Association of Vitamin D Status with Cardiovascular Risk in Prediabetes

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INTRODUCTION

Evidence propounds that VD has an inevitable role in several metabolic processes and its deficiency may have adverse health implications. The study focuses on prediabetic patients and the impact of VD status on their cardiovascular health.

Aims: To determine the association between VD status and cardiovascular risk in prediabetic patients.

Methods: The study included retrospectively collected data on 270 prediabetic patients and 299 normoglycemic subjects. Prediabetes was diagnosed by HbA1c as 5.7 - 6.4%. Increased cardiovascular risk was assessed based on the Atherogenic Index of Plasma (AIP) more than 0.1. Lipid parameters and AIP were compared between two groups by t-test and chi-square and separately by ANOVA under VD categories; Sufficient (>75 nmol/L), Insufficient (50-75 nmol/L) and Deficient (<50 nmol/L). Regression analysis was used to find the association of VD status with risk of prediabetes and unfavourable AIP ( > 0.1).

Results: VD deficiency was more prevalent in prediabetic subjects (56.9%; 57.9 ± 20.8 nmol/L; p<0.05). AIP was significantly higher in prediabetic subjects (0.13 ± 0.29; p < 0.05). AIP showed a significant increasing trend with declining Vitamin D status among prediabetic patients (p<0.05) but not in normoglycemic subjects. The risk of prediabetes (p = 0.141) and unfavourable AIP (p <0.05 ) decreased with improved Vitamin D status.

Conclusion: Vitamin D status is important in prediabetes as it potentially increases cardiovascular risk in the already vulnerable group.

Key Words: Prediabetes, Vitamin D, Atherogenic Index of Plasma, Cardiovascular disease, Dyslipidemia
induces the formation of calcium fatty acid complexes in the intestine thereby reducing its absorption and increasing faecal fat excretion. Small and dense low-density lipoprotein (sd LDL) have a stronger predisposition to atherosclerosis compared to other lipid parameters. AIP is an excellent marker of sd LDL and well predicts CVD as shown in several studies. Current study aims to assess serum VD status in prediabetic patients and its relation with AIP.

**MATERIALS AND METHODS**

Retrospective collection of data was accomplished on first time diagnosed prediabetic patients in the age group of 18 - 65 years during the period January 2019 to December 2020. Prediabetes was diagnosed based on an HbA1c level of 5.7 - 6.4%. The selected patients also had concurrent lab investigations for lipid profile and vitamin D. The tests were requested as part of routine investigations based on the clinical history and not done exclusively for the study purpose. Age, gender-matched normoglycemic control subjects were selected with HbA1c < 5.7 % in the same duration. Exclusion criteria were previous history of diabetes, malignancies, other chronic illnesses, diseases that affect VD levels like thyroid, parathyroid disorders, Cushing syndrome etc. Those with a history of VD supplementation and those with incomplete lab data were also eliminated. Age, gender of subjects along with other information was retrieved from health records and entered on a Microsoft excel sheet with proper coding while keeping the identity of all participants strictly confidential. Ethical approval was waived due to the retrospective nature of the study.

**Anthropometric and laboratory parameters**

Height, weight, systolic and diastolic blood pressures of all subjects were noted. Body mass index was calculated as Height / (weight)²(kg/m²).

The laboratory tests were performed after fasting of 8 hours and tests included were fasting blood sugar (FBS), HbA1C, TC, triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), HDL-C, 25(OH) VD. All lab parameters were measured on an Alinity ci analyzer, Abbott, Germany. For study purposes VD levels were categorized as Deficient, 25(OH)D < 50 nmol/L; Insufficient, 50-75 nmol/L and Sufficient, ≥75 nmol/L. AIP was calculated as the logarithm to the base 10 of the ratio TG / HDL-C and value > 0.1 was considered to be associated with increased cardiovascular risk.

