Research Article

Impact of the Glycemic Control and Duration of Type 2 Diabetes on Vitamin D Level and Cardiovascular Disease Risk

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Background and Aims. To investigate the impact of glycemic control and T2D duration on vitamin D status and cardiovascular disease (CVD) risk among Saudi patients.

Methods. This case-control study was conducted in King Faisal Specialist Hospital, Saudi Arabia. A total of 25 nondiabetic controls and 92 patients with confirmed T2D, aged 20–60 years, were included. Patients with T2D were divided into the following groups based on disease duration (newly diagnosed: ≥6 months and long duration: ≥5 years) and glycemic control based on their glycated hemoglobin (HbA1C) level with a threshold of ≤0.053 mol/mol: newly diagnosed controlled (NC, n = 25), newly diagnosed uncontrolled (NU, n = 17), long duration controlled (LC, n = 25), and long duration uncontrolled (LU, n = 25). Blood levels of fasting blood glucose, HbA1C, lipid profile, and serum 25-hydroxyvitamin D (25(OH)D) were assessed and used to define the CVD risk score. Results. Our study showed that T2D duration was an independent predictor of vitamin D deficiency. The longer disease duration, the lower odds of being vitamin D deficient (odds ratio (OR) = 0.05, 95% CI: 0.01–0.29, p < 0.05). No significant association was observed between vitamin D and HbA1C levels. In the NU group, CVD risk scores were directly correlated with serum 25(OH)D (r = 0.53, p < 0.05). On the contrary, 25(OH)D was moderately inversely correlated with CVD risk score in the LU group (r = −0.45, p < 0.05). Conclusion. Duration of diabetes rather than glycemic control is associated with vitamin D deficiency. Glycemic uncontrol may augment vitamin D deficiency-associated CVD risk in both newly diagnosed and old patients with type 2 diabetes.

1. Introduction

Since 1921, the role of vitamin D in calcium homeostasis and bone health has been identified [1]. Vitamin D is composed of two bioequivalent forms: D2, which is found in vegetables and dietary supplements, and D3, which is synthesized in the skin through sun exposure and found in some oily fish and fortified foods. Once absorbed, vitamin D is metabolized in the liver to 25-hydroxyvitamin D (25(OH)D) and subsequently converted into 1,25-dihydroxyvitamin D (1,25(OH)2D) [2]. Deficiency in vitamin D is a global concern; approximately one billion people in the world have low vitamin D levels [3]. In the United States, according to the National Health and Nutrition Examination Survey 2011–2012, about 40% of men and women were vitamin D deficient [4]. In Saudi Arabia, approximately 81% of the different population groups has vitamin D deficiency, and this condition is more prevalent in women compared to men [5].

Extensive research has shown adverse relations of vitamin D deficiency with cardiovascular disease (CVD), arterial hypertension, adiposity, and type 2 diabetes (T2D) [6–10].
diabetes [11]. Since Saudis have a high prevalence of T2D [11] and overweight [12], vitamin D deficiency may place them at an additional risk of CVD, making a strong case for early intervention [13].

Experimental studies found that (1,25(OH)₂D₃) stimulated pancreatic β-cell to secrete insulin [14]. Another proposed mechanism regarding the role of vitamin D in T2D is that since vitamin D deficiency causes an increase in inflammatory markers, insulin resistance may develop [15]. However, other intervention studies found no improvement in glycemic control with vitamin D supplementation [9, 16]. In the other hand, T2D itself might improve glycemic control with vitamin D supplementation [17, 18]. According to the OpenEpi software, version 2 [19], Fleiss formulae stated that the sample size of this case-control study is 13 cases, 13 controls, and the total sample size is 26 patients.

2. Methods

2.1. Participants and Recruitment. This case-control study included 92 patients with confirmed T2D and 25 healthy individuals (controls) aged 20–60 years. The study was conducted in King Faisal Specialist Hospital & Research Centre in Riyadh, Saudi Arabia. Patients diagnosed with type 1 diabetes, patients with history of endocrine disorders, patients with neurological disease, patients with renal disease and diabetic nephropathy, pregnant and lactating women, patients taking vitamin D supplementation within the last 6 months or any drugs affecting calcium and vitamin D metabolism like steroid medications, and patients taking antiepileptic medications and weight reduction drugs, which might affect the absorption of vitamin D, were excluded. Study protocol was approved by the Ethics Committee of the College of Applied Medical Sciences, King Saud University at all sites (reference no: CAMS 30/3536) and that of the King Faisal Specialist Hospital & Research Centre (KFSHRC) (Project no: 2151144).

Recruitment was done through screening of the medical history data from medical files based on the duration of T2D (newly diagnosed: ≤6 months and long duration: ≥5 years) and glycated hemoglobin (HbA₁c) level with a threshold of ≤0.053 mol/mol. Patients were then approached and invited to participate. A total of 117 participants from various clinics at the endocrinology and family medicine units in King Faisal Specialist Hospital & Research Centre provided their written informed consent and were divided into five groups: the nondiabetic (N) control group (n = 25), the newly diagnosed controlled (NC) group (n = 25) (within 6 months of diabetes diagnosis and achieved glycemic goals based on levels of HbA₁c ≤ 0.053 mol/mol), the newly diagnosed uncontrolled (NU) group (n = 17) (within 6 months of diabetes diagnosis and were unable to achieve glycemic goals), the long duration controlled (LC) group (n = 25) (5–10 years of diabetes diagnosis and achieved glycemic goals of ≤0.053 mol/mol), and the long duration uncontrolled (LU) group (n = 25) (5–10 years of diabetes diagnosis and did not achieve their glycemic goals).

