Association between serum 25-hydroxyvitamin D and glycated hemoglobin levels in type 2 diabetes patients with chronic kidney disease

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ABSTRACT

Aims/Introduction: Vitamin D is suggested to influence glucose homeostasis. An inverse relationship between serum 25-hydroxyvitamin D (25(OH)D) and glycemic control in non-chronic kidney disease (CKD) patients with type 2 diabetes was reported. We aimed to examine this association among type 2 diabetes patients with CKD.

Materials and Methods: A total of 100 type 2 diabetes participants with stage 3–4 CKD were recruited. Blood for glycated hemoglobin (HbA1c), serum 25(OH)D, renal and lipid profiles were drawn at enrollment. Correlation and regression analyses were carried out to assess the relationship of serum 25(OH)D, HbA1c and other metabolic traits.

Results: A total of 30, 42, and 28% of participants were in CKD stage 3a, 3b and 4, respectively. The proportions of participants based on ethnicity were 51% Malay, 24% Chinese and 25% Indian. The mean (±SD) age and body mass index were 60.5 ± 9.0 years and 28.3 ± 5.9 kg/m², whereas mean HbA1c and serum 25(OH)D were 7.9 ± 1.6% and 37.1 ± 22.2 nmol/L. HbA1c was negatively correlated with serum 25(OH)D (r = −0.314, P = 0.002), but positively correlated with body mass index (r = 0.272, P = 0.006) and serum low-density lipoprotein cholesterol (P = 0.006). There was a significant negative correlation between serum 25(OH)D and total daily dose of insulin prescribed (r = −0.257, P = 0.042). Regression analyses showed that every 10-nmol/L decline in serum 25(OH)D was associated with a 0.2% increase in HbA1c.

Conclusions: Lower serum 25(OH)D was associated with poorer glycemic control and higher insulin use among multi-ethnic Asians with type 2 diabetes and stage 3–4 CKD.

INTRODUCTION

It has been recognized that vitamin D plays a pivotal role in bone and mineral metabolism, in which vitamin D inadequacy is a known risk factor for osteoporosis. As vitamin D is widely distributed in many cell types (e.g., pancreatic β-cells and adipose tissues), the extraskeletal role of vitamin D has gained interest, especially in glucose homeostasis, cardiovascular diseases, infection, malignancy and autoimmune disorders.

Type 2 diabetes is characterized by pancreatic β-cell insufficiency and increased insulin resistance. Low-grade inflammatory state mediated through intracellular activation of c-Jun N-terminal kinase and nuclear factor-κB pathways is closely related to worsening hyperglycemia. Vitamin D therapy can reduce systemic inflammation and improve glucose tolerance by inhibiting the release of pro-inflammatory cytokine tumor necrosis factor alpha, and regulates the activity of nuclear factor-κB. Likewise, it might affect β-cell activity through direct binding of intracellular vitamin D receptor and indirect regulation of extracellular calcium metabolism, enhancing insulin sensitivity and improving insulin secretion.

Several cross-sectional studies observed an inverse relationship between serum 25-hydroxyvitamin D (25(OH)D) and glycated hemoglobin (HbA1c) levels in type 2 diabetes patients without chronic kidney disease (CKD). Certain complications, such as rickets and osteomalacia, tend to occur only in the presence of severe vitamin D deficiency, and glycemic complication might be the same. Notably, a recent randomized controlled trial by Krul-Poel et al. reported that vitamin D supplementation only improved glycemic control among well-controlled type 2 diabetes participants with serum 25(OH)
D < 30 nmol/L, rather than those who were less deficient. Patients with CKD have an increased prevalence (up to 80%) of severe vitamin D deficiency and impaired glucose tolerance, compared with non-CKD population. To our knowledge, there were just two studies on the association between serum 25(OH)D and HbA1c levels among type 2 diabetes patients with CKD, which reported conflicting results (Table 3). We aimed to examine the relationship between serum 25(OH)D and HbA1c levels among multi-ethnic type 2 diabetes adults with stage 3–4 CKD.