**Statistical Analysis**

Statistical analysis was performed using SPSS 20.0 version. Descriptive statistics were presented as frequency, the percentage for qualitative variables and mean with standard deviation for numerical variables respectively. For inferential statistics, categorical variables were compared by chi-square analysis and continuous variables by t-test and analysis of variance (ANOVA). The variables were compared in prediabetic and normoglycemic groups, stratified analysis for two groups under three categories of VD; deficient, insufficient and sufficient. Pearson’s correlation coefficients were deduced for all variables with HbA1c and AIP among prediabetic subjects. Regression analysis was performed for the risk of prediabetes and higher AIP (> 0.1). According to VD categories and model adjustments were done for age, gender and BMI. Statistical significance was defined as p-value < 0.05.

**RESULTS**

Table 1 summarizes the clinical and biochemical variables of all subjects. Means of TG, TC, LDL-C, were significantly higher while the mean of HDL-C was significantly lower in the prediabetes group. Mean AIP in prediabetic group was 0.13 ± 0.30 whereas in control group it was significantly lower, - 0.049 ± 0.245. VD deficiency was significantly more prevalent in the prediabetic group (56.9%) compared to the control group (43.1%). The mean VD level in prediabetic subjects was 57.9 ± 20.8 nmol/l while in the control group it was 63.27 ± 23.7 nmol/L.

Tables 2, 3 show stratified analysis of variables in prediabetic and control groups based on VD level. A significant increasing trend was noticed in BMI with decreasing VD in the prediabetes group. Additionally, in the prediabetic group HbA1c, TG, TC, LDL-C exhibited distinct increasing tendency and HDL-C showed decreasing bent analogous to reducing VD level categories with statistical significance. AIP was highest in deficient VD category in prediabetes group (0.35 ± 0.19), lower in insufficient (0.05 ± 0.25) and lowest insufficient category (-0.13 ± 0.22) although no distinguishable trend was perceptible in control group.

Table 4 shows a positive correlation of AIP with BMI, HbA1c, TC, TG, LDL and a negative correlation with VD and HDL- C in the prediabetic population, with statistical significance. HbA1c had a significant positive correlation with BMI, TC, TG and AIP and a negative correlation with VD and HDL-C among prediabetic subjects.

Table 5 depicts logistic regression showing that the risk of prediabetes dropped to 0.513 times in the insufficient category and 0.673 times in the sufficient category when compared to the VD deficient category (considered as reference). The risk lessened with rising VD levels even after adjusting for age, gender and BMI. As for increased cardiovascular risk in prediabetic patients, based on AIP > 0.1, the risk was 0.101 times and 0.015 times lower in insufficient and sufficient categories as related to the risk in deficient categories. The risk still showed a similar downswing when adjusted for age, gender and BMI.
DISCUSSION

There has been an augmented indication of the protective role of VD against several metabolic disorders including prediabetes and CVD. The current study affirms that VD inadequacy is associated with prediabetes and increased cardiovascular risk. Additionally, in prediabetic patients who are already predisposed to CVD, the threat is further exaggerated due to VD deficiency.

Based on a recent study, metabolic risk factors are accentuated in prediabetes due to VD inadequacy. Keeping up with previous findings, the study showed inverse association of BMI and 25(OH)D with a clear increasing trend of BMI with decreasing 25(OH)D level in prediabetic patients. The linkage is explained by VD receptor polymorphism which when expressed on preadipocytes leads to increased adiposity. Other experiments suggest that by stimulating parathormone, VD deficiency causes more influx of calcium into adipocytes and hence lipogenesis. As an indicator of cardiovascular risk, AIP was significantly higher in prediabetes in the current study similar to a previous one that also emphasized on early identification of prediabetes to prevent CVD. Standing by our findings, previous studies have shown a similar association of VD and lipids. Several mechanisms have been proposed; firstly by modulating the Apolipoprotein A-1 levels VD regulates cholesterol transportation, secondly by increasing lipoprotein lipase gene expression it enhances clearance of lipoprotein particles. Additionally, 25(OH)D induced hyperparathyroidism leads to decreased peripheral TG clearance and a rise in hepatocellular Ca2+ stimulates microsomal triglyceride transfer protein leading to hypertriglyceridemia. It may also reduce the formation of foam cells hence increasing HDL-C. 25(OH)D is also shown to suppress sterol regulatory element-binding proteins (SREBPs), associated with lipogenesis of cholesterol and triglycerides, by proteolysis and ubiquitin-mediated degradation of SREBP cleavage activating protein (SCAP). Besides, VD indirectly influences lipid metabolism by affecting insulin resistance and inflammation.