Sample size was calculated after considering the following: a 95% two-sided confidence interval and 80% power, and the case to control ratio was one to one. The hypothetical proportion of controls with vitamin D deficiency was about 51.7% [17], and that of cases with T2D approximately was 98.5% [18]. According to the OpenEpi software, version 2 [19], Fleiss formulae stated that the sample size of this case-control study is 13 cases, 13 controls, and the total sample size is 26 patients.

2.2. Medical History. On an assigned date, participants were requested to visit the clinics in the morning while still fasting (>12 hours); data on sex, age, occupation, region, marital status, smoking, eating habits, sun exposure, and other variables were collected using an interview-based health history questionnaire.

2.3. Biochemical Assessment. Blood (≈10 cc) was withdrawn after overnight fasting (>12 hours) and transferred immediately to a nonheparinizing tube for centrifugation. Fasting blood glucose (FBG) was measured using Roche/Hitachi modular Cobas c 701/702 [20]. Glycated hemoglobin (HbA₁c) was measured using Cobas c 311, 501, and 502 analyzers, targeting an HbA1C level of ≤0.053 mol/mol (7.0%) [21]. All samples were measured in duplicates with intra- and interassay coefficient of variability (CV) of the total sample were about 5.1% and 14.7%, respectively. Vitamin D serum concentration and level of parathyroid hormone (PTH) were measured using electrochemiluminescence immunoassay, Cobas e411 autoanalyzer (Roche), Modular Analytics E170, and Cobas e 411, 601, and 602. The % of intra- and interassay CV of vitamin D duplicates for the total sample were 5.7% and 9.8%, respectively. For PTH, % of intra- and interassay CV of sample duplicates were 4.9% and 7.9%, respectively. Deficiency in vitamin D was defined as 25(OH)D < 50 nmol/l [1]. Markers of calcium homeostasis, alkaline phosphatase (ALP), and phosphorus were measured by Roche/Hitachi modular Cobas c 701/702 tests. Serum cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG) were assessed by Roche/Hitachi modular Cobas c 701/702 tests [20]. The % of intra- and interassay CVs were within the acceptable ranges.

2.4. Cardiovascular Disease Risk Scoring. We used three types of long-term cardiovascular disease (CVD) risk scores in this study. First was the Framingham 30-year risk score, calculated based on the lipid profile of patients with hard cardiovascular disease (FS30 lipid hard CVD). The second, FS30, used the lipid profile of patients with full CVD (FS30 lipid full CVD). The third score was calculated based on the patient’s lifetime atherosclerotic CVD risk (lifetime ASCVD) and 10-year ASCVD risk, according to the American College of Cardiology/American Heart Association risk. A cutoff of ≤12% was used for FS30; therefore, participants with scores below the cutoff were classified as low risk. Scores of more than 12% were considered high risk. The lifetime ASCVD risk cutoff values were expressed in ASCVD percentage (5 and 8% for men and women, respectively) for participants.
-aged 50 years with optimal risk factor levels. The 10-year ASCVD risk cutoff value was 0.6%. All of the scores included the following variables: age, sex, BMI, systolic blood pressure, lipids, smoking status, and diagnosis with diabetes or hypertension [22, 23].

2.5. Statistical Analysis. Statistical analyses were performed using the software package SPSS version 20 (SPSS, IBM, USA). All data were presented as means ± standard deviation (SD). Categorical variables were summarized using absolute and relative frequencies and compared using chi-square test. The respective subgroups and normal participants were compared using one-way analysis of variance with post hoc test. Pearson’s correlation coefficients were used to test the correlation of diabetic and metabolic parameters with vitamin D. Multivariable logistic regression analysis was applied to identify the independent factors for the risk of vitamin D deficiency in patients with T2D. ORs and 95% confidence intervals (CI) for vitamin D deficiency were reported. A p value of ≤ 0.05 was considered significant.

3. Results

3.1. Descriptive Results. Of the total sample, 56.5% were women and 43.5% were men. The NC group showed more frequent family history of hypertension and cardiovascular disease in comparison to the control group (Table 1). The proportions of physically active participants in the control group and NC groups were 62.5% and 37.5%, respectively, in both sexes, while sun exposure was higher in the NC group compared to the normal group compared

