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Vitamin D levels, prediabetes risk and hemoglobin A1c levels in young non-diabetic Saudi women

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ABSTRACT

Aims/Introduction: Vitamin D levels are negatively correlated with prediabetes risk and hemoglobin A1c levels in individuals with prediabetes. The data are, however, scarce and inconsistent among different populations. We aimed to assess the association of vitamin D with prediabetes risk and hemoglobin A1c levels in young Saudi women with normoglycemia and prediabetes.

Materials and Methods: We analyzed the data of individuals without diabetes (without diabetes history and hemoglobin A1c <6.4%) from the Princess Nourah bint Abdulrahman University's non-communicable diseases student registry. Demographic data, anthropometric and blood pressure measurements, and hemoglobin A1c and vitamin D results were retrieved and analyzed.

Results: In total, 345 participants were included in the analysis. The prediabetes status showed no association with vitamin D levels, but it was significantly associated with the participants' weight and body mass index. Additionally, there was no correlation between the levels of vitamin D and hemoglobin A1c across the whole population, even after correction for body mass index. However, in the body mass index subgroups, when individuals with potentially harmful levels of vitamin D (>125 nmol/L) were excluded, a positive association was detected between vitamin D and hemoglobin A1c levels in the underweight individuals. Hemoglobin A1c values showed a positive correlation only with bodyweight and body mass index.

Conclusions: Vitamin D levels did not predict prediabetes status and showed no correlation with hemoglobin A1c levels in this population. Vitamin D levels' effect on the risk of prediabetes might be small compared with other well-established risk factors, such as obesity.

INTRODUCTION

There is a growing debate over the association between low 25-hydroxyvitamin D (vitamin D) levels and the risk of diabetes mellitus/prediabetes development[1,2]. A large number of cross-sectional studies[3–5], but not all of them[6–8], have shown an inverse association between vitamin D status and impaired glucose tolerance, insulin resistance or diabetes mellitus[9]. Reported data also suggest an association between low vitamin D levels with poor diabetes mellitus control[10,11] and diabetes mellitus related complications[12]. However, generally, there has been a lack of consistency in vitamin D intervention studies on insulin secretion and sensitivity[13,14].

Although the relationship between vitamin D and insulin resistance is, relatively, better investigated in patients with diabetes mellitus, data from individuals with prediabetes are limited[3,4,7,8]. Some observational data have suggested that vitamin D levels are negatively correlated with the risk of prediabetes, and with hemoglobin A1c (HbA1c) levels in individuals with prediabetes[3,4], particularly in obese individuals[15]. These findings, however, have been inconsistent among different populations[7] and in an ethnic subgroup analysis of large national cohorts[4].

In the past three decades, a 10-fold increase in the prevalence of diabetes mellitus has been registered in Saudi Arabia

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(SA), which ranks among the top countries in the world in terms of the incidence of diabetes mellitus[16]. The observed increase is mainly registered among Saudi women and adolescents[17]. Similarly, vitamin D deficiency is common in SA[18], and is more pronounced in Saudi women and in the younger age groups[19] due insufficient vitamin D intake and rare sun exposure[20]. Identification of an association between the vitamin D levels and risk of prediabetes among young Saudi women is, therefore, of importance, and might aid in the prevention of diabetes mellitus. Diabetes mellitus is particularly hazardous to women, who are at a higher risk of early-onset and fatal cardiovascular disease compared with mean with diabetes[21]. The present study aimed to evaluate the association of vitamin D levels with the risk of prediabetes and HbA1c levels in young Saudi women without diabetes mellitus. Subgroup analyses were also carried out to evaluate the association between the levels of vitamin D and HbA1c based on the body mass index (BMI) of the participants.