AIP exhibited an increasing trend with falling VD categories with statistical significance in prediabetic subjects, but not in the control group. This was an additional finding to the previous claim that subjects with prediabetes have worse cardiometabolic risk profiles as compared to those with normoglycemia which is shown in the present study as well. Similarly, HbA1C showed a rising tendency from sufficient to deficient VD categories in the prediabetic group. VD showed a negative correlation with HbA1c and AIP which corroborates with previous studies. Further, regression analysis divulged an increasing risk of prediabetes with diminishing VD level as also proven in a recent meta-analysis.

There were certain limitations in the present study that are noteworthy while considering the results. Firstly, it was a retrospective data collection and selection bias could not be avoided. Calcium and parathormone levels were not measured which could have possibly impacted the association of Vitamin D and lipids. Furthermore, it was a small scale study which might have affected the statistical power. Nevertheless, the study found a significant association between Vitamin D status and AIP in prediabetic patients but was not evident in normoglycemic subjects.

CONCLUSION

To summarize, Vitamin D levels are lower in prediabetic subjects and are inversely related to HbA1c and the Atherogenic index of plasma. Vitamin D inadequacy in prediabetes poses a cardiovascular risk. Since these patients have an equal propensity for progression to various complications of type 2 diabetes mellitus it would be worth knowing Vitamin D status and intervening timely with supplementation if needed which would enable to improve future prognosis and perhaps better quality of life.

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Conflict of Interest: None

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Table 1: Clinical and Biochemical parameters of all subjects

|                      | Normoglycemic (n=299) | Prediabetic (n=270) | p value   |
|----------------------|-----------------------|---------------------|-----------|
| Age (years)          | 35.71 ± 8.43          | 44.98 ± 9.40        | <0.001*   |
| Gender (Female/Male) | 142/157               | 134/136             | 0.610     |
| BMI (kg/m²)          | 22.79 ± 1.92          | 25.53 ± 2.89        | <0.001*   |
| Systolic BP (mm Hg)  | 130.79 ± 8.21         | 135.53 ± 11.09      | <0.001*   |
| Diastolic BP (mm Hg) | 78.02 ± 6.59          | 79.12 ± 9.11        | 0.097     |
| HbA1C (%)            | 4.89 ± 0.29           | 5.93 ± 0.19         | <0.001*   |
| FBS (mmol/L)         | 6.50 ± 0.27           | 5.41 ± 0.59         | 0.521     |
| TotalCholesterol (mmol/L) | 4.75 ± 0.81 | 5.17 ± 0.79        | <0.001*   |
| LDL-C (mmol/L)       | 2.6389 ± 0.86828      | 2.34 ± 0.89         | <0.001*   |
| HDL-C (mmol/L)       | 1.4477 ± 0.39888      | 1.15 ± 0.31         | <0.001*   |
| Vitamin D (nmol/L)   | 63.2742±23.78350      | 57.91 ± 20.83       | 0.005*    |
| Deficient (%)        | 81 (43.1%)            | 107 (56.9%)         |           |
| Insufficient (%)     | 146 (59.6%)           | 99 (40.4%)          | 0.003*    |
| Sufficient (%)       | 72 (52.9%)            | 64 (47.1%)          |           |
| AIP                  | -0.049+2.45           | 0.130+2.98          | <0.001*   |

Continuos data presented as Mean + standard deviation and categortical data as frequency (%) / proportion.

p-value calculated using t-test and chi-square analysis; (*) p-value significant BMI: Body Mass Index; BP: blood pressure, HbA1c: glycosylated haemoglobin; FBS: fasting blood sugar, LDL-C: low density lipoprotein-cholesterol HDL-C: high-density lipoprotein-cholesterol, AIP: atherogenic index of plasma;
Table 2: Clinical and Biochemical parameters of Prediabetic subjects under Vitamin D Categories.