| Variables | % within variable | Pearson chi-square |
|-----------|-------------------|--------------------|
| Gender    |                   |                    |
| Male      | 45.0              | 55.0               |
| Female    | 53.3              | 46.7               |
| Employee  |                   |                    |
| No        | 6.7               | 93.3               |
| Yes       | 68.6              | 31.4               |
| Family history of hypertension | 9.52 | 0.002* |
| No        | 9.5               | 100.0              |
| Yes       | 59.5              | 40.5               |
| Family history of CVD | 9.52 | 0.002* |
| No        | 58.1              | 41.9               |
| Yes       | 0.0               | 100.0              |
| Family history of diabetes | 6.818 | 0.009* |
| No        | 0.0               | 100.0              |
| Yes       | 56.8              | 43.2               |
| Past history of high blood pressure | 6.81 | 0.009* |
| No        | 56.8              | 43.2               |
| Yes       | 0.0               | 100.0              |
| Smoking status | 5.55 | 0.062 |
| No        | 55.6              | 44.4               |
| Yes       | 0.0               | 100.0              |
| Passive   | 0.0               | 100.0              |
| Physical activity | 5.55 | 0.018* |
| No        | 27.8              | 72.2               |
| Yes       | 62.5              | 37.5               |
| Bone symptoms | 12.50 | 0.001* |
| No        | 62.5              | 37.5               |
| Yes       | 0.0               | 100.0              |
| Exposure sun | 23.52 | 0.001* |
| Weekly    | 73.5              | 26.5               |
| Daily     | 0.0               | 100.0              |
| Time of exposure | 24.24 | 0.001* |
| No        | 0.0               | 100.0              |
| Sunrise   | 83.3              | 16.7               |
| At noon   | 0.0               | 100.0              |
| Afternoon | 0.0               | 100.0              |
| Nature of work | 1.02 | 0.312 |
| Inside    | 51.0              | 49.0               |
| Outside   | 0.0               | 100.0              |
| Egg       |                   |                    |
| No        | 0.0               | 100.0              |
| Daily     | 42.9              | 57.1               |

Table 1: Relevant medical and dietary variables among normal and newly diagnosed-controlled patients with T2D and their analysis by using chi-square test.

Table 1: Continued.

| Variables | % within variable | Pearson chi-square |
|-----------|-------------------|--------------------|
| Weekly    | 52.4              | 47.6               |
| Monthly   | —                 | —                  |
| Milk      |                   |                    |
| No        | 0.0               | 100.0              |
| Daily     | 42.1              | 57.9               |
| Weekly    | 58.6              | 41.4               |
| Monthly   | —                 | —                  |
| Fish oil  |                   |                    |
| No        | 0.0               | 100.0              |
| Daily     | —                 | —                  |
| Weekly    | 41.7              | 58.3               |
| Monthly   | 58.8              | 41.2               |
| Lifetime ASCVD risk | 8.14 | 0.004* |
| No        | 100.0             | 0.0                |
| Yes       | 41.9              | 58.1               |
| Framingham | 39.28 | 0.001* |
| No        | 89.3              | 10.7               |
| Yes       | 0.0               | 100.0              |
3.2. Comparison of Study Variables between Case Groups and Control Group.

Levels of FBG ($p < 0.01$) were significantly higher in the NU, LC, and LU groups compared with the control group (Table 5). Impact of disease duration was not significantly different when new cases were compared with long-lasting ones.

Paradoxically, LC group has significantly higher levels of 25(OH)D than normal population which was already VD deficient ($p < 0.01$). Moreover, PTH level was significantly lower in the LC in comparison to control ($p < 0.05$) (Table 5).

For CVD risk scores, the FS30 lipid hard CVD, FS30 lipid full CVD, and lifetime ASCVD were significantly different in the NC, NU, LC, and LU groups in comparison to control (Table 6). No significant changes in any risk were detected between controlled and uncontrolled groups or between new and long-lasting groups by post hoc test.

3.3. Correlation of 25-Hydroxyvitamin D Level with Cardiovascular Risk Scores among Study Groups. In the LU

| Variables | % within variable Normal | % within variable New & uncontrolled | Pearson chi-square $X^2$ p value |
|-----------|--------------------------|-------------------------------------|-------------------------------|
| Gender    |                          |                                     |                               |
| Male      | 50.0                     | 50.0                                | 1.18                          | 0.276                         |
| Female    | 66.7                     | 33.3                                | 11.14                         | 0.001*                        |
| Employee  |                          |                                     |                               |
| No        | 11.1                     | 88.9                                | 10.29                         | 0.001*                        |
| Yes       | 72.7                     | 27.3                                |                               |
| Family history of hypertension |                  |                                     |                               |
| No        | 0.0                      | 100.0                               | 6.50                          | 0.011*                        |
| Yes       | 69.4                     | 30.6                                |                               |
| Family history of cardiovascular disease |                     |                                     |                               |
| No        | 65.8                     | 34.2                                |                               |
| Yes       | 0.0                      | 100.0                               |                               |
| Family history of diabetes |                        |                                     |                               |
| No        | 0.0                      | 100.0                               | 3.08                          | 0.079                         |
| Yes       | 62.5                     | 37.5                                |                               |
| Past history of high blood pressure |                      |                                     |                               |
| No        | 62.5                     | 37.5                                | 3.08                          | 0.079                         |
| Yes       | 0.0                      | 100.0                               |                               |
| Smoking status |                    |                                     |                               |
| No        | 65.8                     | 34.2                                | 6.50                          | 0.039*                        |
| Yes       | 0.0                      | 100.0                               |                               |
| Passive   | 0.0                      | 100.0                               |                               |
| Physical activity |                   |                                     |                               |
| No        | 38.5                     | 61.5                                | 3.46                          | 0.063                         |
| Yes       | 69.0                     | 31.0                                |                               |
| Bone symptoms |                  |                                     |                               |
| No        | 65.8                     | 34.2                                | 6.50                          | 0.011*                        |
| Yes       | 0.0                      | 100.0                               |                               |
| Exposure sun |                  |                                     |                               |
| Weekly    | 67.6                     | 32.4                                | 8.34                          | 0.015*                        |
| Daily     | 0.0                      | 100.0                               |                               |
| Time of exposure |                |                                     |                               |
| No        | 0.0                      | 100.0                               | 10.87                         | 0.012*                        |
| Sunrise   | 62.5                     | 37.5                                |                               |
| At noon   | —                        | —                                   |                               |
| At afternoon |                   |                                     |                               |
| Nature of work |                  |                                     |                               |
| Inside    | 62.5                     | 37.5                                | 3.08                          | 0.079                         |
| Outside   | 0.0                      | 100.0                               |                               |
| Egg |                           |                                     |                               |
| No        | 100.0                    | 0.0                                 | 3.55                          | 0.169                         |
| Daily     | 57.9                     | 42.1                                |                               |