METHODS

Study design and participant selection
A cross-sectional study was carried out between September 2015 and July 2016 at the University of Malaya Medical Center, an academic-affiliated medical institution with 1,300 beds, serving a population of 1.8 million in Kuala Lumpur, Malaysia. Eligible participants were recruited consecutively from the specialized diabetes, renal and general outpatient clinics. The inclusion criteria were participants with a known diagnosis of type 2 diabetes for at least 6 months and coexistent stage 3–4 CKD (estimated glomerular filtration rate [eGFR] by Chronic Kidney Disease Epidemiology Collaboration formula 15–59 mL/min/1.73 m²), age ≥18 years, and able and willing to provide written informed consent. Participants with end-stage renal disease, active infections, autoimmune diseases, malignancies and receiving immunosuppressive therapy or taking vitamin D supplements were excluded. The estimated sample size of 100 participants was able to detect a significant association between HbA1c and serum 25(OH)D levels, with a statistical power of 93 and 5% significance, based on a previous study. The study protocol complied with the Declaration of Helsinki. This study was approved by the University of Malaya Medical Center Medical Ethics Committee (MECID 201412-878), and was registered with ClinicalTrials.gov (NCT 02906319). Written informed consent was obtained from all participants before study enrollment.

Study procedures
Baseline demographic data and laboratory results were obtained from face-to-face interviews and retrieved from electronic medical records. Repeat blood analyses were carried out for participants with laboratory tests done >2 weeks before study enrollment. All blood samples were taken at the accredited chemical pathology laboratory at the University of Malaya Medical Center. Participants were categorized into three stages of CKD, according to Kidney Disease Outcome Quality Initiative criteria; that is, CKD stage 3a (eGFR 45–59 mL/min/1.73 m²), stage 3b (eGFR 30–44 mL/min/1.73 m²) and stage 4 (eGFR 15–29 mL/min/1.73 m²), irrespective of the status of proteinuria.

Laboratory assays
Serum 25(OH)D level was measured using direct chemiluminescent immunoassay (ADVIA Centaur XP; Siemens Healthcare Diagnostics, Tarrytown, New York, USA). The detection limit was <10.0 nmol/L, with intra- and interassay coefficients of variation of 4.2 and 11.9%, respectively. This assay showed comparable performance with the liquid-chromatography tandem mass spectrometry method. A mean value of 5.0 nmol/L was taken for results reported as <10.0 nmol/L. Serum HbA1c level was analyzed by ion-exchange high-performance liquid chromatography technique (National Glycohemoglobin Standardization Program/Diabetes Control and Complications Trial-aligned; Bio-Rad Variant™ II Turbo; Bio-Rad, Hercules, California, USA). The intra- and interassay correlation of variance were <2.0 and <2.3%, respectively. Renal profiles were measured using colorimetric methods (ADVIA 2400 Chemistry System; Siemens Healthcare Diagnostics). Complete blood counts were analyzed using fluorescent flow cytometry (XN-10; Sysmex, Kobe, Japan).

Statistical analysis
All statistical analyses were carried out using Spss version 23.0 for Windows (IBM Corp., Armonk, New York, USA). Participants’ baseline characteristic data were expressed as mean ± SD or number (%). Logarithmic or square root transformations were carried out to ensure normality or linearity assumptions were met. Correlation was determined using Pearson’s correlation coefficients if both variables were normally distributed, or Spearman’s rank-order correlation for skewed variables. Multiple linear regression analysis was used to determine the predictors of HbA1c levels. The relationship between serum 25(OH)D and use of insulin therapy was assessed by logistic regression analysis. All P-values of <0.05 were considered to denote statistical significance.

RESULTS

Baseline demographic data
A total of 100 participants were enrolled; 59% were women. The proportions of participants based on ethnicity were 51% Malay, 24% Chinese and 25% Indian. The mean age was 60.5 ± 9.0 years. Suboptimal glycemic control was observed among these high-risk participants, with a mean HbA1c level of 7.9 ± 1.6%. In addition, the current study cohort was in the obesity 1 category, with a mean body mass index (BMI) of 28.3 ± 5.9 kg/m². Based on Kidney Disease Outcome Quality Initiative criteria, 30% of participants were in stage 3a, 42% in stage 3b and 28% in stage 4 of CKD. The prevalence of vitamin D deficiency (<50 nmol/L) was as high as 74% in the present CKD cohort, with a mean serum 25(OH)D level of 37.1 ± 22.2 nmol/L. The mean serum 25(OH)D levels stratified by ethnicity were Chinese 52.2 ± 4.0 nmol/L, Malay 34.9 ± 3.1 nmol/L and Indian 29.2 ± 3.2 nmol/L (Chinese vs Malay, P = 0.002; Chinese vs Indian, P < 0.001; Malay vs Indian, P = 0.478). Most participants had multiple medical comorbidities, such as concomitant hypertension (88%) and dyslipidemia (82%). The majority of participants were receiving statin therapy (90%) and at least one antihypertensive agent.
D was associated with a 0.2% increase in HbA1c level (Table 2).

