Original Article

DOI: 10.7860/JCDR/2026/79844.22553

Biochemistry Section

# Correlation of 25-hydroxy Vitamin D Deficiency with Advanced Glycation End Products and Their Receptors in Type 2 Diabetic Patients with Coronary Artery Disease: A Cross-sectional Study

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## ABSTRACT

**Introduction:** Vitamin D Deficiency (VDD) has emerged as a possible risk factor for Insulin resistance and Type 2 Diabetes Mellitus (T2DM), which in turn is an established risk factor for Coronary Artery Disease (CAD). Advanced glycation End Products (AGEs) measurements may be considered promising biomarkers of late diabetic complications.

**Aim:** To assess the correlation of 25-OH vitamin D levels with advanced glycation end products and its receptors in T2DM patients with CAD.

**Materials and Methods:** The present cross-sectional study included 130 T2DM patients with CAD, aged between 35-65 years, admitted in Yenepoya Medical College Hospital, Mangalore, Karnataka, India, during the time period of July 2019 to August 2022. Total 25-OH vitamin D, fasting insulin (Chemiluminescence Immunoassay method), and fasting plasma glucose (Glucose oxidase-peroxidase method) and Glycated Haemoglobin (HbA1c) were estimated. Insulin resistance was calculated using the HOMA-IR method. AGE and soluble receptors for AGE were estimated using an ELISA kit. The correlation of 25-OH vitamin D with with advanced glycation end products and its receptors was done by Spearmann correlation. The comparison of parameters among the groups based on 25-OH vitamin D was done by Analysis of Variance (ANOVA) and p-value <0.05 was considered to be statistically significant.

**Results:** The mean age of the study population was 54.06 ± 7.31 years with a gender distribution of 71.5% (93/130) males and 28.5% (37/130) females. The mean value of 25-OH vitamin D among the study population was 22.92±8.67. Among 130 study participants, 103 (80%) of study participants had insufficient or deficient vitamin D. A significant negative correlation was seen with HbA1c (r=-0.287; p<0.001). The HbA1C value was significantly higher in vitamin D deficient group compared to insufficient and sufficient group with a p value of <0.001.

**Conclusion:** There was a significant negative correlation between the 25-OH vitamin D level and HbA1c. The HbA1c was significantly higher in Vitamin D deficient group compared to insufficient and sufficient group (p value <0.001). This indicates that vitamin D may play an indirect role in the pathophysiology of CAD, which emphasizes the significance of adequate vitamin D in a diabetic population.

**Keywords:** Cardiovascular disease, Diabetes mellitus, Glycated Haemoglobin, 25-OH Vitamin D, Insulin resistance

## INTRODUCTION

Vitamin D Deficiency (VDD) has emerged as a possible risk factor for T2DM, and supplementation of vitamin D has been proposed as a potential intervention to lower diabetes risk and its complications [1].

Long term hyperglycaemia leads to non enzymatic glycation of proteins, lipids and nucleic acids under oxidative and carbonyl stress, and is responsible for chronic vascular complications of diabetes [2]. It provides a biomarker in widespread clinical use: glycated haemoglobin (HbA1c). $HbA_{1c}$ is an early-stage glycation adduct of haemoglobin with glucose. In later stage reactions, the product degrades to stable endstage adducts called advanced glycation endproducts (AGEs) [2]. Soluble Receptor of Advanced Glycation End Product (sRAGE) is a soluble receptor that competes with full-length Receptors of Advanced Glycation end Products (RAGE) for ligand binding while acting as a pawn for AGE. Individually, AGE or sRAGE cannot be regarded as a universal biomarker. Regardless of low or high serum sRAGE, all patient groups had higher serum levels of AGE and a higher ratio of AGE/sRAGE than control subjects [3].

Given the increasing burden of T2DM-related cardiovascular complications leading to a 2-fold to 4-fold increased risk of CVD [4]. The particular concerns for Indians are the early age of onset, rapid progression and high mortality rate.[4] Hence, it is imperative to explore novel biomarkers and therapeutic targets for disease prevention.

As per the study by Kheirouri et al., 2020, vitamin D treatment may possibly be beneficial to reduce AGE levels and to augment sRAGE levels, particularly in vitamin D-deficient situations [5]. Establishing a link between vitamin D and glycation biomarkers could offer a potential avenue for early risk stratification and personalized interventions. However, Indian data about potential relationships between 25-OH vitamin D deficiency and AGE accumulation are scarce.