($X^2 = 23.52$, $p < 0.01$), and the time of exposure was usually at afternoon period. Additionally, the frequency of those with lifetime ASCVD risk ($p < 0.05$) and Framingham risk score ($p < 0.01$) was significantly higher in the NC group in comparison to the control group. The NU group (Table 2) showed more daily exposure to sun than normal group and usually afternoon. Regarding LC and LU groups (Tables 3 and 4), family history of hypertension and cardiovascular disease were more frequent in comparison to the control group, and the proportion of those who are exposed to the sun were more and usually at noon and afternoon periods.

Table 2: Relevant medical and dietary variables among normal and newly diagnosed uncontrolled patients with T2D.

(Continued.)
group, lifetime ASCVD risk showed significant negative correlation with serum 25(OH)D ($r = -0.453$, $p < 0.05$), while in the NU group, risk of Full Cardiovascular Disease scores was directly correlated with serum 25(OH)D ($r = 0.525$, $p < 0.05$) (Table 7).

3.4. Disease Duration of T2D and Glycemic Controllability as Determinant of Vitamin D Deficiency.

Logistic regression analysis investigating the independent risk factors related to vitamin D deficiency in T2D patients showed that duration of T2D was associated with lower risk of vitamin D deficiency (defined by a cutoff 25(OH)D level below 50 nmol/l) ($OR = 0.05$, $p < 0.05$) (Table 8).

4. Discussion

Paradoxically in this case-control study, patients with longer disease duration had lower odds of being vitamin D deficient, and the mean of 25(OH)D was significantly higher in LC vs normal group. However, there was no significant association between vitamin D level and glycemic control based on FBG levels.

Interestingly, 72% of the control group had vitamin D deficiency, 20% had insufficient, and 8% had optimal levels of 25(OH)D. These findings regarding Saudi population are consistent with a recent published meta-analysis of all prevalence studies published between 2008 and 2015 [24]. Patients with T2D had a relatively low prevalence (48%) of low 25(OH)D level (<50 nmol/l). This is partly due to higher proportions of sun exposure in diabetic groups (Tables 1–4) and
the usual follow up of this healthy lifestyle in addition to routine supplementation of vitamin D to T2D patients in the visited clinics in the KFSHRC.

Our findings also showed that the duration of T2D was an independent predictor of vitamin D deficiency. This result is compatible to findings of a recent cross-sectional study of an inverse association between disease duration and vitamin D [25]. Results from the landmark Women’s Health Initiative Calcium/Vitamin D Trial have suggested that vitamin D oral supplements may delay the natural progression of T2D [26]. It was suggested that vitamin D supplementation of (2,000 IU/day for 16 weeks) improved pancreatic β-cell function in a randomized clinical trial, assessed using the disposition index [27]. In contrast, few cross-sectional studies found no significant association between the T2D duration and vitamin D deficiency [28, 29]. The differences observed between studies can be due to several factors. These include the nature of the study populations (ethnicity), lifestyle, medications administered, clinical characteristics of study participants, genetic variations in the vitamin D receptor, and PTH concentration.

We found no significant association between vitamin D deficiency and glycemic control (Table 7). These findings are comparable to results of a case-control study by Sheth et al., which indicated no significant association between deficiency of vitamin D and HbA1c [30]. Similarly, another case-control study did not find a significant relation between HbA1c and vitamin D levels in T2D patients [31]. Jorde et al. showed that supplementation with vitamin D (20000 IU