METHODS

Study design and setting

We analyzed data from the Princess Nourah bint Abdulrahman University (PNU; Riyadh, Saudi Arabia) non-communicable diseases (NCD) student registry. The PNU-NCD student registry prospectively enrolled 472 consecutive first-year female health college students who were aged ≥17 years from 31 July to 17 August 2017, from the University Medical Center clinics at the PNU. The registry aimed to provide data regarding NCD, the associated risk factors and lifestyle of young Saudi women to improve the cost-effectiveness of healthcare and outcomes. The registry contained data on the demographic characteristics, medical history, including risk factors for cardiovascular disease, anthropometric measurements and blood pressure of the participants. In addition, it also had the results of laboratory investigations that are routinely carried out by the University Medical Center as a part of the students' health clearance procedure and of some screening/diagnostic tests for NCD, and the associated risk factors. All blood samples were collected by phlebotomists at the University Medical Center, and transferred on the same day and analyzed at the King Abdullah bin Abdulaziz University Hospital main laboratory. The study was approved by the King Fahad Medical City Institutional Review Board (IRB log number: 17-234E, July 12, 2017), and was carried out under the principles of the Declaration of Helsinki. Written informed consent was obtained from all the participating students before carrying out the laboratory investigations or administering the questionnaire. The participants were requested to provide consent for every measurement and test carried out, allowing them to choose the measurements and tests they wanted to be performed. Ethics approval was also obtained for this manuscript from the institutional review board of PNU, before submission for publication (IRB number: 19-0172, date of approval: 6 Oct 2019).

Study population

For the purpose of the present study, all individuals with normoglycemia and prediabetes who had their vitamin D levels assessed were identified from the registry data and included in the analysis. We retrieved the demographic data, medical data, anthropometric measurements and laboratory results on vitamin D and HbA1c levels of the participants. Participants without a laboratory result for vitamin D and/or HbA1c (n = 123) or those who had diabetes mellitus (history of diabetes mellitus and/or HbA1c > 6.4%; n = 4) were excluded from the current analysis.

Vitamin D and HbA1c measurement and status definitions

Total vitamin D was measured from the participants' serum samples. Both vitamin D and HbA1c were assessed by chemiluminescence (Abbott, Chicago, IL, USA) at the King Abdullah bin Abdulaziz University Hospital main laboratory. Prediabetes was diagnosed based on the American Diabetes Association HbA1c criteria[22]. An HbA1c value of 5.7–6.4% was considered as prediabetes[22]. Vitamin D status was defined based on The National Academy of Medicine recommended cut-points for vitamin D status[23], whereby vitamin D levels of <30 nmol/L, 30–49 nmol/L, 50–125 nmol/L and >125 nmol/L were considered to reflect deficiency, inadequacy, sufficiency and possibly harmful (above sufficiency) levels, respectively[23–25].

Statistical analysis

Continuous variables are expressed as the means with standard deviations or as the medians with interquartile ranges. Categorical variables are expressed as numbers and percentages. Comparisons between groups based on the prediabetes status or BMI were made using the analysis of variance (ANOVA) and the Kruskal–Wallis, χ^2 or Fisher's exact tests, as appropriate. Logistic regression was used to compute the odds ratio and its associated 95% confidence interval for these comparisons. Multivariate linear regression was used to examine the association between the levels of vitamin D and HbA1c as a continuum after adjusting for age and BMI. Subgroup analysis based on the BMI was carried out by incorporating an interaction term between the BMI group and vitamin D level into the regression model. For sensitivity analysis, the regression analysis was repeated after excluding participants who were deemed to be influential and leverage points in the residual diagnostics of the main analysis (participants with outlying levels of vitamin D [>125 nmol/L]). A P-value <0.05 was considered to be statistically significant. The analysis was carried out using the Statistical Analysis System (SAS) 9.4 (SAS Institute, Cary, NC, USA) software.

RESULTS

Baseline characteristics of the study population based on prediabetes status

A total of 345 non-diabetic young women were included in the study. There was no statistically significant difference in the baseline characteristics between those included and those who were excluded due to missing laboratory results for vitamin D and/or HbA1c (not shown), except for the mean number of parents/siblings with diabetes mellitus, which was higher among those included in the study (0.5 vs 0.3; P = 0.031). The baseline characteristics of the participants are summarized in Table 1. Their mean age was 18.1 ± 0.5 years, and 40.3% of them had a family history of diabetes mellitus. Based on the HbA1c levels, 28.4% of the participants had prediabetes (HbA1c 5.7–6.4%), whereas 50.7% and 31.9% of them had vitamin D deficiency and inadequacy, respectively. Just 15.9% of the participants had sufficient levels of vitamin D (Table 1).

Association of vitamin D levels with prediabetes and HbA1c levels

When the participants were stratified based on their prediabetes status, no significant difference was observed in the vitamin D levels/status between individuals with normoglycemia and prediabetes. Conversely, individuals with prediabetes had significantly higher BMI and weight compared with those with normoglycemia (23.5 vs 25.3 kg/m^2, P = 0.013 and 58.6 vs 63.8 kg, P = 0.007, respectively; Table 1; Figure 1).

