Association of vitamin D deficiency and type II diabetes mellitus: a cross sectional study in a selected population of Karachi

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Abstract

Objective: To observe the association of serum vitamin D₃ with diabetes duration, anthropometric measurements and glycated haemoglobin levels in type II diabetics.

Methods: The cross-sectional study was conducted in 2010 at the National Institute of Dialectology and Endocrinology, Karachi, and comprised type II diabetic patients of either gender aged 20-60 years. Serum vitamin D₃ was determined by electro-chemiluminescence method. Vitamin D₃ <10ng/mL was considered deficient, 10-30 ng/mL insufficient, 30-100 ng/mL sufficient, and >100 ng/mL toxic. Glycated haemoglobin level was measured using high performance liquid chromatography with a linear range of 3–18%. Pearson correlation coefficient was used to evaluate the correlation of serum vitamin D₃ with glycaemic control and duration of diabetes. Data was analysed using SPSS 16.

Results: Of the 210 patients, 125(59.5%) were females. The overall mean age was 45.7±8 years, mean diabetes duration 7.8±3.7 years And mean body mass index was 28.76±3.87kg/m². On the basis of glycated haemoglobin level, 193(91.91%) revealed
uncontrolled diabetes. Vitamin D$_3$ concentration correlated inversely to glycaemic control (p<0.01).

**Conclusion:** Hypovitaminosis D$_3$ was observed in diabetic patients with increased body mass index, higher glycated haemoglobin and prolonged diabetes duration.

**Key Words:** Vitamin D$_3$, HbA1c, Type II diabetes, Anthropometry, Obesity.

**Introduction**

Diabetes mellitus (DM) is depicted by the presence of severe hyperglycaemia as a result of insulin deficiency which affects body systems as well as bone physiology and composition, and such patients may have more serious bone and joints problem if associated with 25-hydroxy vitamin D (vitamin D$_3$) deficiency$^{(1)}$. Vitamin D$_3$ deficiency has an affect on number of systems, resulting in disease production, disorders and manifestation of type 2 diabetes mellitus (T2DM)$^{(1)}$. However, upright skeletal health needs proper levels of Vitamin D$_3$ and calcium. Sufficient quantities also prevent autoimmune disorders, diabetes and there is less risk of malignancy and hypertension (HTN)$^{(1,2)}$.

It has been found that diabetics are more likely to be vitamin D$_3$-deficient than the non-diabetics. Many researchers have emphasised on the relationship of vitamin D$_3$ with the development and complications of DM$^{(2)}$. The possible mechanism of this association between vitamin D$_3$ and DM is due to the binding of activated circulating form (D$_3$) of vitamin D to the beta cell vitamin D receptors, which, in turn, regulate the extracellular calcium and calcium flux through these cells$^{(3)}$. This change in the calcium flux secondary to insufficient binding of vitamin D$_3$ may alter secretion of insulin by these cells$^{(3,4)}$. Vitamin D$_3$ keeps the normal resting levels of both calcium ions (Ca$^{2+}$) and reactive oxygen species (ROS) that are higher in the beta ($\beta$) cells during diabetes$^{(4)}$. Vitamin D$_3$ also has a very significant role in sustaining the epigenetic alterations called epigenome. When deficiency of vitamin D$_3$ is established, many of these processes start to drop and this triggers the commencement of disorders like DM$^{(5)}$. The current study was planned to observe the
association of serum vitamin D₃ with diabetes duration, glycated haemoglobin (HbA₁c) levels and anthropometric measurements among in T2DM patients.

**Patients and Methods**

The cross-sectional study was conducted in 2010 at the National Institute of Dialectology and Endocrinology (NIDE) along with the Dow Diagnostic Research and Reference Laboratory (DDRRL), Karachi. The study comprised patients of T2DM which was determined in the light of the American Diabetes Association (ADA) criterion(⁶) or of the International Diabetes Federation (IDF) criterion(⁷) After approval from the ethics review committee of the Dow University of Health Sciences (DUHS), Karachi, the sample size was calculated with 95% confidence interval (CI) and 5% bound of error(⁸). Elements taken were population size 1000,000; hypothesised per cent frequency of outcome factor in the population 83%; confidence limit as percentage of 100 (absolute +/- %); d)=5%; design effect for cluster surveys deff = 1; and level of precision formula² using the formula: (⁸)

\[
 n_0 = \frac{Z^2 p(1-p)}{e^2}
\]

Finite population correction factor (⁸)

\[
 n = \frac{nN}{n_0 + (N-1)}
\]

