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Original Research Article

A study of the effects of large dose of parenteral vitamin D (D3) on insulin resistance in type 2 DM patients

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ABSTRACT

Background: Over the past decade, vitamin D is more known as a hormone because of its extra - skeletal outcomes in various disease conditions, including diabetes. Most cells, including the pancreatic β-cells, contain the vitamin D receptor and they also have the capability to produce the biologically active 1,25-dihydroxyvitamin D [1,25(OH)2D3] which allows intracrine and paracrine functions. In vitro studies have shown that the active vitamin D metabolite 1,25(OH)2D stimulated insulin release by the pancreatic β-cells. Vitamin D is known to have immune modulatory and anti-inflammatory effects and reduces peripheral insulin resistance by altering low-grade chronic inflammation. This study was done to assess whether supplementation of vitamin D in type 2 diabetes mellitus (T2DM) patients with Vitamin D deficiency has any favourable effect on insulin resistance.
Methods: It was a short term interventional study conducted at ASCOMS hospital Jammu including a total of 50 vitamin D deficient [25(OH) D <50 nmol/l] T2DM patients with an in-adequate glycemic control (HbA1c > 7.0%). All the 50 study participants completed the study and there were no changes either in anti-hyperglycemic drugs (including insulin) or antihypertensive drugs being used. After supplementation with a single high dose (600000 IU) of parenteral vitamin D3 changes in HOMA-IR (Homeostasis model assessment insulin resistance) were seen on follow up at 3 months.
Results: Vitamin D3 supplementation improved insulin sensitivity, HOMA-IR decreased from 4.05±1.42 to 3.93±1.28 (p =0.011). It decreased equally in males (3.85±1.43 to 3.76±1.30) (p value=0.023) and females (4.24±1.42 to 4.10±1.27) (p value=0.021). HOMA-IR showed negative association with Vitamin D levels both at baseline and after 3 months of follow up.
Conclusions: This improvement in insulin sensitivity is evidenced in our study by decrease in fasting insulin levels (FIL) and improvement in fasting blood sugars (FBS). It is due to both direct and indirect effects of Vitamin D3 on both insulin sensitivity and secretion.

Keywords: Fasting blood sugar, Fasting insulin levels, Homeostatic model for assessment of insulin resistance, Glycosylated hemoglobin, Type 2 diabetes mellitus

INTRODUCTION

Changes in human behavior and lifestyle in the last century have caused a great increase in prevalence of type 2 diabetes mellitus as well as that of deficiency of Vitamin D worldwide, both now threatening as global epidemics. Several potential mechanisms involving vitamin D might affect glycemic control in patients with type 2 diabetes.[1] The presence of vitamin D receptors (VDRs) in β-cells of the pancreas and their expression of 1-α-hydroxylase enzyme signifies the influence of Vitamin D in insulin secretion.[2,3] 1,25-(OH)2D activates transcription of the gene of human insulin and thus play

an essential role in insulin secretion besides its regulatory role in maintaining calcium pool of β-cell.[4] Another plausible mechanism is whereby low vitamin D status induces secondary hyperparathyroidism (SHPT). The raised parathyroid hormone (PTH) inhibits insulin synthesis and secretion in β-cells and insulin resistance in target cells by regulating intracellular calcium.

It is currently recognized that T2DM is associated with systemic inflammation being primarily to insulin resistance, but elevated cytokines may also play a role in β -cell dysfunction by triggering β-cell apoptosis. Vitamin D is thought to modulate the expression and activity of cytokines and protect the β-cell against cytokine-induced apoptosis. There is down-regulating of Fas-related pathways (Fas/Fas-L) which has an anti-apoptotic effect on beta cells.[5] Other immune modulating effects of vitamin D include blockade of dendritic cell differentiation, inhibition of lymphocyte proliferation, enhanced regulation of T-lymphocytes, development and down- regulation of cytokine expression. These immune modulatory effects of vitamin D might provide additional protection against inflammation -triggered worsening of insulin resistance and potentially β-cell dysfunction. Specifically, to insulin insensitivity, vitamin D was demonstrated to under-regulate the activation of nuclear factor-κB which plays a regulatory role for genes of cytokines of pro-inflammation implied in resistance of insulin.[6] Vitamin D enhances insulin sensitivity by stimulating the expression of insulin receptors and by activating peroxisome proliferator- activated receptor-δ (PPAR- δ).[7]