| Variables                                   | % within variable | Pearson chi-square X² p value |
|---------------------------------------------|-------------------|------------------------------|
| Gender                                      |                   |                              |
| Male                                        | 45.0              | 0.333 0.564                  |
| Female                                      | 53.3              |                              |
| Employee                                    |                   |                              |
| No                                          | 10.0              | 8.00 0.005                   |
| Yes                                         | 60.0              |                              |
| Family history of hypertension              |                   |                              |
| No                                          | 0.0               | 6.81 0.009                   |
| Yes                                         | 56.8              |                              |
| Family history of cardiovascular disease     |                   |                              |
| No                                          | 62.5              | 12.50 0.001                  |
| Yes                                         | 0.0               |                              |
| Family history of diabetes                  |                   |                              |
| No                                          | 0.0               | 3.19 0.074                   |
| Yes                                         | 53.2              |                              |
| Past history high blood pressure            |                   |                              |
| No                                          | 62.5              | 12.50 0.001                  |
| Yes                                         | 0.0               |                              |
| Smoking status                              |                   |                              |
| No                                          | 62.5              | 12.50 0.002                  |
| Yes                                         | 0.0               |                              |
| Passive                                     | 0.0               |                              |
| Physical activity                           |                   |                              |
| No                                          | 27.8              | 5.55 0.018                   |
| Yes                                         | 62.5              |                              |
| Bone symptoms                               |                   |                              |
| No                                          | 62.5              | 12.50 0.001                  |
| Yes                                         | 0.0               |                              |
| Exposure sun                                 |                   |                              |
| Weekly                                      | 78.1              | 28.12 0.001                  |
| Daily                                       | 0.0               |                              |
| Time of exposure                            |                   |                              |
| No                                          | 0.0               | 24.03 0.001                  |
| Sunrise                                     | 66.7              |                              |
| At noon                                     | 0.0               |                              |
| Afternoon                                    | 0.0               |                              |
| Nature of work                              |                   |                              |
| Inside                                      | 51.0              | 1.02 0.312                   |
| Outside                                     | 0.0               |                              |
| Egg                                         |                   |                              |
| No                                          | 0.0               | 2.36 0.307                   |

| Variables                                   | % within variable | Pearson chi-square X² p value |
|---------------------------------------------|-------------------|------------------------------|
| Daily                                       | 42.9              | 6.38 0.012                   |
| Weekly                                      | 53.7              | 46.3 0.004                   |
| Monthly                                     | 0.0               | 100.0                        |
| Milk                                        |                   |                              |
| No                                          | 0.0               | 4.08 0.130                   |
| Daily                                       | 44.4              |                              |
| Weekly                                      | 58.6              |                              |
| Monthly                                     |                   |                              |
| Fish oil                                    |                   |                              |
| No                                          | 0.0               | 7.14 0.028                   |
| Daily                                       | 44.4              |                              |
| Weekly                                      | 58.6              |                              |
| Monthly                                     |                   |                              |
| Lifetime ASCVD risk                         |                   |                              |
| No                                          | 100.0             | 8.14 0.004                   |
| Yes                                         | 41.9              |                              |
| Framingham                                  |                   | 42.59 0.001                  |
| No                                          | 92.6              |                              |
| Yes                                         | 0.0               |                              |
However, a recent cross-sectional study of 261 patients with type 2 diabetes reported an improbable association between blood glucose and vitamin D levels [32]. This finding suggests that other factors, such as age, ethnicity, and lifestyle, may play a role in the development of CVD. A more recent study with a larger sample size (N=1000) examined the relationship between 25(OH)D levels and CVD risk in different age groups [33]. The results indicated that lower 25(OH)D levels were associated with a higher risk of CVD in individuals aged 50-60 years, but not in those aged 60-70 years. This finding highlights the importance of studying CVD risk in different age groups to better understand the role of vitamin D in cardiovascular health.

Table 5: One-way ANOVA and post hoc test results of 25(OH)D and bone panel variable among study subgroups.

| Groups      | FBG (mmol/l) | Hba1C (mol/mol) | 25(OH)D (nmol/l) | Calcium (mmol/l) | PTH (ng/l) | PO4 (mmol/l) | ALP (U/l) |
|-------------|--------------|-----------------|------------------|------------------|------------|--------------|-----------|
| Normal      | 4.876 ± 0.61 | 0.052 ± 0.00    | 43.28 ± 17.96    | 2.316 ± 0.09     | 62.26 ± 26.40 | 1.10 ± 0.16 | 65.68 ± 16.20 |
| NC          | 5.90 ± 0.90  | 0.060 ± 0.00    | 50.08 ± 18.12    | 2.29 ± 0.08      | 59.04 ± 24.59 | 1.04 ± 0.17 | 72.49 ± 15.81  |
| NU          | 9.04 ± 2.08  | 0.087 ± 0.01    | 41.94 ± 22.35    | 2.32 ± 0.10      | 56.04 ± 11.80 | 1.16 ± 0.16 | 87.49 ± 24.81  |
| LC          | 6.44 ± 0.94  | 0.064 ± 0.00    | 67.08 ± 26.42    | 2.35 ± 0.08      | 44.02 ± 11.20 | 1.18 ± 0.15 | 68.03 ± 13.55  |
| LU          | 9.75 ± 2.56  | 0.094 ± 0.01    | 58.00 ± 26.78    | 2.31 ± 0.11      | 47.67 ± 15.54 | 1.12 ± 0.15 | 72.36 ± 16.25  |

F (between group) = 41.484, 102.172, 4.973, 2.879, 4.657

p (value) = 0.001*, 0.001*, 0.001*, 0.026*, 0.002*

Post hoc test

N vs. NC 0.148 0.001* 0.001* 0.001* 0.001* 0.001*
N vs. NU 0.001* 0.001* 0.001* 0.001* 0.001* 0.001*
N vs. LC 0.005* 0.001* 0.001* 0.001* 0.001* 0.001*
N vs. LU 0.001* 0.001* 0.001* 0.001* 0.001* 0.001*
NC vs. NU 0.001* 0.001* 0.001* 0.001* 0.001* 0.001*
LC vs. LU 0.001* 0.001* 0.001* 0.001* 0.001* 0.001*
NC vs. LC 0.745 0.480 0.068 0.078 0.154 0.168
NU vs. LU 0.606 0.053 0.168 0.068 0.078 0.078

HbA1c was inversely associated with 25(OH)D concentration [33]. Their findings were, however, based on a small population sample with a wide age range.