|                          | Deficient VD (<50 nmol/L) | Insufficient VD (50-74.9 nmol/L) | Sufficient VD (≥75 nmol/L) | p value |
|--------------------------|---------------------------|----------------------------------|---------------------------|---------|
| Age                      | 43.71 + 9.45              | 44.73 + 8.86                     | 47.51 + 9.77              | 0.038*  |
| Gender (Female/Male)     | 61/ 46                    | 50/ 49                           | 23/ 41                    | 0.028*  |
| BMI (kg/m²)              | 26.69 + 3.04              | 25.07 + 2.78                     | 24.31 + 2.02              | <0.001* |
| Systolic BP (mm Hg)      | 136.25 + 12.20            | 135.90 + 11.04                   | 133.75 + 9.00             | 0.700   |
| Diastolic BP (mm Hg)     | 80.16 + 8.38              | 78.93 + 10.38                    | 77.68 + 8.03              | 0.273   |
| Median Vitamin D         | 38.65 +7.19               | 59.49 + 6.87                     | 87.65+12.69               | <0.001* |
| HbA1C (%)                | 6.0 + 0.2156              | 5.90 + 0.17                      | 5.86 + 0.14               | <0.001* |
| FBS (mmol/L)             | 5.50 +0.56                | 5.36 + 0.57                      | 5.34 + 0.64               | 0.097   |
| Triglycerides (mmol/L)   | 2.1 + 0.50                | 1.51 + 0.61                      | 1.08 + 0.45               | <0.001* |
| TotalCholesterol(mmol/L) | 5.53 + 0.65               | 5.10 + 0.76                      | 4.68 +0.74                | <0.001* |
| LDL C (mmol/L)           | 2.58 + 0.86               | 2.32 + 0.96                      | 1.99 + 0.72               | <0.001* |
| HDL C (mmol/L)           | 0.93 + 0.27               | 1.25 + 0.28                      | 1.37 + 0.19               | <0.001* |
| AIP                      | 0.35 + 0.19               | 0.05 + 0.25                      | -0.13 + 0.22              | <0.001* |

Continuous data presented as Mean + standard deviation and categorical data as frequency (%) / proportion, p-value calculated from one way ANOVA; (*) p-value significant.

VD: Vitamin D; BMI: Body mass Index; BP: blood pressure, HbA1c: glycosylated haemoglobin; FBS: fasting blood sugar, LDL-C: low-density lipoprotein-cholesterol HDL: high-density lipoprotein cholesterol, AIP: atherogenic index of plasma

Table 3: Clinical and Biochemical variables of Normoglycemic subjects under Vitamin D Categories.

|                          | Deficient VD (<50nmol/L) | Insufficient VD (50-74.9nmol/L) | Sufficient VD (≥75nmol/L) | p value |
|--------------------------|--------------------------|----------------------------------|---------------------------|---------|
| Age                      | 33.81 +8.18              | 35.36+8.24                       | 38.62 +8.44               | 0.001*  |
| Gender (F/M)             | 42/ 39                   | 59/ 87                           | 41/ 31                    | 0.047*  |
| BMI (kg/m²)              | 22.48 +1.75              | 22.87 + 1.97                     | 22.99 + 1.99              | 0.310   |
| Systolic BP(mmHg)        | 129.59 +7.53             | 130.70 + 7.69                    | 132.34 + 9.70             | 0.293   |
| Diastolic BP(mmHg)       | 77.86 +6.37              | 77.95 + 6.36                     | 78.34 + 7.34              | 0.879   |
| Median Vitamin D(nmol/L) | 38.36 +8.93              | 61.33 + 7.30                     | 95.23+20.59               | <0.001* |
| HbA1C (%)                | 4.91 +0.29               | 4.88 + 0.30                      | 4.88 + 0.25               | 0.470   |
| FBS(mmol/L)              | 10.85 +53.56             | 4.85 + 0.40                      | 4.95 + 0.40               | 0.139   |
| Triglycerides(mmol/L)    | 1.49 +0.58               | 1.30 + 0.57                      | 1.32 + 0.52               | 0.053   |
| TotalCholesterol(mmol/L) | 4.99 + 0.69              | 4.65 + 0.83                      | 4.69 + 0.85               | 0.009*  |
| LDL-C (mmol/L)           | 2.69 + 0.88              | 2.59 + 0.86                      | 2.66 + 0.86               | 0.672   |
| HDL-C (mmol/L)           | 1.50 + 0.48              | 1.46 + 0.34                      | 1.35 + 0.37               | 0.020*  |
| AIP                      | -0.015+ 0.26             | -0.080+0.24                      | -0.026+0.21               | 0.161   |

Continuous data presented as Mean + standard deviation and categorical data as frequency (%) / proportion, p-value calculated from one way ANOVA; (*) p-value significant.