METHODS

This study was carried out in Post Graduate Department of Medicine ASCOMS and Hospital Jammu. We enrolled 50 patients of T2DM with Vitamin D deficiency and inadequate glycemic control. Patients fulfilling the inclusion criteria were apprised of the type of study being carried out and their written consent was obtained. Vitamin D 25(OH)D, fasting blood sugar and fasting insulin levels were obtained at the baseline. HOMA- IR was calculated using the published HOMA formula, HOMA-IR= [fasting glucose (mmol/L) ×insulin (μIU/mL)] / 22.5. One single dose 600000-unit vitamin D3 was given intramuscularly and changes in HOMA-IR were seen on follow up at 3 months. The descriptive statistics were used in accordance with the level of variable measurements. Cohen's D was used to estimate the effect size of the variables, association between the variables was estimated through Pearson's correlation coefficient, with their significance levels and the relationship between dependent variables with one or more independent variables was estimated by linear regression model. The level of significance for all analyses was set at $p < 0.05$. All analyses were performed using the statistical package for Social Science (SPSS for windows version 16, SPSS Inc, Chicago, IL).

RESULTS

Study included a total of 50 vitamin D deficient [25(OH) D <50 nmol/l] T2DM patients with an inadequate glycemic control. 30 out of 50 participants (60%) were above 50 years of age. After supplementation with single high dose of 600000 IU of parenteral Vitamin D3, 25(OH) D levels increased from 33.34±4.19 to 56.12±4.70 nmol/l) (p value <0.001) (Table 1).

Fasting insulin levels decreased from 13.46±4.68 mU/L to 13.19±4.34 mU/L in all cases over 3 months. This decrease in FIL was highly significant with p value of 0.003.FIL decreased both in males (12.53±4.28 to 12.31±3.96) (p value=0.047) and females (14.39±4.97 to 14.06±4.59) (p value=0.031) (Table 2).

Table 1: Vitamin D levels in all patients before and after supplementation.

Variables	Mean±SD		Cohen's d	95% CI	p-value	Remarks
	Vit. D (basal)	Vit. D (3 months)				
All cases	33.34±4.19	56.12±4.70	5.117	4.067 to 6.162	0.0001	S
Male	33.99±4.10	56.58±4.89	5.815	4.130 to 7.490	0.0001	S
Female	32.70±3.94	55.65±4.55	4.566	3.219 to 5.902	0.0001	S

Table 2: Fasting insulin levels in all patients before and after vitamin D supplementation.

Variables	Mean±SD		Cohen's d	95% CI	p-value	Remarks
	FIL (basal)	FIL (3 months)				
All cases	13.46±4.68	13.19±4.34	-0.457	-0.776 to -0.163	0.003	S
Male	12.53±4.28	12.31±3.96	-0.421	-0.825 to -0.006	0.047	S
Female	14.39±4.97	14.06±4.59	-0.488	-0.899 to 0.069	0.031	S

Table 3: Fasting blood sugar levels in all patients before and after vitamin D supplementation.

Variables	Mean±SD		Cohen's d	95% CI	p-value	Remarks
	FBS (basal)	FBS (3 months)				
All cases	121.9±6.5	120.9±6.3	-0.4	-0.7 to -0.1	0.010	S
Male	123.8±6.4	123.0±5.4	-0.4	-0.9 to -0.0	0.036	S
Female	119.9±6.1	118.8±6.6	-0.4	-0.8 to -0.0	0.038	S

Table 4: Homeostatic model for assessment of insulin resistance changes in all patients.