Hence, the present study was conducted to assess the correlation of vitamin D levels with advanced glycation endproducts and its receptors in T2DM patients with CAD, contributing to a better understanding of the interplay between vitamin D status and glycation.

## MATERIALS AND METHODS

The present cross-sectional study was conducted in the Cardiology Department of Yenepoya Medical College Hospital, Mangalore, Karnataka, India, during the time period of July 2019 to August 2022,

after obtaining the informed consent. The study was approved by Institutional Ethics Committee [Protocol No.YEC-1/2019/106]. The study adhered to the ethical guidelines established by the Helsinki Declaration 2013 and its subsequent modifications.

**Inclusion criteria:** The T2DM patients with recently diagnosed CAD by angiography, aged between 35-65 years of both gender and willing to participate in the study were included.

**Exclusion criteria:** The patients with chronic hepatic and renal disease, history of vitamin D supplementation and history of drug intake that can affect Vitamin D metabolism were excluded from the study.

**Sample size calculation:** The sample size of 130 was calculated based on the following formula [6]:

$$N = \frac{Z_{1-\alpha/2} + Z_{1-\beta^2} + 3}{\frac{1}{2} Log_{e}\frac{1+r}{1-r}} = 130$$

$Z_{1-\alpha/2}$=1.96, $\alpha$=0.05, 1-$\beta$=20%, $Z_{1-\beta}$=0.84, r=0.246

## Study Procedure

**Data collection:** A fasting blood sample (5 mL) in plain tubes and 2.0 mL in grey vacutainer (fluoride) were collected from the subjects. The plain sample estimated serum 25- hydroxyvitamin D, fasting insulin, AGE and sRAGE. Serum was separated after centrifuging at 3000 rpm for 5 minutes. A fluoride sample was used for the analysis of fasting glucose. The method and the normal range of parameters are expressed in [Table/Fig-1] [7-9].

| Parameter | Method | Normal range |
|---|---|---|
| Total 25-OH vitamin D | CLIA | ≥30 ng/mL |
| Insulin | CLIA | 2.30-26.0 µIU/mL |
| Fasting plasma glucose | GOD-POD | 70-100 mg/dL |
| #AGE | ELISA | 300 ng/mL to 4800 ng/mL [7] |
| #sRAGE | ELISA | 150 pg/mL to 2400 pg/mL [8] |
| $HbA_{1c}$ | HPLC | 4% to 5.6% [9] |

**[Table/Fig-1]:** Method and normal range of the parameters estimated [7-9].
CLIA: Chemiluminescence Immunoassay; GOD-POD: Glucose oxidase-peroxidase; ELISA: Enzyme linked immunosorbent assay; HPLC: High-performance liquid chromatography; #The range mentioned is the measuring range

**Laboratory investigation:** Insulin resistance was calculated using HOMA-IR formula [10]:

HOMA-IR = (FPI × FPG)/405

FPI is the fasting plasma insulin concentration (µIU/L); FPG is fasting plasma glucose (mg/dL).

The participants were grouped based on their 25 (OH) vit D level as group I (sufficient: ≥ 30 ng/mL), group II (insufficient: 20-29 ng/mL), and group III (deficient: < 20 ng/mL) [11].

## STATISTICAL ANALYSIS

The statistical package SPSS. vers. 23 was used to analyse the data. The Shapiro-Wilks test was used to check the normality distribution. The continuous variables are expressed as mean±standard deviation. The categorical variables are expressed as frequency (percentage). The Spearmann correlation test was used for correlation analysis. ANOVA was used to compare between groups. Statistical significance: p<0.05 was considered significant.

## RESULTS

The mean age of the study population was 54.06±7.31 years with a gender distribution of 71.5% (93/130) males and 28.5% (37/130) females. The mean value of 25-OH vitamin D among the study population (N=130), was 22.92±8.67. The categorization of the study participants based on their serum 25-OH vitamin D levels is as follows: sufficient 27(19%) < insufficient 46 (35%) < deficient 57 (45%) [Table/Fig-2].

| Groups | Frequency n (%) | 25 (OH) Vitamin D (ng/mL) (Mean±SD) |
|---|---|---|
| Group I | 27 (20.7%) | 36±4.7 |
| Group II | 46 (35.5%) | 25.6±2.7 |
| Group III | 57 (43.8%) | 15.2±4.0 |
| Total | 130 (100%) | 22.92±8.67 |