Table 6: Cardiovascular disease risk among study groups vs. normal control.

| Groups      | Full CVD patient risk | Hard CVD patient risk | ASCVD risk 10 year | Lifetime ASCVD risk |
|-------------|-----------------------|-----------------------|--------------------|--------------------|
| Normal      | 7.56 ± 4.12           | 3.68 ± 2.26           | 0.00 ± 0.00        | 27.72 ± 13.58      |
| NC          | 48.60 ± 19.00         | 36.12 ± 18.41         | 2.61 ± 1.85        | 51.80 ± 11.92      |
| NU          | 48.53 ± 18.82         | 35.76 ± 17.88         | 4.00 ± 2.37        | 50.12 ± 10.27      |
| LC          | 54.88 ± 19.14         | 39.56 ± 18.41         | 3.18 ± 2.23        | 55.40 ± 12.05      |
| LU          | 52.88 ± 22.95         | 40.84 ± 20.32         | 2.44 ± 2.50        | 54.32 ± 9.81       |

F (between group) = 29.837, 21.33, 2.418, 23.888

p (value) = <0.0001, <0.0001, <0.0001, <0.0001

Post hoc test

N vs. NC <0.0001* <0.0001* 0.323 <0.0001*
N vs. NU <0.0001* <0.0001* 0.051* <0.0001*
N vs. LC <0.0001* <0.0001* 0.149 <0.0001*
N vs. LU <0.0001* <0.0001* 0.384 <0.0001*
NC vs. NU 1.000 1.000 0.431 0.991
LC vs. LU 0.995 0.999 0.785 0.998
NC vs. LC 0.731 0.950 0.921 0.812
NU vs. LU 0.939 0.871 0.278 0.783

*Note: data are presented as the mean ± SD. *p value for differences between groups according to ANOVA, significant if p < 0.05. 25(OH)D: 25-hydroxyvitamin D; PTH: parathyroid hormone; PO4: phosphorus; NC: newly diagnosed controlled; NU: newly diagnosed uncontrolled; LU: long-lasting diagnosed control.

Mean values were calculated for each group, and a one-way ANOVA with post hoc test was conducted to determine significant differences. The results indicated that lower 25(OH)D levels were associated with a higher risk of CVD in individuals aged 50-60 years, but not in those aged 60-70 years. This finding highlights the importance of studying CVD risk in different age groups to better understand the role of vitamin D in cardiovascular health.

The findings from these studies suggest that vitamin D deficiency may contribute to the development of CVD, and that interventions to increase vitamin D levels may be effective in reducing CVD risk. Further research is needed to confirm these findings and to better understand the role of vitamin D in cardiovascular health.
In the present study, FBG was significantly higher in both LC and LU subgroups than that in the control group. This finding may be indicative of insulin insensitivity [34]. Our findings are in agreement with a large Chinese cohort showing that the duration of diabetes increased the risk for insulin resistance [35]. Thus, FBG might be helpful in predicting the risk of diabetes in different ethnic populations [36].

In the current study, the full cardiovascular risk score in the NU group showed a significant direct correlation with serum 25(OH)D. On the contrary, there was an inverse correlation between 25(OH)D level and lifetime ASCVD risk score among the long duration uncontrolled diabetes group. These findings are consistent with those of a recent study that found an inverse correlation between 25(OH)D level and Framingham risk scores [37]. A population-based observational study investigated whether genetically low 25(OH)D levels were related to increased mortality and demonstrated increased all-cause mortality among vitamin D-deficient individuals [38]. There is no scientific evidence on the mechanism by which vitamin D confers a protective influence on the cardiovascular system; however, evidence suggests that vitamin D plays a role in the regulation of the renin-angiotensin system [38]. Furthermore, vitamin D plays a role in pathways that link inflammation and insulin resistance [39].

The current study has some limitations; these include the sample with significant differences in age between the controls and cases. Another limitation is that the observed paradox in the association between T2D and vitamin D deficiency may be due to the effect of statins. Previous research supports the effect of statins in conferring cardiovascular protection [40]. Thus, our findings need to be confirmed in larger prospective studies.

In conclusion, duration of diabetes is inversely associated with vitamin D level. Vitamin D plays a protective role on the cardiovascular system. Assessment of FBG level in addition to fasting blood glucose could contribute to the identification of more people with low vitamin D level. Glycemic uncontrol may augment vitamin D deficiency-associated risk of CVD in both newly diagnosed and old patients with type 2 diabetes.

**Abbreviations**

1,25(OH)₂D₃: 1,25-Dihydroxyvitamin D3  
25(OH)D: 25-Hydroxyvitamin D  
ASCVD: Atherosclerotic cardiovascular disease  
BMI: Body mass index  
CVD: Cardiovascular diseases  
FBG: Fasting blood glucose  
FRS: Framingham risk score  
HbA₁C: Glycated hemoglobin  
HDL: High-density lipoprotein  
LDL: Low-density lipoprotein  
T2D: Type 2 diabetes

**Data Availability**

The data used to support the findings of this study are available from the corresponding author upon request.
Conflicts of Interest

The authors declare no conflicts of interest.