Variables	Mean±SD		Cohen's d	95% CI	p-value	Remarks
	HOMA-IR (basal)	HOMA-IR (3 months)				
All cases	4.05±1.42	3.93±1.28	-0.505	-0.797 to -0.208	0.011	S
Male	3.85±1.43	3.76±1.30	-0.504	-0.916 to -0.082	0.023	S
Female	4.24±1.42	4.10±1.27	-0.516	-0.929 to -0.093	0.021	S

FBS levels decreased in all cases from 121.9±6.5 to 120.9±6.3 mg/dl (p value=0.010). In males FBS improved from 123.8±6.4 to 123.0±5.4 (p=0.036) and in females from 119.9±6.0 to 118.8±6.6 (p value=0.038) (Table 3).

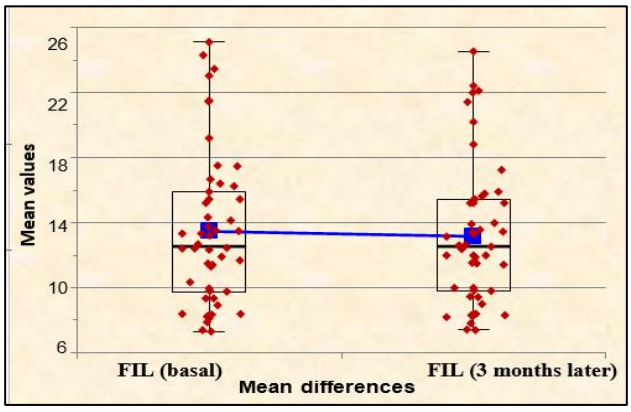

Figure 1: Mean differences of fasting insulin levels after vitamin D supplementation.

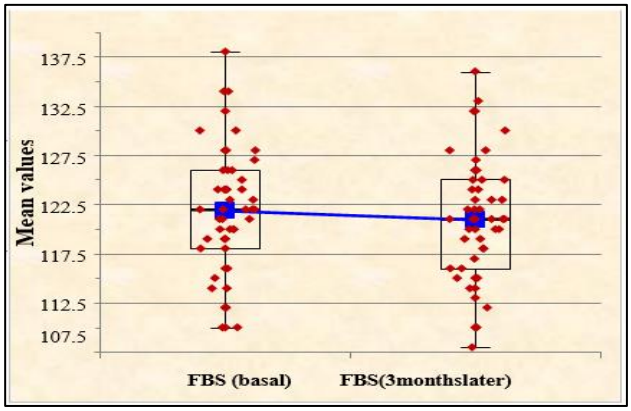

Figure 2: Mean differences of fasting blood sugars after vitamin D supplementation.

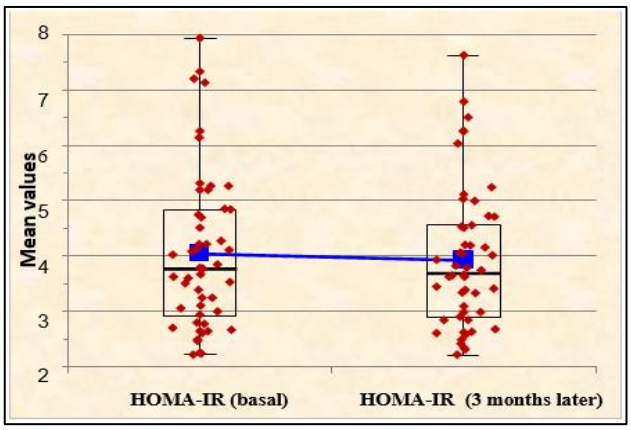

Figure 3: Mean differences in HOMA-IR after vitamin D supplementation.

There was a significant treatment effect on HOMA-IR which decreased from 4.05±1.42 to 3.93±1.28 (p =0.011). It decreased equally in males (3.85±1.43 to 3.76±1.30) (p value=0.023) and females (4.24±1.42 to 4.10±1.27) (p value=0.021). HOMA-IR had a positive association with age (p value<0.0001), both at baseline and at 3 months and shows negative association with vitamin D levels both at baseline and after 3 months of follow up (Table 4).