**[Table/Fig-2]:** Categorisation of the study population based on their serum 25-OH vitamin D level (N=130).
Study participants were categorized based on their serum 25-OH vitamin D levels. Group I: 25-OH vitamin D - ≥30 ng/mL; sufficient, Group II: 25-OH vitamin D - 20-29 ng/mL; insufficient, Group III- 25-OH vitamin D - <20 ng/mL; deficient. The 25-OH vitamin D was estimated using Autoanalyser –Vitros 5600 under the principle of chemiluminescent immunoassay

Fasting Blood Sugar (FBS), insulin and Insulin Resistance (IR) were assessed for diabetic status. HbA1c, AGE, sRAGE and AGE/sRAGE ratio were used as glycation biomarkers. [Table/Fig-3] shows that the FBS, insulin, IR, and HbA1c were higher than the normal range. [Table/Fig-4], the comparison of glycation biomarkers among the categories based on the 25-OH vitamin D levels showed a significant increase in blood HbA1c levels as follows: deficient > insufficient > sufficient (p<0.001). However, there was no significance found with FBS (p=0.505), IR (p=0.897), AGE (p=0.115) and sRAGE (p=0.864). [Table/Fig-5] showed a significant negative correlation (r=-0.287) only with HbA1c (p<0.001). However, FBS and IR showed a negative trend with vitamin D though not significant.

| Glycation biomarkers | Serum/plasma levels |
|---|---|
| Diabetic status | |
| FBS (mg/dL) | 159.64±60.51 |
| Insulin (µIU/L) | 9.21±6.89 |
| Insulin resistance | 4.47±1.99 |
| Glycation biomarkers | |
| HbA1c (%) | 9.49±2.57 |
| AGE (ng/mL) | 809.19±383.32 |
| sRAGE (pg/mL) | 446.81±230.91 |
| AGE/sRAGE | 2.08±1.17 |

**[Table/Fig-3]:** Glycation biomarkers in the study population.
FBS was estimated under the principle of GOD-POD and Insulin was estimated under the principle of enhanced chemiluminescence. The instrument used was Vitros 5600. AGE and sRage were estimated using ELISA

| S. No. | Glycation Biomarkers | Group I (n=27) | Group II (n=46) | Group III (n=57) | p value |
|---|---|---|---|---|---|
| 1 | FBS (mg/dL) | 155.8±55.3 | 158.6±59.6 | 171.9±69.9 | 0.505 |
| 2 | HbA1c (%) | 8.5±1.8 | 9.2±2.1 | 10.8±2.9 | <0.001* |
| 3 | #IR | 5.3±3.3 | 5.6±6.5 | 5.4±4.0 | 0.897 |
| 4 | #AGE (ng/mL) | 763.9±264.3 | 888.8±280.8 | 795.2±461.7 | 0.115 |
| 5 | #sRAGE (pg/mL) | 458.0±200.9 | 448.1±167.8 | 494.1±261.1 | 0.864 |
| 6 | AGE/sRAGE | 1.9±0.8 | 2.1±0.8 | 1.8±0.8 | 0.267 |
| 7 | #Insulin (µIU/L) | 12.9±7.9 | 13.2±11.2 | 12.2±7.9 | 0.852 |

**[Table/Fig-4]:** Comparison of glycation biomarkers and insulin resistance among 3 groups based on 25-OH vitamin D status.
Statistical test used is ANOVA; #Kruskal Wallis analysis done; *p<0.05 is considered significant

| Parameters | Total participants (N=130) | | Group I (n=27) | | Group II (n=46) | | Group III (n=57) | |
|---|---|---|---|---|---|---|---|---|
| | r | p | r | p | r | p | r | p |
| FBS (mg/dL) | -0.079 | 0.370 | 0.07 | 0.72 | -0.07 | 0.64 | -0.03 | 0.82 |
| HbA1c (%) | -0.287 | 0.001* | 0.319 | 0.103 | -0.047 | 0.75 | 0.025 | 0.851 |
| AGE (ng/mL) | 0.140 | 0.115 | -0.028 | 0.889 | 0.209 | 0.163 | 0.194 | 0.148 |
| sRAGE (pg/mL) | 0.021 | 0.818 | 0.004 | 0.98 | 0.216 | 0.149 | 0.056 | 0.679 |
| AGE/sRAGE | 0.116 | 0.192 | -0.191 | 0.337 | 0.197 | 0.189 | 0.057 | 0.673 |
| Insulin (µIU/L) | 0.043 | 0.626 | 0.103 | 0.607 | -0.016 | 0.913 | -0.015 | 0.911 |
| IR | -0.063 | 0.475 | 0.168 | 0.402 | 0.054 | 0.717 | -0.019 | 0.887 |