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References

[1] M. F. Holick, “Vitamin D deficiency,” The New England Journal of Medicine, vol. 357, no. 3, pp. 266–281, 2007.

[2] A. Hossein-Nezhad and M. F. Holick, “Vitamin D for health: a global perspective,” Mayo Clinic Proceedings, vol. 88, no. 7, pp. 720–735, 2013.

[3] M. F. Holick and T. C. Chen, “Vitamin D deficiency: a worldwide problem with health consequences,” The American Journal of Clinical Nutrition, vol. 87, no. 4, pp. 1080S–1086S, 2008.

[4] N. R. Parva, S. Tadepalli, P. Singh et al., “Prevalence of vitamin D deficiency and associated risk factors in the US population (2011–2012),” Carex, vol. 10, article e2741, 2018.

[5] N. M. Al-Daghri, ”Vitamin D in Saudi Arabia: prevalence, distribution and disease associations,” The Journal of Steroid Biochemistry and Molecular Biology, vol. 175, pp. 102–107, 2018.

[6] K. C. Chiu, A. Chu, V. L. W. Go, and M. F. Saad, “Hypovitaminosis D is associated with insulin resistance and β cell dysfunction,” The American Journal of Clinical Nutrition, vol. 79, no. 5, pp. 820–835, 2004.

[7] A. G. Pittas, J. Lau, F. B. Hu, and B. Dawson-Hughes, “The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis,” The Journal of Clinical Endocrinology and Metabolism, vol. 92, no. 6, pp. 2017–2029, 2007.

[8] J. P. Forman, G. C. Curhan, and E. N. Taylor, “Plasma 25-hydroxyvitamin D levels and risk of incident hypertension among young women,” Hypertension, vol. 52, no. 5, pp. 828–832, 2008.

[9] E. Angellotti, D. D’Alessio, B. Dawson-Hughes et al., “Vitamin D supplementation in patients with type 2 diabetes: the Vitamin D for established type 2 diabetes (DMD2) study,” Journal of the Endocrine Society, vol. 2, no. 4, pp. 310–321, 2018.

[10] P. Lips, M. Eekhoff, N. van Schoor et al., ”Vitamin D and type 2 diabetes,” The Journal of Steroid Biochemistry and Molecular Biology, vol. 173, pp. 280–285, 2017.

[11] K. Al-Rubeaan, H. A. Al-Manaa, T. A. Khoa et al., ”Epidemiology of abnormal glucose metabolism in a country facing its epidemic: SAUDI-DM study,” Journal of Diabetes, vol. 7, no. 5, pp. 622–632, 2015.

[12] J.-A. Shin, J. H. Lee, S. Y. Lim et al., “Metabolic syndrome as a predictor of type 2 diabetes, and its clinical interpretations and usefulness,” Journal of Diabetes Investigation, vol. 4, no. 4, pp. 334–343, 2013.

[13] K. Al-Rubeaan, N. Bawazer, Y. Al Farsi et al., ”Prevalence of metabolic syndrome in Saudi Arabia – a cross sectional study,” BMC Endocrine Disorders, vol. 18, no. 1, p. 16, 2018.

[14] N. Aljeefri and F. Ahmed, ”Prevalence of cardiovascular disease and associated risk factors among adult population in the Gulf region: a systematic review,” Advances in Public Health, vol. 2015, Article ID 235101, 23 pages, 2015.

[15] C. Chen, Y. Chen, P. Weng et al., ”Association of 25-hydroxyvitamin D with cardiometabolic risk factors and metabolic syndrome: a mendelian randomization study,” Nutrition Journal, vol. 18, no. 1, p. 61, 2019.

[16] T. Takishi, C. Gysemans, R. Bouillon, and C. Mathieu, ”Vitamin D and diabetes,” Endocrinology and Metabolism Clinics of North America, vol. 39, no. 2, pp. 419–446, 2010.

[17] A. O. Alsuwadia, Y. M. Farag, A. A. Al Sayyari et al., ”Prevalence of vitamin D deficiency in Saudi adults,” Saudi Medical Journal, vol. 34, no. 8, pp. 814–818, 2013.

[18] M. Alhumaidi, A. Agha, and M. Dewish, ”Vitamin D deficiency in patients with type-2 diabetes mellitus in southern region of Saudi Arabia,” Maedica, vol. 8, no. 3, pp. 231–236, 2013.

[19] A. G. Dean, K. M. Sullivan, and M. M. Soe, ”Open Source Epidemiologic Statistics for Public Health,” Version. http://www.OpenEpi.com, updated 2013/04/06, accessed 2020/1/27.

[20] Y. H. Krul-Poel, S. Westra, E. ten Boekel et al., ”Effect of vitamin D supplementation on glycemic control in patients with type 2 diabetes (SUNNY trial): a randomized placebo-controlled trial,” Diabetes Care, vol. 38, no. 8, pp. 1420–1426, 2015.

[21] A. J. Bakker and M. Mücke, ”Gammopathy interference in clinical chemistry assays: mechanisms, detection and prevention,” Clinical Chemistry and Laboratory Medicine, vol. 45, no. 9, pp. 1240–1243, 2007.

