Role of Vitamin D3 in Manifestations of Endocrinological Disorders

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ABSTRACT
Introduction: Deficiency of vitamin D is also one of the factor involved in the occurrence of DM and Thyroid Disorders. The identification of 1,25(OH)2D receptors and 1-α-hydroxylase expression in pancreatic beta cells in cells of the immune system and in other tissues support the role of vitamin D in the pathogenesis of Diabetes Mellitus and thyroid disorders. Vitamin D mediates its effect through binding to vitamin D receptor (VDR), and activation of VDR-responsive genes. This study aims to assess the vitamin D3 levels among the diabetic and thyroid patients and to correlate the levels with the various blood sugar parameters and thyroid levels.

Methodology: It is a prospective observational study and was done for a period of 6 months. Data was collected from outpatient department of diabetes clinic. 634 patients blood samples were collected and assessed for serum concentrations of 25-hydroxyvitamin D (25(OH)D). We studied the prevalence of Diabetes Mellitus and thyroid based on patient records, past medical history, laboratory data and direct communication with patients.

Results: Among 634 patients, 37 % DM, 50.7 % hypothyroidism, 11.62 % hyperthyroidism patients were observed. Serum Vitamin D test was done for 80 patients and 75 patients were found with serum vitamin D less than 30ng/ml. Follow-up of 60 patients was done by comparing their lab values before and after vitamin D3 supplementation there was an improvement of disease conditions due to compliance of vitamin D3.

Conclusion: Decreased serum vitamin D3 with increased TSH levels was observed in hypothyroidism patients. In hyperthyroidism patients there was increase in T4 and decrease in TSH levels with decrease in serum vitamin D3 level. We found that Vitamin D supplements have significant control on Diabetes Mellitus and thyroid disorders biochemical values.

Keywords: Vitamin D Receptor, Thyroid stimulating hormone, Diabetes Mellitus, Thyroxin,25-hydroxyvitamin D.

INTRODUCTION

Vitamin D is essential for the maintenance of calcium and phosphorus homeostasis, skeletal growth and various other metabolic processes. The major source of vitamin D for humans is exposure to sunlight. The prevalence of vitamin D deficiency in India is 50-90% in various studies. Factors such as slow sunlight exposure, age-related decrease in cutaneous synthesis, and low dietary intake of vitamin D contribute to the high prevalence of vitamin D inadequacy which has emerged as a highly pervasive condition.[1] Bone diseases such as rickets in children, osteomalacia and osteoporosis in adults are related with vitamin D insufficiency. Literature evidence show that low vitamin D levels are also related to increased risk of falls, fractures, muscle pain, muscle weakness, cardiovascular risk, diabetes mellitus, Thyroid disorders, Poly Cystic Ovary Syndrome (PCOS), infections, and autoimmune disorders also. Adequate intake of vitamin D is necessary for all individuals of any age group.[1] It has been suggested that ~ 5–30 minutes of sun exposure between 10:00 a.m. and 3:00 p.m at least twice per week on face,
arms, back and legs (without sunscreen) is usually adequate for vitamin D synthesis,[2,3] also by taking food fortification and routine supplementation can fulfill the deficiency of vitamin D.

**Clinical understanding of Vitamin D:** There are two main forms of vitamin D: ergocalciferol (vitamin D$_2$) and cholecalciferol (vitamin D$_3$). Vitamin D$_2$ is synthesized by plants (mainly mushrooms and yeast), whereas vitamin D$_3$ is synthesized in the skin when it is exposed to ultraviolet B rays from sunlight. Vitamin D$_3$ is also found in a few foods such as fish.[4]

Vitamin D, as either D$_3$ or D$_2$, does not have significant biological activity. Rather, it must be metabolized within the body to the hormonally-active form is known as 1,25-dihydroxycholecalciferol. This transformation occurs in two steps:

1) Within the liver, cholecalciferol is hydroxylated to 25-hydroxycholecalciferol by the enzyme 25-hydroxylase.