Table 2 shows the relationship between vitamin D and HbA1c levels in the study population. After adjusting for age and BMI, we found no significant association between the levels of vitamin D and HbA1c (P = 0.626). Similarly, there was no significant difference in the HbA1c values with each 1-year increase in the participants' age (P = 0.904). In contrast, a significant association was detected between the HbA1c levels and BMI; for every five-unit decrease in BMI, a 0.038% decrease in the levels of HbA1c was detected.

Table 1 | Baseline characteristics of the study population based on prediabetes status

Variable	All n = 345	Normoglycemia (HbA1c <5.7%; n = 247)	Prediabetes (HbA1c 5.7–6.4%; n = 98)	P
Age (years)				
Mean (SD)	18.1 (0.5)	18.2 (0.5)	18.1 (0.5)	0.331
Range	(17.3–21.8)	(17.3–21.8)	(17.4–21.3)	
Family history of DM (parents/siblings), n (%)				
No	206 (59.7)	147 (59.5)	59 (60.2)	0.906
Yes	139 (40.3)	100 (40.5)	39 (39.8)	
Number of parents/siblings with DM				
Mean (SD)	0.5 (0.7)	0.5 (0.7)	0.4 (0.6)	0.533
Range	(0.0–3.0)	(0.0–3.0)	(0.0–2.0)	
Height (cm)†				
Mean (SD)	157.8 (6.1)	157.7 (5.7)	158.3 (6.9)	0.374
Range	(125.0–175.0)	(136.0–175.0)	(125.0–174.0)	
Weight (kg)†				
Mean (SD)	60.0 (16.0)	58.6 (14.0)	63.8 (19.9)	0.007
Range	(30.5–126.3)	(30.5–107.6)	(36.1–126.3)	
BMI (kg/m^2)†				
Mean (SD)	24.0 (5.9)	23.5 (5.3)	25.3 (7.0)	0.013
Range	(13.6–50.0)	(13.6–49.1)	(15.4–50.0)	
sBP (mmHg)†				
Mean (SD)	114.9 (8.3)	115.3 (8.5)	113.8 (7.6)	0.126
Range	(95.0–199.0)	(96.0–199.0)	(95.0–135.0)	
dBP (mmHg)†				
Mean (SD)	74.2 (6.7)	74.3 (6.9)	74.1 (6.2)	0.764
Range	(51.0–97.0)	(51.0–97.0)	(60.0–92.0)	
25-Hydroxyvitamin D (nmol/L)				
Mean (SD)	36.4 (23.7)	36.3 (22.7)	36.6 (26.0)	0.843
Median (IQR)	29.4 (21.6, 43.1)	29.0 (21.7, 43.1)	29.5 (20.9, 43.5)	
Range	(9.4–186.4)	(9.4–150.4)	(10.2–186.4)	
25-Hydroxyvitamin D (nmol/L), n (%)				
<30	175 (50.7)	125 (50.6)	50 (51.0)	0.937
30–49	110 (31.9)	80 (32.4)	30 (30.6)	
50–125	55 (15.9)	39 (15.8)	16 (16.3)	
>125	5 (1.4)	3 (1.2)	2 (2.0)	

†Data were missing for up to 13 participants. BMI, body mass index; dBP, diastolic blood pressure; DM, diabetes mellitus; HbA1c, hemoglobin A1c; IQR, interquartile range; sBP, systolic blood pressure; SD, standard deviation.

