS) to include in their diet increased amounts of vitamin D-rich foods, such as cod liver oil, salmon, tuna, cow liver, dairy products, and vitamin D-fortified foods. To ensure compliance, they were instructed to keep a diary in which they recorded sun exposure times and outdoor physical activity; such diaries were submitted at the end of the study period.

### 2.5. Power calculations and data analyses

G\*Power version 3.1 (Dusseldorf, Germany) was used for sample size calculations. Power size was calculated by multinomial logistic regression analysis using vitamin D as independent variable and components of the MetS as the dependent variables. A sample size of 45 had 80% power to detect significant odds at the .05 level. Data were analyzed using the Statistical Package for the Social Sciences version 16.0 (SPSS, Chicago, IL). All parameters, with the exception of vitamin D and glucose, exhibited a Gaussian distribution. These 2 parameters were normalized and presented as mean  $\pm$  standard deviation. Repeated-measures analysis of variance with a post hoc Bonferroni correction for multiple comparisons was done to compare differences between groups.  $\chi^2$  was done to compare frequencies in the prevalence of MetS. Odds ratio was calculated using vitamin D

**Table 1 – General characteristics of subjects at baseline and at 6 and 12 months postintervention**

	Baseline	6 mo	12 mo
n	59	59	54
Sex (M/F)	31/28		
Age (y)	38.6 $\pm$ 14.1		
BMI (kg/m <sup>2</sup> )	29.2 $\pm$ 9.1	27.7 $\pm$ 6.1	27.1 $\pm$ 7.0
Waist circumference (cm)	90.8 $\pm$ 19.6	95.9 $\pm$ 13.6	86.1 $\pm$ 18.2
Hip circumference (cm)	104.6 $\pm$ 16.6	107.6 $\pm$ 11.9	104.1 $\pm$ 22.7
Waist-hip ratio	0.85 $\pm$ 0.07	0.89 $\pm$ 0.06	0.88 $\pm$ 0.10
Systolic BP (mm Hg)	118.3 $\pm$ 15.4	116.4 $\pm$ 15.2	112.6 $\pm$ 12.6
Diastolic BP (mm Hg)	76.0 $\pm$ 11.0	75.9 $\pm$ 10.8	73.9 $\pm$ 7.7
Glucose (mmol/L)	5.4 $\pm$ 1.7	5.7 $\pm$ 1.1	5.6 $\pm$ 0.7
Triglycerides (mmol/L)	1.4 $\pm$ 0.15	1.3 $\pm$ 0.1	1.3 $\pm$ 0.11
Total cholesterol (mmol/L)	4.7 $\pm$ 1.0	4.7 $\pm$ 1.2	4.7 $\pm$ 1.3
LDL-C (mmol/L)	3.4 $\pm$ 0.7	3.18 $\pm$ 1.1	3.1 $\pm$ 1.1
HDL-C (mmol/L)	0.66 $\pm$ 0.25	0.97 $\pm$ 0.24*	1.05 $\pm$ 0.33*
Calcium (mmol/L)	2.27 $\pm$ 0.21	2.5 $\pm$ 0.30	2.3 $\pm$ 0.20
Phosphorous (mmol/L)	1.06 $\pm$ 0.14	1.15 $\pm$ 0.27	1.1 $\pm$ 0.21
Vitamin D (nmol/L) <sup>a</sup>	19.1 $\pm$ 1.5	26.7 $\pm$ 1.6*	28.4 $\pm$ 1.5*

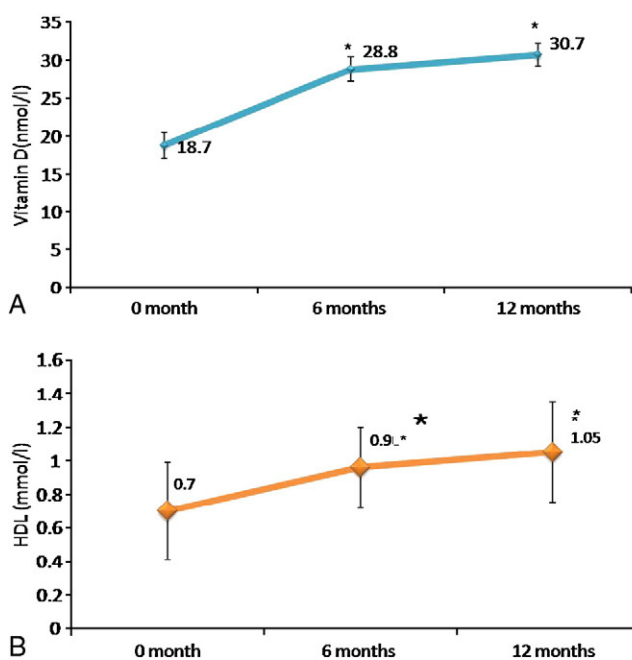
BP indicates blood pressure; LDL-C, low-density lipoprotein cholesterol.  
\* Denotes significance compared with baseline. Significance at P < .05.

cutoff to assess risk of having a component manifestation of the MetS. Significance was set at P < .05.