The study sample was raised using non-probability, convenience sampling, and comprised T2DM patients of either gender aged 20-60 years. Those excluded were pregnant and post-menopausal women, those with coexisting conditions like T1DM, cardiovascular diseases, tuberculosis (TB), kidney disorders, severe hepatic disorders, endocrine disorders, like parathyroid and thyroid dysfunction and those on anti-TB therapy. Written consent was taken from all the subjects.
Body Mass index (BMI) was calculated using weight in kilogram(Kg) divided by height in meter-square. Waist and hip measurements were done with the help of a measurement tape. The cases were classified using the Waist Hip Ratio (WHR) classification for Asians. Random blood sugar (RBS) was measured using automatic biochemical analyser (Hitachi 902). HbA1c was assessed with turbid metric inhibitor immunoassay using high performance liquid chromatography (HPLC) with a linear range of 3–18%. Serum vitamin D3 was measured with electro-chemiluminescence method. Vitamin D3 was measured in samples collected at the time of the subjects’ first visit to the clinic using enzyme-linked immunosorbent assay (ELISA) (Glory Science Co. Ltd.; Catalogue No. 95503). Manufacturer’s protocol was followed for detection. The intra-assay and inter-assay coefficient of variation (CV) for vitamin D3 was 2.7% and 4.3% respectively. The lowest limit of detection was 2pg/ml. Serum levels of Vitamin D3 <10ng/mL were considered deficient, 10-30ng/mL as insufficient, 30-100ng/mL as sufficient and >100ng/mL as toxic.

Data was analysed using SPSS 16. Pearson’s correlation coefficient was used to assess correlation between serum vitamin D3 levels and glycaemic control.

Results
Of the 210 patients, 125(59.5%) were females. The overall mean age was 45.7±8 years, mean diabetes duration was 7.8±3.7 years, mean BMI was 28.76±3.87kg/m², and mean WHR was 0.97±0.788 (Table). Also, 113(53.8%) subjects had T2DM for 5-10 years, and 54(25.7%) had it for <5 years. Mean HbA1c of the sample was 8.47±3.79 and 193(91.90%) had uncontrolled diabetes. Overall, 131(62.4%) patients were Vitamin D3-deficient and also had severely uncontrolled diabetes with a mean of 9.41±4.39. Also, 51(37.1%) patients who had insufficient level of Vitamin D3 had initial level of uncontrolled diabetes with a mean of 6.90±1.94. Only 1(0.5%) patients had sufficient vitamin D3 level as well as uncontrolled diabetes (7.50±0.0). Vitamin D3 levels were correlated inversely to glycaemic control and duration of diabetes (p<0.010) (Figure 1A-B).
Discussion

Vitamin D deficiency affects nearly half of the population globally and a predictable 1 billion people across ethnicities and ages suffer with hypovitaminosis D. This epidemic of Vitamin D₃ deficiency can mainly be attributed to lifestyle changes and environmental modification that decrease sun exposure which is vital for ultraviolet-B (UVB)-induced vitamin D₃ dermal synthesis (12). Low serum vitamin D₃ disturbs the cellular performance in pancreas that leads to the increased tendency to gain weight and T2DM. Hypovitaminosis D₃ has been associated with obesity, whether obesity is evaluated by BMI or waist circumference (WC). Central obesity, by means of waist as the substitute, is related with metabolic syndrome, resistance to insulin and T2DM(13). The current study analysed how vitamin D₃ is associated with anthropometric measurements, HbA₁c and duration of the disease in 210 adult samples of T2DM of different ethnicities in which the majority of the subjects were overweight and centrally obese.

In the past two decades, the incidence and prevalence of T2DM appear to be strongly linked with obesity(14,15). Adjusting with age, gender, BMI, physical exercise and whether changes, analysis revealed a strong inverse drift between the probability of rising T2DM and serum vitamin D₃ amongst white and Mexican Americans(14). This association was not seen amongst African Americans, signifying the ethничal dissimilarities in T2DM risk and vitamin D₃ deficit(14). Yet, the exact mechanisms linking both conditions are unclear(15). It is documented that obesity observed in more than 34% of American adults (BMI 30kg/m²), and over 11% of citizens aged >20 years have diabetes(15); a prevalence expected to go up to 21% by 2050(16). The pressure of obesity on risk of T2DM calculated by the extent of obesity and increased upper body visceral adiposity, which resulted in increased abdominal girth or WHR, showed high-degree association with T2DM(15).

The current study revealed mean HbA₁c of 8.47 and majority cases revealed uncontrolled diabetes as evaluated by HbA₁c measurement. Vitamin D₃ levels revealed significant inverse correlation to glycaemic control of diabetes in the study (-0.303). Vitamin D₃ status and
HbA1c described an inverse association in adult population of America\(^{(17)}\). Similar results were observed in overweight and obese adolescents in New Zealand\(^{(12)}\) and among British Caucasians\(^{(17,18)}\). An observational research has shown an association between low serum vitamin D\(_3\) and raised glycaemic levels and high threat for diabetes\(^{(19)}\). Raised HbA1c levels are associated with a low concentration of vitamin D\(_3\) in T2DM independent of the length of diabetes and its nephropathic complications\(^{(20)}\). The negative correlation of vitamin D\(_3\) with raised and extremely raised concentrations of HbA1c may point out that it is the long-term, rigorously atypical (carbohydrate) metabolism of T2DM and muscle insulin resistance that is associated with vitamin D\(_3\) deficiency\(^{(21)}\).