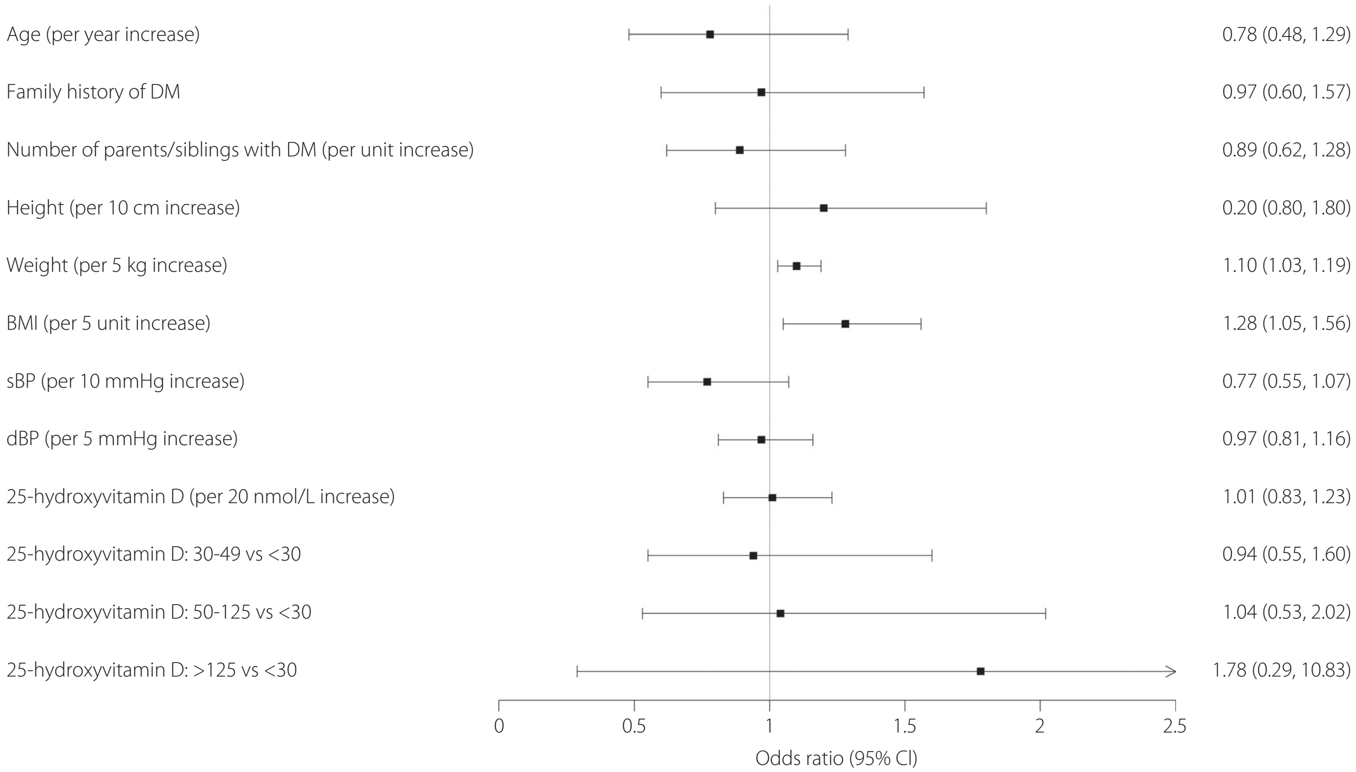

Figure 1 | Odds ratio of being prediabetic and its associated 95% confidence interval for various baseline characteristics. BMI, body mass index; dBP, diastolic blood pressure; DM, diabetes mellitus; sBP, systolic blood pressure; CI, confidence interval.

Association between vitamin D and HbA1c levels based on BMI

The relationship between the levels of vitamin D and HbA1c was further studied in the subgroups of participants defined on the basis of BMI (Table 3). There appeared to be an association between the levels of vitamin D and HbA1c among participants with a BMI <18.5, although it did not reach statistical significance. In this subgroup, for every 20-nmol/L increase in vitamin D levels, HbA1c levels increased by 0.052 ($P = 0.054$). After the exclusion of participants with possibly harmful vitamin D levels (vitamin D >125 nmol/L; $n = 5$) from the analysis, the estimated increase in HbA1c was 0.118 ($P = 0.029$). However, for the other BMI subgroups, we did not observe any significant relationship between the levels of vitamin D and HbA1c.

DISCUSSION

The present results showed that vitamin D levels were not significant predictors of prediabetes among young Saudi women. Additionally, no correlation was detected between the vitamin D and HbA1c levels in this population as a whole, and in the subgroups based on BMI. However, after elimination of participants with potentially harmful levels of vitamin D, a statistically significant positive association was observed between the levels of HbA1c and vitamin D in underweight participants, with an estimated increase of 0.118% in HbA1c levels for every 20-nmol/L increase in vitamin D levels ($P = 0.029$), albeit with a limited sample size of 45 participants. In contrast, BMI and weight were significant predictors of the risk of prediabetes in this population ($P = 0.013$ and $P = 0.007$, respectively). A significant positive association was seen between HbA1c levels and BMI. The present findings on the prevalence of prediabetes (28.4%)[26,27] and vitamin D status are consistent with those reported by other investigators from SA[18,28].