Correlation analyses
Figure 1 shows the correlation analyses of HbA1c level with patients’ characteristics and other metabolic traits. In the current CKD cohort, a significant negative correlation between serum 25(OH)D and HbA1c was identified ($r_s = -0.314, P = 0.002$), though there was no significant correlation found in each ethnicity subgroup. BMI ($r_s = 0.272, P = 0.006$) and logarithmic-transformed low-density lipoprotein (LDL) cholesterol ($r_s = 0.274, P = 0.006$) were positively correlated with HbA1c. These results signified CKD participants with poor glycemic control had reduced serum 25(OH)D, and elevated BMI and LDL cholesterol levels. There were no significant correlations between HbA1c level with age, eGFR, serum hemoglobin, logarithmic-transformed high-density lipoprotein cholesterol and triglyceride levels.

Among the three factors that had significant correlations with HbA1c level, a negative correlation between serum 25(OH)D and logarithmic-transformed LDL cholesterol was observed ($r_s = -0.248, P = 0.013$). There was a non-significant trend of lower serum 25(OH)D with higher BMI levels ($r_s = -0.114, P = 0.261$).

Regression analyses on predictors of HbA1c
Table 2 shows the predictors of HbA1c in different models of adjustments. Among type 2 diabetes participants with CKD stage 3–4, a significant inverse relationship between HbA1c and serum 25(OH)D levels with or without adjustments for age, sex, eGFR, serum hemoglobin, smoking status, antihypertensive, oral antidiabetic agents, statin therapy, logarithmic-transformed high-density lipoprotein cholesterol and triglyceride levels was shown. This significance diminished after additional adjustment for insulin therapy. Every 10-nmol/L decline in serum 25(OH)D was associated with a 0.2% increase in HbA1c level (Table 2). With regard to the relationship among several metabolic traits, BMI and LDL cholesterol were found to have significant positive associations with HbA1c level with or without adjustments for confounders in this high-risk cohort.

Logistic regression analysis showed that reduced serum 25(OH)D level predicted increased use of insulin therapy (odds ratio 1.03, 95% confidence interval 1.01–1.05, $P = 0.004$). Among insulin-treated type 2 diabetes participants with CKD ($n = 65$), the mean total daily dose of insulin was $61.5 \pm 41.4$ units, which was negatively correlated with serum 25(OH)D ($r_s = -0.257, P = 0.042$; Figure 2) and inversely associated with square root transformed serum 25(OH)D ($P = 0.021$).

**DISCUSSION**

The present study showed an inverse relationship between serum 25(OH)D and HbA1c levels among multi-ethnic Asians with type 2 diabetes and stage 3–4 CKD. Despite interethnic differences in serum 25(OH)D levels that were related to skin

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**Table 1 | Baseline characteristics of study participants**

| Participants ($n = 100$) | Mean ± SD |
|--------------------------|-----------|
| Age (years)              | 60.5 ± 9.0|
| Male                     | 41 |
| Ethnicity (Malay/Chinese/Indian) | 51/24/25 |
| BMI (kg/m$^2$)           | 28.3 ± 5.9 |
| Smokers                  | 18 |
| Hypertension             | 88 |
| Dyslipidemia             |          |
| Total cholesterol (mmol/L) | 4.5 ± 1.4 |
| Triglyceride (mmol/L)    | 2.0 ± 1.1 |
| HDL cholesterol (mmol/L) | 1.2 ± 0.3 |
| LDL cholesterol (mmol/L) | 2.5 ± 1.2 |
| CKD (stage 3a/3b/4)      | 30/42/28 |
| Urea (mmol/L)            | 9.8 ± 3.2 |
| Creatinine (mmol/L)      | 160.8 ± 49.2 |
| eGFR (mL/min/1.73 m$^2$) | 36.9 ± 11.7 |
| Hemoglobin (g/dL)        | 11.8 ± 1.7 |
| HbA1c, NGSP (%)          | 7.9 ± 1.6 |
| 25(OH)D (nmol/L)         | 37.1 ± 22.2 |
| Malay                    | 34.9 ± 3.1 |
| Chinese                  | 52.2 ± 4.0 |
| Indian                   | 292.2 ± 32.2 |
| Vitamin D status         |          |
| Sufficiency (≥75 nmol/L) | 8 |
| Insufficiency (50–74 nmol/L) | 18 |
| Deficiency (26–49 nmol/L) | 43 |
| Severe deficiency (≤25 nmol/L) | 31 |
| On statin therapy        |          |
| High intensity           | 13 |
| Moderate intensity       | 70 |
| Low intensity            | 7 |
| On antihypertensive agent|          |
| No. antihypertensive agent| 95 |
| One                      | 18 |
| Two                      | 33 |
| Three                    | 32 |
| Four                     | 7 |
| Five                     | 5 |
| On oral antidiabetic medications | 69 |
| Type of oral antidiabetic medications | |
| Biguanide                 | 39 |
| Sulfonylurea              | 37 |
| DPP-4i                    | 16 |
| On injectable GLP-1 RA    | 1 |
| On insulin therapy        |          |
| Insulin regime            | 65 |
| Basal                     | 16 |
| Basal–bolus               | 41 |
| Premix                    | 8 |