2) Within the kidney, 25 hydroxycholecalciferol serves as a substrate for 1-alpha-hydroxylase, yielding 1,25-dihydroxycholecalciferol, the biologically active form.

Each of the forms of vitamin D is hydrophobic, and is transported in the blood bound to carrier proteins. The major carrier is vitamin D-binding protein. The half-life of 25-hydroxycholecalciferol is several weeks, while that of 1,25-dihydroxycholecalciferol is only a few hours.[5,6]

**Role of vitamin D in Diabetes Mellitus and Thyroid disorders:** Vitamin D may improve pancreatic β-cell function, decrease insulin resistance, and improve systemic inflammation. Vitamin D directly acts on pancreatic β - cells by binding β-cell vitamin D receptor to produce insulin and to improve insulin action by reducing insulin resistance. Further, it indirectly improves insulin production and its action by increasing the level of calcium inside the cells, which is essential for insulin-mediated intracellular processes in insulin-responsive tissues such as skeletal muscles and adipose tissues. Vitamin D also increases insulin sensitivity and β - cell survival by modulating the generation and effects of cytokines which play an important role in β-cell dysfunction by triggering β-cell apoptosis.

Evidence indicates that vitamin D treatment improves glucose tolerance and insulin resistance.[8,9] Vitamin D deficiency leads to reduced insulin secretion. Supplementation with vitamin D has been shown to restore insulin secretion in animals.[10] Researchers have also found an indirect effect on insulin secretion, potentially by a calcium effect on insulin secretion. Vitamin D contributes to normalization of extracellular calcium, ensuring normal calcium flux through cell membranes; therefore, low vitamin D may diminish calcium’s ability to affect insulin secretion.[11]

One of the two mechanisms may explain the low levels of vitamin D in patients with hypothyroidism. First, the low levels of vitamin D may be due to poor absorption of vitamin D from the intestine. Second, the body may not activate vitamin D properly.[12] Other articles have demonstrated that patients with Graves’s disease also have low levels of Vitamin D. Importantly, both vitamin D and thyroid hormone bind to similar receptors called steroid hormone receptors. A different gene in the Vitamin D receptor was shown to predispose people to autoimmune thyroid disease including Graves’ disease and Hashimoto’s thyroiditis.[13,4]

The most accurate way to determine vitamin D status is to measure 25-hydroxy vitamin D [(25(OH)D)]. The optimal range is 25–80 ng/ml. However, normal value ranges may vary slightly among different laboratories.[13]

The Food and Nutrition Board of the Institute of Medicine (IOM) recently updated the Dietary Reference Intake (DRI) for vitamin D.[15,16] The IOM recommends 600 IU/day of vitamin D for individuals aged 9–70 years and 800 IU/day for those > 70 years of age. However, others recommend that supplementation with vitamin D$_3$ should be prescribed with the objective of achieving a serum 25(OH)D level of at least 40 ng/ml and possibly even 60 ng/ml.[17]

The following are recommendations for vitamin D in the DRIs developed by the Food and Nutrition Board at the Institute of Medicine. DRI is the general term for a set of reference values used to plan and assess the nutrient intake of healthy people. These values, which vary by age and sex, include:

Recommended Dietary Allowance (RDA): average daily level of intake sufficient to meet the nutrient requirements of nearly all (97–98%) healthy people
Adequate Intake (AI): established when evidence is insufficient to develop an RDA and is set at a level assumed to ensure nutritional adequacy.\(^{[15,16]}\)

The aim of our study was to determine the level of vitamin D\(3\) in diabetic and thyroid patients and to study the relationship between 25(OH)D\(3\) levels, glycemic control and Thyroid Hormones levels in the group of patients.

