Original Article

ID:JCDR/2012/4408:2224

Biochemistry Section

# Serum 25(OH)D and Type 2 Diabetes Mellitus

BALASUBRAMANIAN SHANTHI, CARNAGARIN REVATHY, ARCOT JAGDEESHWARAN MANJULA DEVI, PARTHASARATHY JAGANATHAN PARAMESHWARI, THATIPARTHI STEPHEN

## ABSTRACT

**Background:** 25(OH) Vitamin D is the circulating form of vitamin D which is measurable in the blood. Vitamin D insufficiency has been defined as serum 25-hydroxyvitamin D (25(OH) D) levels below 30 ng/mL and it is common among patients with type 2 diabetes mellitus (DM).

**Aim and Objectives:** Our aim was to investigate the clinically meaningful associations which implicated low serum levels of 25(OH) D with impaired diabetic control in DM type 2.

**Methods:** The serum 25(OH) D and the HbA1c levels were determined in 50 patients with DM type 2, along with their FBS, PPBS and HBA1c and other parameters which were required to assess the diabetic control were also measured.

**Results:** The results of our study revealed a trend towards an inverse vitamin D - FBS (Pearson correlation, r = -0.090) and inverse vitamin D – PPBS (Pearson correlation, r = -0.095) association. The lower serum 25(OH) D levels were associated with the higher HbA1c levels (Pearson correlation, r = -0.173). This was a borderline association which may have probably occurred due to the small sample size.

**Conclusion:** The association between the low serum 25(OH) D levels and elevated HBA1c in the study population may be inscribed into a wider context, portraying vitamin D insufficiency as a poor prognostic factor, which may play a vital role in impairing the glycaemic control.

**Key Words:** Vitamin D, HbA1c, type 2 diabetes.

## INTRODUCTION

Diabetes mellitus is a metabolic disease which is caused by absolute or relative insulin deficiency. About 10% of the Indian population suffers from this disease. Various factors play a role in the aetiopathogenesis and in the glycaemic control among the type 2 diabetic patients.

Vitamin D is derived from 7 dehydro cholesterol or ergosterol by UV irradiation [1]. Cholecalciferol is hydroxylated at the 25th position in the liver to form 25 hydroxy cholecalciferol. This is the major transport form of the vitamin. It then gets hydroxylated at the first position to form calcitriol, which is the active form of vitamin D. Interestingly, many studies have revealed that Vitamin D3 (calcitriol) has a role in the synthesis and the secretion of insulin [2] by receptor mediated molecular mechanisms [3].

Various definitions for vitamin D insufficiency have appeared in the literature; the best established one pertains to serum levels which are below 30 ng/mL [4]. A recent meta-analysis has demonstrated low vitamin D levels in the middle-aged and the elderly populations and these represent a risk factor for type 2 diabetes mellitus (DM), cardiovascular disease and metabolic syndrome [5]. The deficiency of Vitamin D is associated with impairment of insulin synthesis and secretion and also an increase in the insulin resistance.

This study was done to find out the correlation between the vitamin D3 levels and the blood glucose levels, as well as the glycaemic control in already diagnosed type 2 diabetic patients.

## MATERIALS AND METHODS

Blood samples (5ml) which were obtained from 50 DM type 2 patients of age (43.42 ±7.877 years) with a disease duration of 5 years and without complications, were recruited from the Medicine Outpatient Department of our institute, Sree Balaji Medical College and Hospital, Chrompet, Chennai, India and all the participants were interviewed at the baseline by the same investigator( to assess the sunlight exposure). Those with hypercalcaemia, intake of vitamin D for osteoporosis in dietary supplements, other orthopaedic problems like rickets, osteomalacia or end-stage renal failure and pregnancy were excluded from the study.