**[Table/Fig-5]:** Correlation of 25-OH vitamin D with glycation parameters
Statistical significance: *p<0.05 was considered significant

## DISCUSSION

The current study used FBS, HbA1c, AGE, sRAGE and AGE/sRAGE as glycation biomarkers. It was expected that low levels of vitamin D could be associated with an increased FBS, HbA1c, IR, AGE, sRAGE and AGE/sRAGE, while, in the presence of sufficient vitamin D, lower concentrations of FBS, HbA1c, IR, AGE, sRAGE and AGE/sRAGE would occur. However, the findings showed significant negative trend only with HbA1c (p=0.001). Although a negative trend was seen with FBS, PPBS and IR, it was non significant (p>0.05). There were no significant correlation with AGE and sRAGE (p>0.05).

T2DM is one of the major risk factors of CAD, due to enhanced prothrombotic and pro-inflammatory status which leads to atherosclerosis [12]. Achieving adequate glycaemic control is one of the key elements that contributes to the reduction of T2DM complications. Apart from its function in maintaining calcium homeostasis, vitamin D also plays an important role in type 2 diabetes. Hypovitaminosis D is thought to be a possible risk factor for type 2 diabetes. The relationship between vitamin D levels and glucose metabolism, particularly glycaemic control, and insulin sensitivity has garnered a lot of focus recently. VDD exhibits an increase in IR there by leading to compromised control of blood glucose [13,14].

Zhao et al., (2020), [15] found a significant negative correlation between 25-OH vitamin D and HbA1c (r=-0.259, p<0.01) which supports the current study with r value of -0.287 and p<0.01). On the other hand, Madar AA et al., (2014), in their double blinded RCT, reported no improvement in $HbA_{1c}$, lipid and fructosamine in those with low vitamin D status after oral vitamin D supplementation for 3 months among T2DM patients [16]. This contrasts with our findings, as $HbA_{1c}$ showed significant correlation with vitamin D in the current study, suggesting that the impact of vitamin D may be more evident in observational correlations than in short-term interventional trials. Furthermore, Upreti V et al., (2018), in their RCT with vitamin D supplementation of 6 months, T2DM and hypovitaminosis D showed significant decrease in mean FPG levels (131.4 to 102.6 mg/dL; p=0.04) , $HbA_{1c}$ levels (7.29% to 7.02%; p=0.01), and PPPG levels (196.2 to 135.0 mg/dL; p<0.001) [17]. Compared to their results, the current study showed a more limited effect, as the significant correlation was confined only to $HbA_{1c}$, while no such correlation was found with FPG, AGE or sRAGE. These differences could be attributed to study design observational versus interventional, duration of intervention, baseline vitamin D levels, and the population studied.

Ehrampoush E et al., (2021), reported the average serum vitamin D as 22.3+8.9 nmol/L, which was similiar to that of the present study. As per the study, age, BMI, waist circumference, and all metabolic indicators were inversely correlated with vitamin D levels (p<0.001). To account for confounding variables, they employed two logistic regression models: (i) For smoking, age, and gender, and (ii) In addition to BMI and energy consumption. Vitamin D levels with insulin and FPG were significantly inversely correlated in both models [18]. The present study showed a negative trend between vitamin D and IR though there was no significant correlation .

According to Lontchi-Yimagou et al., (2020), 25-OH vitamin D replenishment was linked to improvements in human hepatic insulin sensitivity, decreased collagen immunofluorescence, and lower expression of profibrotic and pro-inflammatory genes in adipose tissue. After six months on a placebo, worsening trends point to VDD's developing metabolic impacts. Vitamin D receptor knock out mice mirrored the VDD humans, displaying increased adipose tissue fibrosis and inflammation and hepatic IR [12].