Observational data on the association of vitamin D levels with the risk of prediabetes and HbA1c levels are generally limited, and the results are somewhat conflicting[9,13]. To the best of our knowledge, this is the first study to report this association in a Saudi population. In an analysis of 960 adults enrolled in the first National Nutrition Survey in Kuwait, an almost two-fold increase in the odds of prediabetes was found in participants with vitamin D inadequacy and deficiency[5]. Two analyses from the National Health and Nutrition Examination Survey have reported a significant association between low vitamin D levels and prediabetes status[3,4]. However, in a subgroup analysis, the odds ratio for prediabetes was positive only in non-Hispanic white individuals, but not in non-Hispanic black individuals or individuals of Mexican origin[4]. Modi *et al.*[7], in a cross-sectional study involving 606 patients from India (72% women), found lower vitamin D levels in the control group

Table 2 | Relationship between levels of hemoglobin A1c and vitamin D, age and body mass index

Comparison	All patients	
	Estimate difference in HbA1c (95% CI)	*P*
25-Hydroxyvitamin D level (per 20 nmol/L increase)	0.006 (–0.019, 0.031)	0.626
Age (per year increase)	–0.004 (–0.061, 0.054)	0.904
BMI (per 5-unit decrease)	–0.038 (–0.063, –0.012)	0.004

compared with the prediabetes and diabetes mellitus groups (P = 0.0124)[7]. The authors found no association between vitamin D deficiency and HbA1c levels[7]. In a smaller cross-sectional study of Brazilian patients, Giorelli *et al.*[8] found no association between vitamin D levels and the risk of prediabetes. The present findings are in accordance with those of Modi *et al.*[7] and Giorelli *et al.*[8]

There are potential explanations for the discrepancies in the present study results, including the size of the effect. It is possible that the effect of vitamin D on glucose hemostasis was very small, and it would require a larger population to establish it. Although we could not show an association between vitamin D levels and the risk of prediabetes or HbA1c levels, we have shown a clear association between prediabetes and BMI. The effect of vitamin D levels on glucose metabolism and HbA1c levels might be much lower than other well-established risk factors, such as obesity[29–33]. Such information will help in directing prevention efforts in a cost-effective manner.

Another potential explanation might be related to the effect of sex[32]. Sex-related risk factors[34] and differences in the traditional risk factors for prediabetes exist, with some factors having a more significant effect in one sex than in the other[32]. Pittas *et al.*[6], in a large prospective Nurses' Health Study, found no association between the total vitamin D intake and type 2 diabetes mellitus in 83,779 women with no history of diabetes mellitus during 20 years of follow up, even after adjusting for multiple potential confounders. However, although female sex might account for the negative association between vitamin D deficiency and prediabetes[6], it does not explain it fully. Modi *et al.*[7], in a study of an all-female population, and Nur-Eke *et al.*[35], in a study of a predominantly (80.4%) female population from Turkey, found a significant negative correlation between levels of vitamin D and HbA1c in individuals with prediabetes.

Race is another potential confounder[13]. Although a positive association was observed in studies from the USA[3,4], Kuwait[5] and Turkey[35], negative results have been reported in studies from India[7] and Brazil[8]. This observation is strengthened by the findings of Shankar *et al.*[4], which showed an association between vitamin D levels and the incidence of prediabetes among adults in the USA. However, in a subgroup analysis, they found that the odds ratio for prediabetes was positive only in non-Hispanic white individuals, and not in non-Hispanic black individuals or individuals of Mexican origin[4]. Therefore, the differential effects of specific genetic mechanisms on the risk of prediabetes/DM should be considered[36].

There is a variability in the mechanisms by which vitamin D improves glucose metabolism[37]. For example, contrary to other tissues, in a culture of adipocytes, vitamin D reduced glucose utilization as a substrate for fatty acid synthesis[38] and decreased

Table 3 | Relationship between levels of vitamin D and hemoglobin A1c in the body mass index subgroups