**The following investigations were performed:**

**1.** 25 (OH) Vitamin D - Direct ELISA KIT (Immunodiagnostik)

**2.** Plasma blood glucose – Fasting and post prandial (GOD – POD method, Diatek kit, Fully automated analyzer, XL – 300)

**3.** HbA1c (Immuno turbidimetry, direct technique, Futura system kit, by using an appropriate calibrator)

The association of 25(OH) D with FBS, PPBS and HBA1c was evaluated by using the Pearson's correlation coefficient. Statistical analysis was performed by using SPSS, version 15 (Statistical Package for Social Sciences). This study was approved by the institutional ethical committee of the Sree Balaji Medical College and Hospital (Ref no.IEC/54/2011-12). An informed consent was obtained from all the study participants, both in English and in vernacular languages.

| Parameters | Mean±SD | R-value (P-value) |
|---|---|---|
| FBS<br>VITAMIN_D3 | 146.22 ± 45.00<br>18.492 ± 3.49 | - 0.090 (0.534) |
| PPBS<br>VITAMIN_D3 | 275.28±66.40<br>18.492 ± 3.49 | - 0.095 (0.511) |
| HBA1C<br>VITAMIN_D3 | 8.32±1.15<br>18.492±3.49 | -0.173 (0.229 ) |

**[Table/Fig-1]:** Inferential Statistics for the correlation between Vit D & glycemic parameters

## RESULTS

The age of the participants ranged between 43.42 ±7.877 years with the 25(OH)D insufficiency (18.49 ±3.497 ng/ml) and the assessed glycaemic control with FBS(146.22 ± 45.007 mg/dl), PPBS(275.28 ±66.400mg/dl) and HBA1C (8.326 ±1.15843) is shown in [Table/Fig-1].

The low serum vitamin D levels were negatively correlated with the fasting as well as the postprandial blood sugar levels. There was a trend towards an inverse 25(OH) D - HbA1C association, which did not show statistical significance, most probably due to the relatively small sample size.

## DISCUSSION

The present study observed that the type 2 diabetic individuals with a vitamin D insufficiency showed a poor glycaemic control. According to various studies [6], vitamin D has a potential influence on the glucose homeostasis, as was suggested by the following factors.

**Effect of Vitamin D on Insulin Secretion:**

Specific vitamin D cell receptors are present on the pancreatic β cells [7]. The pancreatic β cells express 1 alpha hydroxylase which is responsible for an active vitamin D3 synthesis [8] and also by increasing the insulin response to the glucose stimulation, but not affecting the basal insulin secretion [9]. In some populations, type I diabetes is associated with certain polymorphisms within the VDR gene [10] which is present in the human insulin gene promoter and also in the skeletal muscle and in adipose tissues [11] Pancreatic islets have both VDR and vitamin D-dependent calcium-binding proteins (CaBP) [12,13], thus suggesting a role of vitamin D in insulin secretion. The insulin secretion and sensitivity is influenced by Vitamin D mediated intracellular calcium secretion. Raised intracellular calcium levels enhance the binding of the calcium binding protein to the IRS – 1 (Insulin receptor substrate 1), stimulating tyrosine phosphorylation and PI3 kinase activation and thus promoting insulin secretion [11].

Vitamin D deficiency may also impair the insulin secretion through its associated increase in the PTH levels. It was proposed that vitamin D deficiency-associated hyperparathyroidism may actually cause a paradoxical increase in the intracellular calcium levels [12,13]. This PTH-induced increase in calcium may in turn impair the calcium signal which is needed for glucose-induced insulin secretion [14]. Of significance is the finding, that the vitamin D potentiation of glucose-induced insulin secretion is seen in normal individuals but not in patients with established type-2 DM [15]. This could be because type-2 diabetes by itself may be a condition of impaired intracellular calcium homeostasis [16].

Whether the insulin secretion is influenced by the direct action of Vitamin D or through its receptor or through changes in calcium, or PTH, is a matter of ongoing studies. It is also possible that the insulin secretion may be influenced by a combination of different mechanisms.