**MATERIALS AND METHODS**

This study was conducted in a Samraksha endocrine Super speciality Hospital and research center. It is an observational study conducted in an outpatient (OP) department to assess the role of vitamin D. The study was performed on 634 patients for a period of 6 months. Inclusion criteria were patients who are willing to take part in the study, patients with complete and accurate diagnosis and patients whose condition is chronic. Any disorder except diabetes such as osteomalacia, osteoporosis, inflammatory rheumatism and patients treated with corticosteroids, using drugs which interfere with vitamin D metabolism such as carbamazepine, Phenobarbital, sodium valporate, gabapentin, isoniazid, mineral oil and calcitonin were excluded.

Vitamin D level was measured with quantitative ELISA using IDS kit. It is based on chemiluminescencetechnology. The assay was performed on the IDSiSYSMulti-Discipline Automated Analyzer. 10 μL of serum aliquots were automatically pipetted and subjected to a pre-treatment step with NaOH (part of the reagent used for CLIA and ELISA methods) to denature the DBP inside the IDS-iSYS Multi-Discipline Automated Analyzer. The extraction procedure of 25(OH)D from the DBP was followed by analysis. This assay is not aligned to the NIST SRM(NIST, Gaithersburg, Maryland). The measurement range of this assay is 5-140 ng/ml.

Vitamin D deficiency was defined as serum 25(OH) D concentration of less than 20ng/ml, insufficiency as 20ng/ml <25(OH) D<30 ng/ml and sufficiency were defined as 25(OH) D higher than 30 ng/ml (15). The data were collected and analyzed, to determine the difference in vitamin D levels, before and after treatment of vitamin D3 in diabetes and thyroid groups.

**RESULTS**

Among 634 patients, were female 24.60%, were male 75.39 %. Of the total patients, 21-40 age group (38.01 %) shows high vitamin D deficiency conditions compared to 3.61 % in >20 age groups, 27.7 % in 41-60 age groups and 3.31 % in 61-80 age groups.

Of 80 patients who cooperated for serum vitamin D levels test, 75 patients had serum vitamin D\(3\) less than 30ng/ml. Of 75 patients, 25(31.25%) were male and 50(62.5 %) were female.

During the study period, the total number of patients collected was 634, of which Serum Vitamin D test was done for 80 patients. The highest percentage of patients (65%) was seen between (10-30ng/ml). Serum vitamin D level was found in normal only 6.25% patients (25-80 ng/ml) and 23 % patients had showed (<10 ng/ml).

Of 80 patients, 15 were male 45 were female and 27 had Diabetes Mellitus, 28 had hypothyroidism and 5 had hyperthyroidism. After serum vitamin D level test, vitamin D were given to these patients shows significant improvement in hypothyroidism patient (46.66 %) than in Diabetes Mellitus (45 %) and hyperthyroidism patients (8.33%).

Lab values before supplementation of vitamin D\(3\) and after supplementation of vitamin D\(3\) were compared, there was an improvement of disease conditions due to compliance of vitamin D\(3\) supplements and there was no improvement in disease condition in those patients who didn’t take any vitamin D\(3\) supplementation.

**DISCUSSION**

**Diabetes mellitus:**

As there was no improvement in disease condition of 217 type II DM patients, clinician prescribed vitamin D supplements. After four weeks of vitamin D treatment, we observed that there was significant reduction in blood sugar levels.

As vitamin D affects multiple organs in the body no specific symptoms can be ascertained to its deficiency as serum vitamin D estimation is expensive majority of physicians and patients don’t opt for testing. Hence there is an urgent need for the development of alternate cheaper methods for vitamin D\(3\) screening which can help in the improvement of better patient health care.
These observation are similar to the study conducted by Mohammad Ali Bayani et al.,[18]. Among 120 diabetic patients, the vitamin D level was deficient in 77 patients (64.2%), insufficient in 30 (25%) patients and sufficient in 13 (10.3%) patients. In the healthy group, 44 (36.6%) patients had a deficiency of vitamin D, 46 (38.4%) patients with insufficiency of vitamin D and 30 (25%) patients had a sufficiency of vitamin D. The incidence of prevalence is high in deficiency diabetic patients compare to insufficiency and sufficient.