## 3. Results

### 3.1. Increased risk of low HDL-C in patients with vitamin D deficiency

Odds ratio was done to assess risk of acquiring each of the 5 cardiometabolic components of MetS for those patients



**Fig. 1 – A, Increasing mean serum Vitamin D concentrations over the 12-month intervention period. B, Increasing mean serum HDL-C concentrations over the 12-month intervention period.**

**Table 2 – Prevalence of MetS manifestations (National Cholesterol Education Program Adult Treatment Panel III) over the 12 months postintervention**

	Baseline	6 mo	12 mo	P value
n	59	59	54	
MetS	24.6	20.3	13.0	.002
Abdominal obesity	29.8	25.4	24.1	.884
Hypertension	28.1	25.4	11.1	.185
Elevated fasting glucose	15.8	15.5	14.6	.218
High triglycerides	28.1	27.1	24.1	.023
Low HDL-C	93.0	69.5	57.4	.004

Data presented as percentages.

harboring hypovitaminosis D. The age-, BMI-, and sex-adjusted risk of having low HDL-C was 4.4 (confidence interval [CI], 1.7-11.4); P value = .002. Worthy to note was the borderline significance achieved in the risk for hypertension (.052).

**3.2. Improved metabolic profile observed with increasing vitamin D levels**

Table 1 highlights the general characteristics of patients for the duration of the study. The most notable observations

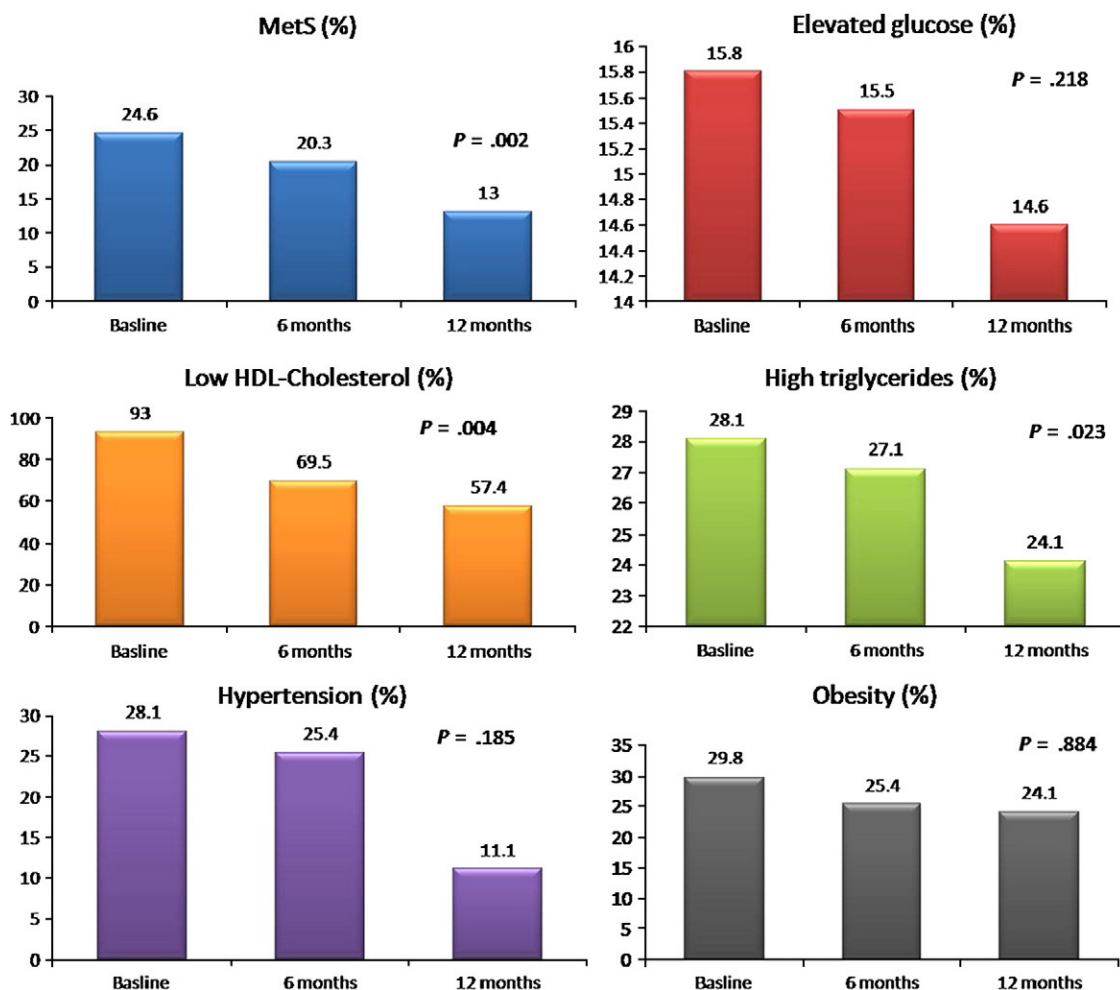
were the improved mean circulating levels of 25(OH)D (Fig. 1A) and the parallel, significantly improved levels of HDL-C (Fig. 1B). Although the rest of the variables were statistically unremarkable, there was a modest but steady decrease of mean systolic and/or diastolic blood pressure and a decrease in low-density lipoprotein cholesterol levels over the 12 months of the study.