**Effect of vitamin D on insulin Sensitivity:**

Type-2 DM is a state of chronic systemic inflammation and it has been found to increase the insulin resistance [17]. Type-2 DM was found to be associated with an increase in the levels of the tumour necrosis factor-a and b, the C reactive protein, the plasminogen activator inhibitor-1 (PAI-1), and interleukin-6 (IL-6) [18-20]. The increase in these inflammatory mediators may precede and even predict the development of type-2 DM. In support of this concept, is the finding that VDR has been found on almost all the cells of the immune system [21] and that vitamin D can repress the type 1 cytokines, inhibit dendritic cell maturation, and upregulate the regulatory T cells. Furthermore, immune cells such as macrophages contain 1α hydroxylase that can be upregulated by the inflammatory mediators and not by PTH [22]. Vitamin D also suppresses the antigen-presenting capacity of the macrophages, it modulates the development of the CD4 lymphocytes and it inhibits the production of IFNc (interferon c) and IL-2 (interleukin 2) [23], among other cytokines. These cytokines are known to activate the macrophages and the cytotoxic T cells, which in turn can lead to the destruction of the pancreatic islets. By the modulation of the immune and the inflammatory processes, vitamin D may also decrease insulin resistance and increase the insulin secretion in type-2 DM [24], which are the two characteristic defects in this condition.

From the above discussion, it is clear that vitamin D has a significant role to play in the molecular mechanisms of the synthesis, secretion and the peripheral sensitivity of insulin. Hence, hypovitaminosis D may be associated with insulin resistance and beta cell dysfunction.

A variety of limitations of this study need however to be addressed. The small sample size did not allow a multivariate approach for incorporating additional, potentially meaningful factors for modifying the levels of serum 25(OH) D, but it should be declared that from the evidence which was provided, that improving the vitamin D status will help in establishing a better glycaemic control in people with DM type 2. Nevertheless, it seems that the routine screening for vitamin D insufficiency may provide meaningful information and that it could be considered for diabetic care. Interventional studies are needed to evaluate whether the long-term supplementation of vitamin D could reduce the morbidity in a diabetic population, with an awareness of the side effects.

**Conflict of Interest:** The authors declare no conflict of interest.

## REFERENCES

[1] Mathieu C, Gysemans C. Vitamin D and diabetes; Laboratory of Ex perimntal Medicine and Endocrinology (LEGENDO). *Diabetol*. 2006; 22(3): 187-93.
[2] Bikle DD, Siiteri PK, Ryzen E, Haddad JG. Serum protein binding of 1,25-dihydroxyvitamin D: a re-evaluation by the direct measurement of the free metabolite levels. *J Clin Endocrinol Metab*.1985;61:969-75.
[3] Maesstro S, Bajo MS, Davila N, Calle C. Transcriptional activation of the human insulin receptor gene by 1, 25 di hydroxyl vitamin D3. *Cell*