VD: Vitamin D; BMI: Body mass Index; BP: blood pressure, HbA1c: glycosylated haemoglobin; FBS: fasting blood sugar, LDL-C: low-density lipoprotein-cholesterol HDL: high-density lipoprotein cholesterol, AIP: atherogenic index of plasma
Table 4: Correlation between HbA1c and AIP with other variables

| Age                  | HbA1c (%) | AIP     |
|----------------------|-----------|---------|
|                      | r         | p value |         | r         | p value |
| BMI (kg/m²)          |           |         |         |           |         |
| r                    | 0.362     | <0.001  | 0.480   | <0.001*   |
| p value              |           |         |         |           |         |
| FBS (mmol/L)         |           |         |         |           |         |
| r                    | 0.298     | <0.001  | 0.115   | 0.058     |
| p value              |           |         |         |           |         |
| Vitamin D (nmol/L)   |           |         |         |           |         |
| r                    | -0.230    | <0.001  | -0.639  | <0.001*   |
| p value              |           |         |         |           |         |
| TotalCholesterol (mmol/L) |         |         |         |           |         |
| r                    | 0.196     | 0.001   | 0.584   |           |
| p-value              |           |         |         |           |         |
| Triglycerides (mmol/L) |         |         |         |           |         |
| r                    | 0.266     | <0.001  | 0.897   | <0.001*   |
| p value              |           |         |         |           |         |
| HDL-C (mmol/L)       |           |         |         |           |         |
| r                    | -0.348    | <0.001  | -0.828  | <0.001*   |
| p value              |           |         |         |           |         |
| LDL-C (mmol/L)       |           |         |         |           |         |
| r                    | 0.071     | <0.001  | 0.349   | <0.001*   |
| p value              |           |         |         |           |         |
| AIP                  |           |         |         |           |         |
| r                    | 0.329     | <0.001  |         |           |
| p value              |           |         |         |           |         |

r: correlation coefficient; (*) p-value significant
BMI: Body mass Index; BP: blood pressure, HbA1c: glycosylated Haemoglobin; FBS: fasting blood sugar, LDL-C: low density Lipoprotein-Cholesterol; HDL-C: high-density lipoprotein cholesterol
AIP: atherogenic index of plasma

Table 5: Regression Model to predict odds ratio for prediabetes and unfavourable AIP (>0.1).

|                  | VD deficiency OR(95% CI) | VD Insufficiency OR(95% CI) | p-value | VD Sufficiency OR(95% CI) | p value |
|------------------|--------------------------|-----------------------------|---------|---------------------------|---------|
|                  | Unadjusted               | Adjusted                    |         |                           |         |
| Prediabetes      |                          |                             |         |                           |         |
| Unadjusted       | 1.00                     | 0.513 (0.349-0.755)         | 0.001*  | 0.673 (0.432-1.048)       | 0.080   |
| Adjusted         | 1.00                     | 0.594 (0.359-0.982)         | 0.042   | 0.648 (0.364-1.155)       | 0.141   |
| AIP (>0.1)       |                          |                             |         |                           |         |
| Unadjusted       | 1.00                     | 0.101 (0.047-0.216)         | <0.001* | 0.015 (0.005-0.039)       | <0.001* |
| Adjusted         | 1.00                     | 0.131 (0.058-0.296)         | <0.001* | 0.018 (0.006-0.053)       | <0.001* |

Model adjusted for age, gender, BMI (*) p-value significant.
OR: odds ratio; CI: confidence interval; AIP: atherogenic index of plasma