Comparison	All patients		Excluded those with vitamin D > 125 nmol/L	
	Estimated difference in HbA1c (95% CI)	*P*	Estimated difference in HbA1c (95% CI)	*P*
Vitamin D level (per 20 nmol/L increase)				
Among those with BMI <18.5 (n = 47; 45)	0.052 (–0.001, 0.106)	0.054	0.118 (0.012, 0.224)	0.029
Among those with BMI 18.5–24.9 (n = 178; 176)	0.000 (–0.033, 0.034)	0.982	–0.009 (–0.047, 0.030)	0.656
Among those with BMI 25–29.9 (n = 62; 62)	–0.024 (–0.104, 0.055)	0.543	–0.025 (–0.104, 0.055)	0.540
Among those with BMI ≥30 (n = 46; 45)	–0.004 (–0.078, 0.071)	0.920	0.025 (–0.102, 0.152)	0.703
Age (per year increase)	–0.019 (–0.078, 0.040)	0.537	–0.012 (–0.073, 0.050)	0.704
BMI				
<18.5 vs ≥30	–0.207 (–0.399, –0.015)	0.034	–0.249 (–0.523, 0.024)	0.073
18.5–24.9 vs ≥30	–0.133 (–0.302, 0.036)	0.122	–0.075 (–0.305, 0.156)	0.525
25–29.9 vs ≥30	–0.038 (–0.252, 0.176)	0.728	0.006 (–0.257, 0.270)	0.963

BMI, body mass index; CI, confidence interval; HbA1c, hemoglobin A1c.

lipid storage[38,39]. Other possible explanations for the varying associations between the levels of vitamin D and HbA1c include vitamin D receptor gene polymorphism, the interaction of vitamin D with the insulin-like growth factor system[13] and the influence of other hormones[40]. Alterations in free vitamin D levels, particularly in obese individuals, should also be considered[41]. How the latter influences the effects of vitamin D in tissues remains to be firmly established[41–43].

Not all risk factors for prediabetes/diabetes mellitus influence disease pathogenesis equally. Very few of the risk factors for type 2 diabetes mellitus that have emerged from observational research have shown a causal relevance[36,44]. Additionally, prediabetes is a highly heterogeneous metabolic condition, with multiple phenotypes. An improved understanding of these phenotypes could help in improving the stratification of prediabetes/DM risk in different populations[36,45]. The present findings emphasize the role of obesity as a major risk factor for developing prediabetes in SA. These findings are in accordance with prior reports from SA[31] and worldwide[29,30,32,46]. Lifestyle interventions, including weight reduction, lowered the risk of progression to diabetes mellitus by 58% in the Diabetes Prevention Program[47]. Combating the obesity epidemic in the Saudi community, particularly among young women, is important to prevent the diabetes mellitus epidemic.

Some of the observational and interventional studies have reported an association between vitamin D levels and prediabetes in obese individuals. Li *et al.*[15] in a study involving 1,514 Chinese adults without diabetes mellitus, of whom 65% had prediabetes, found that poor vitamin D status was significantly related to an increased risk of prediabetes in the overweight or obese individuals ($P = 0.047$), but not in those with a BMI <24 kg/m^2. In a study involving obese Swedish adolescents, a significant interaction effect was found between low vitamin D levels and impaired fasting glycemia[48]. In the present study, when the relationship between the levels of vitamin D and HbA1c was analyzed based on the BMI groups, none of the groups showed a significant association between levels of vitamin D and HbA1c. However, when individuals with possibly harmful vitamin D levels (>125 nmol/L) were excluded from the analysis, a positive association was found between levels of vitamin D and HbA1c in underweight individuals. This observation in the underweight group might be explained by the ability of vitamin D to decrease glucose utilization as a substrate for fatty acid synthesis in the adipose tissue[38,39]. The present findings on the lack of association between levels of vitamin D and HbA1c in obese individuals are consistent with those of other investigators[49,50]. Ter Horst *et al.*[50] found no association between the levels of vitamin D metabolites and glucose metabolism or insulin action in obese women.

In the present study, no association was shown between vitamin D deficiency and the risk of prediabetes in young Saudi women. However, an increase in BMI was a significant predictor of prediabetes development. Further studies, particularly large prospective studies, are required to make a conclusion regarding the association between the levels of vitamin D and the risk of prediabetes in the Saudi population.

The main limitation of the present study was that our analysis was based on registry data. Therefore, the available sample size might not had been adequate to show an association between the levels of vitamin D and risk of prediabetes or HbA1c levels. Our analysis, however, has identified a correlation between BMI and HbA1c levels, as well as prediabetes status. These findings support the lack of an association among Saudi women or that the effect, if present, is likely to be small. These findings guide clinicians to direct disease prevention measures in a cost-effective manner.

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DISCLOSURE

The authors declare no conflict of interest.

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