Lemieux P et al., 2019 demonstrated that taking a vitamin D3 supplement for six months had a positive impact on the disposition index (mean change: 267.0 vs -55.5; p=0.039) and Matsuda 2 value (mean change: 0.92 vs -0.03; p=0.009). Individuals at high risk of T2DM or with newly diagnosed T2DM, vitamin D supplementation for 6 months significantly increased peripheral insulin sensitivity and β-cell function, suggesting that it may slow metabolic deterioration in this population [19].

Although the direct and indirect effects of vitamin D on insulin sensitivity are well established, research examining the same subject have produced a range of results. Kumar PS et al., (2019), conducted a cross-sectional study among patients diagnosed with type 2 DM as per the American Diabetes Association (ADA) criteria. VDD was observed in 25.5% of the patients. Vitamin D levels were not associated with markers of glycemic control or IR [13]. Pittas et al., (2019), in their RCT study, reported that supplementation of vitamin $D_3$ (4000 IU/day) increased vitamin D levels but did not lower the risk of DM compared to placebo after a median follow-up of 2.5years [20].

One of the study's limitations is that all of the measurements made of the T2DM patients in study were taken at a single point in time. Given that vitamin D helps maintain glucose homeostasis, more extensive, carefully monitored research is required to fully understand the connection between vitamin D levels and glycaemic management.

In the current study, no significant correlation of vitamin D was found with AGE, sRAGE and AGE/sRAGE (p>0.05) [Table/Fig-4]. But in vitro and animal studies showed that treatment with vitamin D lowers the toxic effects of AGEs and decreases their formation [21,22].

According to Sebekova et al., 2015, AGE-FI and skin autoflourescence were higher in T2DM patients than in controls, and their levels were correlated with age, the duration of diabetes, and the severity of renal impairment. Among the diabetics group, hypovitaminosis D did not augment accumulation of AGEs, studied markers of microinflammation, and oxidative stress except for sVAP-1 [23].

Omidian M et al., (2019), conducted a placebo-controlled, double blinded RCT, which aimed to determine the effect of vitamin D supplementation on AGEs signaling pathway. Their findings suggest that study result showed, vitamin D supplementation could down-regulate RAGE mRNA [fold change=0.72 in vitamin D vs 0.95 in placebo) (p=0.001) [24].

According to Chen J et al., (2019), serum 25-$OHD_3$ was found to be inversely related to skin autoflourescence (SAF) and to account for 1.5% of the variance [unstandardised B=-0.002, standardized b=-0.125], regardless of medication use and established risk factors. Serum 25-$OHD_3$ concentration was significantly and inversely associated with SAF measured prospectively, also after adjustment for known risk factors for high SAF and the number of medications used, but the causal chain is yet to be explored [14].

### Limitation(s)

The patient's vitamin D status was only assessed once while they were in the hospital, which is not the most thorough long-term measurement of serum vitamin D. This limits the insights into seasonal or chronic trends. This was possibly the most significant research constraint. History of sun exposure, diet, or physical activity was not collected in the study. It was not possible to determine a temporal relationship between cause and effect because this study was cross-sectional. A more detailed understanding of the changes in vitamin D levels and their relationship to other factors might have been obtained by using non-diabetic people as the control group.

## CONCLUSION(S)

The prevalence of VDD was high among the study participants. The significance of adequate vitamin D in a diabetic population is highlighted by the significant negative correlation found between the 25 (OH) vitamin D and HbA1c, which suggests that vitamin D may have an indirect role in the pathophysiology of CAD. Therefore, in cases of VDD, screening and dietary supplements may help slow the

development of diabetic problems. However, the present study did not find a significant correlation of vitamin D with AGE/srAGE ratio and IR as the etiology for T2DM and CAD is multi-factorial. Further longitudinal studies in a larger sample size are desirable to confirm these results. A case control study, with a non diabetic control group may help in providing the risk ratio of diabetic population verse non-diabetic population to cardiovascular complications.

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**PLAGIARISM CHECKING METHODS:** [Jain H et al.]
- Plagiarism X-checker: Jul 08, 2025
- Manual Googling: Nov 12, 2025
- iThenticate Software: Nov 14, 2025 (19%)

**ETYMOLOGY:** Author Origin

**EMENDATIONS:** 7

**AUTHOR DECLARATION:**
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jun 20, 2025**
Date of Peer Review: **Sep 03, 2025**
Date of Acceptance: **Nov 16, 2025**
Online Ahead of Print: **Jan 10, 2026**
Date of Publishing: **Mar 01, 2026**