In the current study, it was observed that in T2DM cases, mean BMI of the sample was 28.76kKg/m\(^2\) which falls in the overweight range of BMI classification for Asian population\(^{(9)}\). Similar result was observed for WHR where mean WHR of the present study sample was 0.97 which falls in the centrally obese category of WHR classification for Asians\(^{(10)}\). Previously it was documented that there was inverse relationship of serum vitamin D\(_3\) to anthropometric measurements and determinants of T2DM (like increase waist and HbA1c) but not to adipose tissue mass or Metabolic syndrome by itself\(^{(13)}\). Another study concluded that Vitamin D\(_3\) deficiency was highly prevailing in morbidly obese people with diabetes compared with controls who did not achieve the criteria for this syndrome\(^{(22)}\). The researchers highlighted noticeable negative relationship between vitamin D\(_3\) and body mass over a wide range of BMI (from 18 to 56 kg/m\(^2\))\(^{(23)}\). Body size was a strong determinant of vitamin D\(_3\), with concentrations being suboptimal in most obese participants\(^{(18)}\). Increased risk for obesity and T2DM was found in immigrants with dark skin resettling to regions with cooler weather and it occurs simultaneously with the increased risk of Vitamin D\(_3\) deficiency\(^{(24)}\). A study found that vitamin D\(_3\) deficiency was significantly associated with BMI of at least 30kg/m\(^2\) in white women, but not in African American women\(^{(25)}\). Researchers also observed that in children, adolescents and adults, increased risk of vitamin D\(_3\) deficiency was detected in obese subjects, with racial variations dependent on the tool needed to assess the
adiposity. It is also revealed that percentage of body fat showed significant inverse relationship with Vitamin D₃, but a study explored the relationship of vitamin D₃ deficiency with increasing percentage of body fat and BMI of 30kg/m² and found it to be strongly significant in fair white females of all ages and non-significant in dark African American females <50 years²⁴. BMI has inverse correlation with high serum vitamin D₃ concentration after sun exposure of skin²³ and high serum vitamin D₂ levels after oral supplementation of vitamin D₂. This noticeable declining in vitamin D₃ bioavailability with increased adiposity may be due to the excessive accumulation of vitamin D₃ in fat²³.

The current study found that Vitamin D₃ levels had significant inverse correlation with the duration of diabetes (-0.250). It is documented that decreased serum vitamin D₃ concentration is frequently observed in Chinese patients of T2DM with peripheral neuropathy, retinopathy and nephropathy²⁶,²⁷. On account of impact of Vitamin D₃ deficiency on a number of organs, it is important that its complete screening should be undertaken in all patients with T2DM²⁸ (Figure 2).

The data of the study relates to almost a decade ago which is a major limitation. However, it has been able to establish an association of hypovitaminosis D₃ in diabetic patients with increased BMI, higher HbA₁c and prolonged diabetes duration, opening new pathways for the prevention of diabetes by correcting Vitamin D₃ levels. Well-designed large-scale prospective studies and randomised control trials (RCTs) are needed to clarify the role of vitamin D₃ as a surrogate marker for poor health status as well as to confirm its role in glucose metabolism, aetiology and progression / protection of T2DM.

**Conclusion**

Hypovitaminosis D₃ was associated with increased BMI, uncontrolled diabetes and prolonged duration of the disease. There is a need for screening vitamin D₃ levels in individuals with increased HbA₁c levels and central obesity.
Disclaimer: The text is part of a postgraduate thesis.

Conflict of Interest: None.

Source of Funding: None.

References


**Table: Anthropometric measurements (n=210)**

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Mean (±SD) (n=210)</th>
<th>Range (Min-Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (in cm)</td>
<td>162.651 (+9.13)</td>
<td>140-185</td>
</tr>
<tr>
<td>Weight (in kg)</td>
<td>61.271 (+9.24)</td>
<td>50-100</td>
</tr>
<tr>
<td>BMI (in kg/m²)</td>
<td>28.76 (+3.87)</td>
<td>19.53-43.28</td>
</tr>
<tr>
<td>Waist (in cm)</td>
<td>53.761 (+14.56)</td>
<td>33-85</td>
</tr>
<tr>
<td>Hip (in cm)</td>
<td>80 (+16.04)</td>
<td>56-110</td>
</tr>
<tr>
<td>WHR</td>
<td>0.97 (+0.788)</td>
<td>0.044-0.098</td>
</tr>
</tbody>
</table>

SD: Standard deviation; BMI: Body mass index; WHR: Waist-hip ratio; Cm: Centimetre, Kg: Kilogram; Kg/m²: Kilogram per square metre.

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**Figure 1(a): Correlation of vitamin D₃ with duration of diabetes (n=210)**

\[ r = -0.250^* \]

**Figure 1(b): Correlation of vitamin D₃ with HbA₁c (n=210)**

\[ r = -0.303^* \]

HbA₁c: Glycated haemoglobin.

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Provisionally Accepted for Publication
Figure 2: Effect of Vitamin D on pancreas and relationship of Vitamin D with Type II DM.
(Concept adopted from: Tom L. Van (2013), reference #26)