25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CKD, chronic kidney disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NGSP, National Glycohemoglobin Standardization Program.
color and dressing habits, the association between serum 25(OH)D and HbA1c was not significant when stratified by ethnicity in this cohort. We posit that a larger sample size is required to evaluate the ethnic-specific association of these two parameters. In addition, serum 25(OH)D level was negatively correlated with increased insulin use. There are several explanations for this, and the most plausible would be related to long-term poorer glycemic control that resulted in CKD complication, requiring treatment intensification, and thus, poorer health status. The literature supported a physiological role of vitamin D in pancreatic β-cell, as evidenced by the local expression of the vitamin D receptor with enhancement in insulin sensitivity and insulin secretion6,7. In experimental models, pancreatic β-cell secretory function and insulin sensitivity improved after calcium and vitamin D replacement, mediated through alteration in intracellular calcium level, direct stimulatory effects on islet-cell growth and vitamin D receptor genetic polymorphisms20–23. A large-scale study among Inuit in Greenland showed worse β-cell function with a decline in serum 25(OH)D level24.

Among type 2 diabetes patients with normal renal function, the relationship between serum 25(OH)D and glycemic control yielded inconsistent results. In a prospective study of >5,000 healthy Danish individuals aged 30–65 years, hypovitaminosis D was associated with worsened insulin resistance and subsequent hyperglycemia25. In addition, every 25-nmol/L elevation in serum 25(OH)D resulted in a 17% reduced risk of incident type 2 diabetes in a prospective cohort of non-diabetes and obesity26. In the large-scale AusDiab study, an inverse relationship between serum 25(OH)D with metabolic parameters; for example, fasting glucose, insulin resistance, triglyceride level
and waist circumference, was reported, observing an increased 5-year risk of new-onset metabolic syndrome among healthy adults27. Based on a meta-analysis of 11 prospective studies, individuals with higher serum 25(OH) levels (>80 vs <48.8 nmol/L) were at 41% diminished risk of developing type 2 diabetes28. Conversely, several studies reported discordant results, whereby hypovitaminosis D was not an independent predictor of incident or worsening type 2 diabetes in healthy adults, as its effect was predominantly modulated by BMI29,30. Recently, a few studies that applied Mendelian randomization analyses to establish the causal link between serum 25(OH)D and type 2 diabetes susceptibility had shown inconsistent findings31-33. To our knowledge, there is no similar Mendelian randomization analysis on this interesting relationship between serum 25(OH)D and HbA1c levels among Asians with type 2 diabetes and concomitant CKD.

Although the prevalence of vitamin D deficiency increases in advanced CKD, studies examining this relationship were limited and discordant, perhaps because of differences in participants’ characteristics, vitamin D status and recruitment difficulty due to ill health34-38. In Asia, nearly 60% of Koreans with stage 3–5 CKD and coexistent vitamin D deficiency (<75 nmol/L) had type 2 diabetes, whereas it was reduced by half among those with adequate vitamin D levels39. The relationship was true vice versa, whereby the presence of diabetes was associated with an approximately eightfold risk of developing hypovitaminosis D (<37.5 nmol/L) among Japanese with stage 3–5 CKD40. Despite the possible link with incident diabetes, a dearth of information is available on the association between serum 25(OH)D and glycemic control among individuals with established diabetes and CKD. A retrospective analysis among a French type 2 diabetes cohort with stage 1–5 CKD identified a negative linear relationship between serum 25(OH)D and HbA1c levels, even after multivariate adjustments15. Conversely, it was not significant in another prospective type 1 and type 2 diabetes cohort with stage 1–4 CKD, which was restricted by a small sample size16. The comparison of the present study with two other available studies, focusing on type 2 diabetes adults with CKD, is summarized in Table 3, which could have further expounded on the discrepancies of the results.