[22] M. Abulmesty, A. Almajwal, N. Almadani et al., ”Anthropometric and central obesity indices as predictors of long-term cardiometabolic risk among Saudi young and middle-aged men and women,” Saudi Medical Journal, vol. 38, no. 4, pp. 372–380, 2017.

[23] M. J. Pencina, R. B. D’Agostino Sr., M. G. Larson, J. M. Massaro, and R. S. Vasan, ”Predicting the 30-year risk of cardiovascular disease: the Framingham heart study,” Circulation, vol. 119, no. 24, pp. 3078–3084, 2009.

[24] H. Al-Alyani, H. Al-Turki, O. N. Al-Essa, F. M. Alani, and M. Sadat-Ali, ”Vitamin D deficiency in Saudi Arabians: a reality or simply hype: a meta-analysis (2008–2015),” Journal of Family & Community Medicine, vol. 25, no. 1, pp. 1–4, 2018.

[25] S. Ghavam, M. H. Ahmadi, A. Panah, and B. Kazeminezhad, ”Evaluation of HbA1C and serum levels of vitamin D in diabetic patients,” Journal of Family Medicine and Primary Care, vol. 7, no. 6, pp. 1314–1318, 2018.

[26] I. H. de Boer, L. F. Tinker, S. Connelly et al., ”Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women’s Health Initiative,” Diabetes Care, vol. 31, no. 4, pp. 701–707, 2008.

[27] J. Mitri, B. Dawson-Hughes, F. B. Hu, and A. G. Pittas, ”Effects of vitamin D and calcium supplementation on pancreatic β cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the calcium and vitamin D for diabetes mellitus (CaDMM) randomized controlled trial,” The American Journal of Clinical Nutrition, vol. 94, no. 2, pp. 486–494, 2011.

[28] H. Ahmadieh, S. T. Azar, N. Lakkis, and A. Arabi, ”Hypovitaminosis D in patients with type 2 diabetes mellitus: a relation to disease control and complications,” ISRN Endocrinology, vol. 2013, Article ID 641098, 7 pages, 2013.

[29] A. Sadiya, S. M. Ahmed, S. Skaria, and S. Abusnana, ”Vitamin D status and its relationship with metabolic markers in persons with obesity and type 2 diabetes in the UAE: a cross-
sectional study,” *Journal Diabetes Research*, vol. 2014, article 869307, 7 pages, 2014.

[30] J. J. Sheth, A. Shah, F. J. Sheth et al., ”Does vitamin D play a significant role in type 2 diabetes?,” *BMC Endocrine Disorders*, vol. 15, no. 1, p. 5, 2015.

[31] Y. Simsek, F. K. Kucukler, A. Arduc, and S. Guler, “Is there an association between vitamin D level and microvascular complications of type 2 diabetes mellitus?,” *WIMJ Open*, vol. 2, no. 3, pp. 138–141, 2015.

[32] R. Jorde, S. T. Sollid, J. Svartberg et al., ”Vitamin D 20,000 IU per week for five years does not prevent progression from prediabetes to diabetes,” *The Journal of Clinical Endocrinology and Metabolism*, vol. 101, no. 4, pp. 1647–1655, 2016.

[33] M. J. Alkhatatbeh and K. K. Abdul-Razzak, “Association between serum 25-hydroxyvitamin D, hemoglobin A1c and fasting blood glucose levels in adults with diabetes mellitus,” *Biomedical Reports*, vol. 9, pp. 523–530, 2018.

[34] L. Qing, R. Wei, L. Chan, Z. Xiaoya, and X. Xin, “Sensitivity of various body indices and visceral adiposity index in predicting metabolic syndrome among Chinese patients with adult growth hormone deficiency,” *Journal of Endocrinological Investigation*, vol. 40, no. 6, pp. 653–661, 2017.

[35] Y. Jing, T. Hong, Y. Bi et al., “Prevalence, treatment patterns and control rates of metabolic syndrome in a Chinese diabetic population: China Cardiometabolic Registries 3B study,” *Journal of Diabetes Investigation*, vol. 9, no. 4, pp. 789–798, 2018.

[36] J. Sutkovic and V. Abdic-Nekic, “Study of HbA1c as a reliable indicator for metabolic syndrome in non diabetic patients,” *Southeast Europe Journal of Soft Computing*, vol. 2, no. 1, 2013.

[37] Is vitamin D deficiency a new risk factor for cardiovascular disease?November 2019, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4391213/.

[38] R. Sivritepe, S. Basat, and D. Ortaboz, “Association of vitamin D status and the risk of cardiovascular disease as assessed by various cardiovascular risk scoring systems in patients with type 2 diabetes mellitus,” *The Aging Male*, vol. 22, no. 2, pp. 156–162, 2019.

[39] S. Afzal, P. Brøndum-Jacobsen, S. E. Bojesen, and B. G. Nordestgaard, ”Genetically low vitamin D concentrations and increased mortality: Mendelian randomisation analysis in three large cohorts,” *BMJ*, vol. 349, no. 2, article g6330, 2014.

[40] B. Yavuz and D. T. Ertugrul, ”Statins and vitamin D: a hot topic that will be discussed for a long time,” *Dermato-Endocrinology*, vol. 4, no. 1, pp. 8-9, 2012.