Majority of our patients were of the age group 45-75 years. In our study out of 202 patients, 45.04% were having vitamin insufficiency, 3.96% had a sufficiency of vitamin D and 60.89% are suffering from vitamin D3 deficiency.

These results are in contrast to the study conducted by Kirubhakaran Kanakaraju et al.,[19]. Minimum age among the study subjects was 34 years and the maximum age was 70 years. The male and female subjects were almost equal in number and the mean age among the male was 53.25 and among the female, it was 55.15 years. Majority of the study subjects were of the age group 50 – 70 years. In this study, the prevalence of severe vitamin D3 deficiency was found to be 37% and 58% of the subjects had insufficient levels of vitamin D3, only 5% of them had normal levels of vitamin D3 and the mean vitamin D3 level was 14.16 ng/dl. There are several lines of evidence to support that vitamin D3 influences impaired β-cell function, Insulin Resistance and Systematic Inflammation. It has been demonstrated that vitamin D3 receptors exist in many tissues including pancreatic β-cells, allowing vitamin D3 to potentially modulate the insulin response to elevated blood glucose.

Thyroid Disorder:

As there was no improvement in disease condition of 363 patients who were suffering from hypothyroidism, 69 patients with hyperthyroidism, clinician prescribed vitamin D supplements for 294 (80.9%) hypothyroidism patients and 37 (10.19%) hyperthyroidism patients. After four weeks of vitamin D treatment, we observed that there was significant improvement in T3, T4 & TSH levels in thyroid patients.

These results are similar to the study conducted by Amal Mohammed Husein Mackawy et al.,[20]. By using the t-test to compare between the two groups, serum 25(OH) Vitamin D level group I(44.53 ± 14.91) group II (14.79 ± 2.11) was significantly lower in hypothyroid patients than in controls (t= -11.128, P=0.000). On comparing serum 25 (OH) Vitamin D levels according to the sex distribution in group I (13 male (43%) 17 female (57%)) and group II(12 Male (40%)18 Female (60%)), they were insignificantly decreased in female than those of male in controls and hypothyroid patients (t= -0.160, and t= -1.32, P>0.05). This shows slightly increased levels in female when compared to low levels in male. Abnormal thyroid function is due to lack of autoantibody detection or iodine deficiency and radiation exposure or idiopathic.[21]

In our study of 363 subjects with Thyroid Disease are observed under the supervision of Endocrinologist 90.9% (330/363) of the patients were prescribed with vitamin D.

45 patients cooperated for vitamin D test among them 33 patients (73%) showed improvement in disease condition after giving vitamin D supplements. This shows the majority of the thyroid patients are having a low level of vitamin D, and by comparing the levels of TSH before and after follow-up, improvement is seen.

These results are in contrast to another study conducted by Shaye Kivity et al.,[22] Serum samples were collected from 92 patients who were suffering from thyroid disorders. 63% (58/92) of them were diagnosed with Vitamin D Deficiency.

In our study, out of 363 thyroid patients, 80 patients are co-operate for serum vitamin D test in that follow-up of 60 patients are divided into male were 2 and female were 31 have 20-50 ng/ml. This shows improvement in disease condition and T3, T4 and TSH levels.

These results are similar to the study of Shaye Kivity et al.,[22] 28 patients have cooperated for the test. As part of the results it was observed that 2 Males and 26 Females had vitamin D level < 5-10 ng/ml and abnormal thyroid Function increase in TSH levels (<0.005 >100). But after supplementation of vitamin D patients had an increase in vitamin D level as greater than 24-50 ng/ml and a drop in TSH levels.
(<0.01-23.44). This shows Vitamin D and thyroid hormone bind to similar receptors called steroid hormone receptors. A different gene in the Vitamin D receptor was shown to predispose people to autoimmune thyroid disease including Graves’ disease and Hashimoto’s Thyroiditis.