**3.3. Decreased prevalence of MetS and/or its components**

Table 2 shows the prevalence of MetS and its components at baseline and succeeding visits. It is apparent that the overall prevalence of MetS decreased from 24.6% to 13.0% (Fig. 2), which was significant (P = .002); and this was largely due to the parallel decrease in the prevalence of its components, most notably dyslipidemia (HDL-C [P = .004] and triglycerides [P = .023]).

**4. Discussion**

To the best of our knowledge, this is the first study that confirms the relation between vitamin D status and cardiometabolic risk factors and expands these associations in a



**Fig. 2 – Overall decrease in the prevalence of MetS manifestations and MetS over the 12-month intervention period.**

prospective, interventional approach, and the first study using a Middle Eastern population. Furthermore, the findings of this study strengthen the cardiometabolic benefits of increasing circulating 25(OH)D levels among patients already harboring complete or partial MetS. The consistently positive correlation between vitamin D status and HDL-C is in accordance with several observational studies conducted in children [20,21]. Furthermore, in this part of the world where the prevalence of vitamin D deficiency is extremely high [18,22] despite a geographic location with increased year-round sunshine [22], these findings confirmed cross-sectional studies in Arab adults with and without DMT2 and children [23,24], and even adult Arab immigrants in the United States [25], suggesting ethnic predisposition.

Our study suggests that vitamin D status correction by natural means, such as exposure to sunshine and a vitamin D-rich diet, is a promising cardioprotective intervention not only in vitamin D-deficient populations but also among select populations where vitamin D deficiency has been linked to metabolic risk factors, such as women with polycystic ovary syndrome [26] and obese children and adolescents [27]. The mechanism of this effect may involve direct promotion of large HDL particle formation, via elevations in serum apolipoprotein A-1 concentrations, a process that increases reverse cholesterol transport [28]. Apolipoprotein A-1 has been constantly correlated with vitamin D levels [28-31], and a recent study by Wehmeier and colleagues [30] demonstrated that the expression of the apolipoprotein A-1 gene in both hepatocytes (HepG2) and intestinal (CaCo-2) cells is regulated by the vitamin D receptor modulators EB1089 and ZK191784, further strengthening this hypothesis.

The association between low 25(OH)D levels and elevations in arterial blood pressure in our study confirms the observations of Burgaz and colleagues [5] in elderly men, in whom a higher prevalence of confirmed hypertension was observed among those with low concentrations of 25(OH)D. The active form of vitamin D 1,25(OH)D is a potent endocrine suppressor of renin biosynthesis and a negative regulator of the renin-angiotensin system in humans [32,33]. In addition, it was shown that mice lacking vitamin D receptor had elevated circulating renin and angiotensin leading to hypertension, cardiac hypertrophy, and increased water intake [34].

The authors acknowledge several limitations. Among subjects, the direct measure of total adiposity and phases and the regularity of the menstrual cycle, which may affect indices of insulin resistance and MetS, and other confounders (caloric intake, fat intake, vitamin D and calcium intake, exercise data) were not noted and might have possibly influenced results. Furthermore, although the sample had sufficient statistical power, it too remains small to conclude definitely as to whether the effects can be evident in a larger-scale and duration scenario. A larger sample size with longer follow-up is needed to establish whether steady normalization will translate to a decreased risk of end points, such as DMT2 and cardiovascular and neurovascular diseases, and whether these benefits will be sustained. Furthermore, although outdoor physical activity was recorded in the diary, the possibility is present that sun exposure without physical activity might influence the results. Lastly, the laboratory that conducted the analyses did not participate in the Vitamin D External Quality

Assessment Scheme. Nevertheless, the study has several strengths worthy of attention from a clinical perspective. The significant increase in the 25(OH)D levels of compliant patients in response to intermediate-term nonpharmacologic interventions (increased sun exposure and a vitamin D-rich diet) was efficacious in the management and prevention of MetS and its components.

In summary, correction of vitamin D status through sun exposure and increased intake of a vitamin D-rich diet translates into reversal of several components of MetS, notably low HDL-C and elevated blood pressure, offering a promising non-pharmacologic intervention in the prevention of MetS.

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## Conflict of Interest

The authors have nothing to disclose.

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