*Biochemistry and function*. 2002; 3: 227-32.
[4] Thacher TD,Clarke BL. Vitamin D insufficiency. *Mayo Clin Proc* 2011; 86:50-60.
[5] Parker J, Hashmi O, Dutton D, Mavrodaris A, Stranges S, Kandala NB, et al. The levels of vitamin D and the cardiometabolic disorders: a systematic review and meta-analysis. *Maturitas* 2010; 65:225-236.
[6] Pittas AJ, Lau J, Hu FB, Dawson-Hughes B. The role of Vitamin D and calcium in type 2 diabetes mellitus. A systemic review and meta-analysis. *Journal of Clinical Endocrinology and Metabolism.*2007;92(6):2017-29.
[7] Johnson JA, Grande JP, Roche PC, Kumar R. Immunohistochemical localization of the 1,25 (OH) 2 D3 receptor and calbindin D 28K in human and rat pancreas. *American Journal of Physiology*.1994; 267 (3), E356-E360.
[8] Bland R, Markovic, Hills CE, et al. Expression of 25-hydroxy vitamin D3-1 alpha hydroxylase in the pancreatic islets. *Journal of Steroid Biochemistry and Molecular Biology*.2004 ;89-90:121-25.
[9] Bourlon PM, Billaudel B, FaureDussert AJ. *Endocrinol.*1999;160:87-90.
[10] Mathieu C, Gysemans C, Giulietti A, Bouillon R. Vitamin D and diabetes. *Diabetologia.* 2006; 49 (1): 217-18.
[11] Simpson RU, Thomas GA, Arnold AJ. "Identification of the 1,25 – di hydroxy vitamin D3 receptors and their activities in the muscle. The *Journal of Biological Chemistry*. 1985; 260(15): 8882-91.
[12] Morrissey RL, Bucci TJ. Richard B, Empson N, Lufkin EG. *Proc. Soc. Exp. Biol. Med*. 1975;149: 56–60.
[13] Ishida H, Norman AW. *Mol.Cell.Endocrinol.*1988; 60: 109–17.
[14] Fujita T, Palmieri GM, J Bone Miner. *Metab.* 2000;18: 109–25.
[15] Kadowaki S, Norman AW. *J Clin. Invest.* 1984;73: 759–66.
[16] Levy J, Gavin JR, Sowers JR. *Am J Med* 1999;96:260–73.
[17] Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, Eur. Cytokine Netw. 2006;17: 4–12.
[18] Kolb H, Mandrup-Poulsen T, *Diabetologia* 2005;48: 1038-50.
[19] Vendrell J, Gutierrez C, Pastor R, Richart C. *Metabolism*.1995; 44:691–94.
[20] Ferna´ndez-Real JM, Vendrell J, Ricart W, Broch M, Gutie´rrez C, Casamitjana R, et al. *Diabetes Care*.2000;23: 831–37.
[21] Vozarova B, et al. Hum. *Genet.* 2003; 112:409–13.
[22] Illig T, et al, Kooperative Gesundheitsforschung im Raum Augsburg/ Cooperative Research in the Region of Augsburg, *J.Clin. Endocrinol. Metab*. 2004; 89: 5053–58.
[23] Hoffstedt J, Andersson IL, Persson L, Isaksson B, Arner P. *Diabetologia* .2002;45:584–87.
[24] Wolford JK, Gruber JD, Ossowski VM, Vozarova B, Antonio P. Tat-

**AUTHOR(S):**
1. Dr. Balasubramanian Shanthi
2. Dr. Carnagarin Revathy
3. Dr. Arcot Jagdeeshwaran Manjula Devi
4. Dr. Parthasarathy Jaganathan Parameshwari
5. Dr. Thatiparthi Stephen

**PARTICULARS OF CONTRIBUTORS:**
1. Associate Professor, Department of Biochemistry, Balaji Medical College And Hospital, C/C Works Road Chrompet Chennai-600044, India.
2. Corresponding Author.
3. Professor & HOD, Department of Biochemistry, Sree Balaji Medical College And Hospital, Chennai-600044, India.
4. Assistant Professor, Department of Community Medicine, Sree Balaji Medical College And Hospital, Chennai-600044, India.
5. Associate Professor, Department of Community Medicine. Sree Balaji Medical College And Hospital, Chennai-600044, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHORS:**
Dr. Carnagarin Revathy,
Department of Biochemistry,
Balaji Medical College And Hospital, Clc Works Road Chrompet
Chennai-600044, India.
Phone : 9952264962.
E-mail: revathycarnagarin@yahoo.com

**FINANCIAL OR OTHER COMPETING INTERESTS:**
None.

Date of Submission: **Apr 17, 2012**
Date of Peer Review: **May 01, 2012**
Date of Acceptance: **May 14, 2012**
Date of Publishing: **Jun 22, 2012**