CONCLUSION

Decreased serum vitamin D₃ with increased TSH levels was observed in hypothyroidism patients. In hyperthyroidism patients there was increase in T₄ and decrease in TSH levels with decrease in serum vitamin D₃ level. We found that Vitamin D supplements have significant control on Diabetes Mellitus and thyroid disorders biochemical values.

Clinical pharmacist can play a vital in explaining the importance of regular intake of vitamin D and encourage patients and caretakers to undergo serum vitamin D test periodically for better control of endocrine disorders and have a good quality of life.

REFERENCES

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16. Institute of Medicine, Food and Nutrition Board Vitamin D deficiency 2012.


### TABLES AND FIGURES

#### Table 1: Categorization of vitamin D levels in blood

<table>
<thead>
<tr>
<th>Vitamin D Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>25–80 ng/ml</td>
<td>Optimal levels</td>
</tr>
<tr>
<td>10–24 ng/ml</td>
<td>Mild to moderate deficiency</td>
</tr>
<tr>
<td>&lt; 10 ng/ml</td>
<td>Severe deficiency</td>
</tr>
<tr>
<td>&gt; 80 ng/ml</td>
<td>Toxicity possible</td>
</tr>
</tbody>
</table>

#### Table 2: Recommended intake of vitamin D in different age groups

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Recommended Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants:</td>
<td></td>
</tr>
<tr>
<td>0–6 months:</td>
<td>AI: 400 IU (10 g/day)</td>
</tr>
<tr>
<td>7–12 months:</td>
<td>AI: 400 IU (5 g/day)</td>
</tr>
<tr>
<td>Children:</td>
<td></td>
</tr>
<tr>
<td>1–3 years:</td>
<td>600 IU (15 g/day)</td>
</tr>
<tr>
<td>4–8 years:</td>
<td>600 IU (15 g/day)</td>
</tr>
<tr>
<td>Older Children and Adults</td>
<td></td>
</tr>
<tr>
<td>9–70 years:</td>
<td>600 IU (15 g/day)</td>
</tr>
<tr>
<td>Adults:</td>
<td></td>
</tr>
<tr>
<td>70 years:</td>
<td>800 IU (20 g/day)</td>
</tr>
<tr>
<td>Pregnancy and lactation:</td>
<td>600 IU (15 g/day)</td>
</tr>
</tbody>
</table>

#### Table 3: Data showing improvement in biochemical values before and after treatment with vitamin D₃
<table>
<thead>
<tr>
<th>S.No</th>
<th>Lab test</th>
<th>Range of Lab values Before supplementation of vitamin D&lt;sub&gt;3&lt;/sub&gt;</th>
<th>Range of Lab value after supplementation of vitamin D&lt;sub&gt;3&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25(OH)D3</td>
<td>5-21.45ng/ml</td>
<td>24.53-33.23ng/ml</td>
</tr>
<tr>
<td>2</td>
<td>TSH</td>
<td>&lt;0.005-&gt;100 mIU/L</td>
<td>&lt;0.01-23.44 mIU/L</td>
</tr>
<tr>
<td>3</td>
<td>T3</td>
<td>0.66-5.5ng/dl</td>
<td>0.83-1.84 ng/dl</td>
</tr>
<tr>
<td>4</td>
<td>T4</td>
<td>3.67-18.44µg/dl</td>
<td>3.66 -11.89 µg/dl</td>
</tr>
<tr>
<td>5</td>
<td>RBS</td>
<td>79-397 mg/dl</td>
<td>75-255 mg/dl</td>
</tr>
<tr>
<td>6</td>
<td>PLBS</td>
<td>127-587 mg/dl</td>
<td>116-377 mg/dl</td>
</tr>
</tbody>
</table>

**Figure 1:** Chart showing distribution of patients according to serum vitamin D levels

**Figure 2:** Gender wise improvement in disease condition after vitamin D<sub>3</sub> supplements