DISCUSSION

As T2DM is associated with systemic inflammation being primarily to insulin resistance, vitamin D has a role in Immunomodulation and its anti-inflammatory effects include both forms of immunity.[8] VDRs are found in activated dendritic cells, macrophages and lymphocytes .Immune modulating effects of vitamin D include blockade of dendritic cell differentiation, inhibition of lymphocyte proliferation, enhanced regulation of T-lymphocytes, development and down- regulation of cytokine expression.[9] These immune modulatory effects

of vitamin D might provide additional protection against inflammation -triggered worsening of insulin resistance and potentially β-cell dysfunction.

Associations between low vitamin D levels and T2DM have been reported in cross- sectional and observational studies.[10] These studies have examined the association between serum 25(OH)D concentrations and prevalence of T2DM. Most studies have reported an inverse association between 25(OH)D levels and T2DM.Large population-based studies such as the Third National Health and Nutrition Examination Survey (NHANES III) have disclosed a positive relationship between serum 25(OH)D3 levels and insulin sensitivity. These studies using NHANES III data have confirmed inverse associations between serum 25(OH)D3 concentrations and fasting hyperglycemia as well as insulin resistance.[11] Besides there are prospective studies on the association between T2DM and vitamin D status in one of the largest prospective studies, the Nurses' Health Study (USA), women with the highest vitamin D intake, i.e. greater than 800 IU/day, had 33% lower risk of incident diabetes compared to women with intakes of less than 200 IU/day. Intervention studies on the effect of vitamin D supplementation on T2DM like Jehle S et al and Tabesh M et al show improvement of insulin secretion six months after supplementation of vitamin D in vitamin D deficient T2DM subjects.[12,13]

From 50 diabetic patients included in study, 34 patients used oral hypoglycemic drugs and 16 were on insulin.30 out of 50 participants (60%) were above 50 years of age This is in accordance to the epidemiological evidence of hypovitaminosis D being more prevalent in elderly because they produce 75% less cutaneous vitamin D3 than young adults. After supplementation with parenteral Vitamin D3 circulating levels of 25-hydroxy vitamin D were adequate in patients at follow up.

So, cholecalciferol via intramuscular route has effective and immediate response. This study shows significant improvement in fasting blood sugar levels which is an evidence of glycemic improvement. FBS levels decreased in all cases from 121.9±6.5 to 120.9±6.3 mg/dl (p value=0.010). There was a significant decrease in insulin resistance after 3 months as HOMA-IR decreased from 4.05±1.42 to 3.93±1.28 (p =0.011). This improvement in insulin sensitivity is evidenced in our study by decrease in fasting insulin levels and improvement in fasting blood sugars. It may be due to both direct and indirect effects of Vitamin D3 on both insulin sensitivity and secretion which have been investigated largely in animal and in-vitro studies. Vitamin D may increase transcriptional activation and expression of the insulin receptor gene, which facilitates both basal and insulin-stimulated glucose oxidation resulting in improved insulin sensitivity.[14] HOMA-IR has a positive association with age (p value<0.0001), both at baseline and at 3 months. This is because of increase in insulin resistance with chronological age.[15] HOMA- IR shows negative association with vitamin D levels both at baseline and after 3 months of follow up. This association again is an evidence for role of vitamin D deficiency in insulin resistance.

CONCLUSION

This study is a prospective interventional study and no potentially confounding concomitant medication changes were made during the observation period. The findings of our study have potentially important public health implications. The modest effect of vitamin D supplementation on insulin sensitivity in individual persons can translate to a dramatic effect in the population as a whole because of the high prevalence of hypovitaminosis D. This study encourages the design and conduct of studies that further explore the roles of Vitamin D in insulin resistance of T2DM patients for longer durations of follow up.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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