Trials on the effects of cholecalciferol supplementation on glucose homeostasis in type 2 diabetes with CKD patients were underexplored. In the Nurses’ Health Study, involving non-diabetic middle-aged women, the relative risk of type 2 diabetes was lowered by 17–33% with at least 400 IU cholecalciferol and 1,200 mg calcium intake after 20 years of follow up40. This was consistent with a post-hoc analysis that observed favorable impacts on glycemic traits after 3-year therapy with 700 IU cholecalciferol and 500 mg calcium citrate among elderly Caucasians with impaired fasting glucose41. In healthy middle-aged Japanese, increased vitamin D and calcium intake was protective against type 2 diabetes, with a 40% relative risk reduction after 5 years42. Conversely, in the 7-year follow up of the Women’s Health Initiative study, 400 IU cholecalciferol and 1,000 mg elemental calcium did not diminish the incident type 2 diabetes risk among post-menopausal women43. Among well-controlled type 2 diabetes patients, monthly 50,000 IU cholecalciferol for 6 months failed to show a significant change in glycemic control, insulin sensitivity and β-cell function; although its exploratory analysis revealed a significant HbA1c reduction by 3.5 mmol/mol in type 2 diabetes patients with more severe vitamin D deficiency (serum 25(OH)D < 30 nmol/L)44. Considering a higher cholecalciferol dose might improve glucose metabolism, a large-scale randomized trial examining the effect of 4,000 IU cholecalciferol on risk of type 2 diabetes development among prediabetes adults is ongoing44. The discrepancy between these intervention studies could be attributed to differences in participants’ characteristics, the severity of underlying metabolic disorders, vitamin D status and supplementation regime. The importance of identification of the susceptible group, who will most likely benefit from vitamin D repletion therapy, is highlighted in a recent meta-analysis involving 1,797
patients with type 2 diabetes, which reported a favorable improvement in fasting glucose post-vitamin D supplementation only among those with poorly controlled glycemia (HbA1c ≥ 8%)45. Of note, these trials were not carried out in CKD cohorts, who were phenotypically distinct from the non-CKD population and therefore required a different treatment approach. Questions were raised on the variations of dosage and treatment duration of cholecalciferol replacement in CKD patients with concomitant vitamin D deficiency, compared with osteoporosis or CKD-free type 2 diabetes cohorts. It was interesting to highlight the presence of heavier baseline proteinuria and a reduction in serum 25(OH)D level as sequela of vitamin D binding protein loss were two independent risk factors of poorer response to vitamin D2/D3 supplementation37,38. Ethnic disparities in the treatment response towards vitamin D replacement among CKD patients must be considered. Hispanic people with CKD and coexistent vitamin D deficiency were more resistant towards ergocalciferol supplementation than age- and CKD stage-matched Caucasians38. Although it was of retrospective design, additional information was offered on possible influences of interethnic differences and environmental factors in deciding the optimal vitamin D repletion regime among the CKD cohort. Short-term (<12 weeks) vitamin D repletion was significantly associated with a decrease in fasting glucose level in a meta-analysis of 17 trials involving end-stage renal disease patients46. However, those trials were of small sample sizes, heterogenous population and mainly using an activated vitamin D formulation.

The present study had several strengths. This study involved very high-risk participants of suboptimal type 2 diabetes control with CKD in the presence of more severe vitamin D status, compared with previous research. Multi-ethnic Asians with type
2 diabetes were recruited, which offered different perspectives on this relationship, as previous studies involved Caucasian populations only. In addition, we considered additional factors that could exert substantial effects on either serum 25(OH)D or HbA1c levels, for instance BMI, serum hemoglobin, lipid profiles, statin therapy and antidiabetic medications. However, a few limitations were recognized. The present study had a cross-sectional design; therefore, causality could not be ascertained. Limited generalizability was also anticipated, as this was a single-center study. Finally, the current sample size was underpowered to analyze interethnic differences in this relationship.

In conclusion, the present study reported a significant inverse relationship between serum 25(OH)D and HbA1c levels in a multi-ethnic type 2 diabetes cohort with suboptimal glycemic control and concomitant stage 3–4 CKD. This highlights the need for vitamin D screening among high-risk patients, necessitating early and timely vitamin D repletion therapy to achieve better glycemic control, and prevent development or worsening of type 2 diabetes-related complications. Hence, the current research calls for an urgent need for large-scale longitudinal randomized controlled trials to elucidate not only the causal link between vitamin D deficiency and worsening glycemia, but also the ethnic-specific effects of vitamin D2/D3 repletion therapy on the susceptibility to type 2 diabetes and/or CKD.

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DISCLOSURE
The authors declare no conflict of interest.

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