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Vitamin D Supplementation in Alleviation of Oxidative Stress among Type 2 Diabetics

Nadia Begum[1,2*], Mahbuba Kawser[1], Sheikh Khalid Saifullah Sadi[1], Monowar Ahmad Tarafdar[2], Sheikh Nazrul Islam[1]

[1]Institute of Nutrition and Food Science, University of Dhaka, Dhaka, Bangladesh
[2]Department of Community Medicine. Z.H Sikder Women's Medical College, Dhaka, Bangladesh

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ABSTRACT: *Globally diabetes mellitus (T2DM) is a burning issue. Prediction of global estimation that the proportion of diabetes with adult will increase 69% for the year 2030. Hans Selye, the Canadian physiologist, was the first scientist to study the effects of psychological stress on the human body in 1936.Diabetic patients are in a state of high oxidative stress which leading to impaired glucose homeostasis, insulin insufficiency, and other complications.***:** *A randomized controlled trial was conducted to see the effect of the vitamin D supplementation on oxidative stress in vitamin D deficientT2DM patients. In this study, a total of 124 T2DM patients were randomly enrolled, among them Treatment group 61 and placebo 63. In treatment group received 20,000IU vitamin D every 5thDay for three months in addition to regular treatment. Analysis of fasting plasma glucose (FPG), Vitamin D 25(OH)2, malondialdehyde (MDA) and superoxide dismutase (SOD) have been estimated both at the time of study recruitment, at 6th weeks and after 12-weeks of vitamin D supplementation (endline). Present study showed after vitamin D supplementation, baseline mean FBG gradually significantly (P<0.001) decreased at the end line in treatment group as compared to placebo. All biochemical indices by P- trend like FBG, vitamin D, MDA and SOD were significantly different (P<0.05). Whenever, consider between groups vitamin D increased (P<0.05) and FBG decreased significantly (P<0.05) in treatment group as compared to placebo. However, no significant impact on socio-demography variables, vitamin D and Stress-related characteristics between treatment and control groups after vitamin D supplementation as those variables are somewhat independent (p>0.05) both at baseline and end line. The results were considered significant at P<0.05. The statistical calculations were done using SPSS version 26 software. A strong positive co-relation between diabetes and oxidative stress were observed in this study and showed beneficial impact of vitamin D supplementation to reduce oxidative stress those who were vitamin D deficient.*

KEYWORDS: Type 2 Diabetes, Vitamin D deficiency, Oxidative Stress.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic endocrine disease characterized by an inability to maintain normal glucose homeostasis that results from an alteration of the insulin secretion or action or both. This insulin helps for the uptake of glucose in the body. Sometimes, the pancreas fails to produce adequate amounts of insulin in relation to the carbohydrates intake and sometimes the release of insulin may adequate, but the body becomes resistant to response of that insulin. Generally, T2DM can be controlled through 3D like drug, diet and discipline which stimulate hormone production or reduce insulin resistance. In secondary pancreatic failure cases insulin therapy is required as treatment purpose.[1]

Oxidative stress denotes as imbalance between free radical production and antioxidants defense mechanisms.[3]Vitamin D deficiency plays a key role in the development of impaired glucose tolerance, type 2 diabetes mellitus (T2DM), and metabolic syndrome. This study attempted to investigate vitamin D supplementation in alleviation of oxidative stress in T2DM patients. In Diabetes Mellitus, oxidative stress is due to an increased formation of plasma-free radicals and a reduction in antioxidant defenses or both. Hyperinsulinemia and hyperglycemia may enhance the production of free radicals and induce oxidative stress which plays a key role in insulin resistance, impaired insulin secretion, and many of the complications of diabetes such as micro-/macro-vascular damage. Antioxidant enzymes like Superoxide dismutase (SOD) that protect the body against active oxygen-free radicals.[4]Vitamin D deficiency, the most prevalent micronutrient deficiency, has been associated with insulin resistance in diabetes and its late complications,[5]which accounts for premature mortality, social and economic burden in the long term diabetes.[6]

METHODS AND MATERIALS

This study was a single blind randomized clinical trial among vitamin D deficient type 2 diabetic patients aged 30-70 years who were vitamin D deficient. It was conducted among 61 diabetics who received vitamin D tablets and 63 diabetics who received placebo. Ethical approval was taken from the ethical review committee of the Biological Faculty, University of Dhaka, Bangladesh. Tab Cholecalciferol (D-Rise) USP 20,000 IU (Beximco Pharmaceuticals) was supplemented to the "Treatment group" for every 5thday for 12 weeks. Placebo group received placebo simultaneously along with treatment group.

Outcome measures and testing methods:

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Blood analysis	Method	Reference
Plasma Fasting Blood Glucose	Enzymatic method (Hexokinase-mediated reaction) by Hexokinase (Roche Diagnostics, Switzerland) through Roche/Hitachi Cobas c 311/501 Analyzer mechine	T.A. Alaidarous.2020[7]
Serum Vitamin D	Chemiluminescence Microparticle Immunoassay (CMIA) by ARCHITECT (Abbott Laboratories, Lake Forest, IL, USA) through Architect4100 mechine	K. Hutchinson.2017[8]
MDA and SOD	Spectrophotometric methods	

RESULTS

Characteristics	Total(N=124)	TreatmentN=61)	Placebo(N=63)	p-value
Age in years (Mean±SD)	(46.2±9.9)	(46.4±9.6)	(46.1±10.3)	
30-40	39(31.5)	17(27.9)	22(34.9)	P=.861
41-50	57(46.0)	28(45.9)	29(46.0)	
≥51	28(22.6)	16(26.2)	12(19.0)	
Sex				
Male	56(45.2)	26(42.6)	30(47.6)	P=.576
Female	68(54.8)	35(57.4)	33(52.4)	
Education				
Illiterate	42(33.9)	21(34.4)	21(33.3)	
Primary(1-5y)	41(33.1)	18(29.5)	23(36.5)	P=.790
Secondary(6-12y)	31(25.0)	16(26.2)	15(23.8)	
Masters	10(8.0)	06(9.9)	4(6.3)	
Occupation				
Services	45(36.3)	17(27.9)	28(44.4)	
Business	23(18.5)	10(16.4)	13(20.6)	P=.129
Housewives	29(23.4)	18(29.5)	11(17.5)	
Others	27(21.8)	16(26.2)	11(17.5)	
Income(BDT) (Mean±SD)	(31,967.7±10150.8)	(31,098.4±10738.9)	(32,809.5±9557.7)	
≤20000	22(17.7)	11(18.0)	11(17.5)	
20001-30000	48(38.7)	27(44.3)	21(33.3)	
≤20000	22(17.7)	11(18.0)	11(17.5)	P=.350
20001-30000	48(38.7)	27(44.3)	21(33.3)	
≥30001	54(43.5)	23(37.7)	31(49.2)	

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Table 1 According totable 1 nosignificant(P>0.05) differences were observed between 'treatment' and 'placebo' group in terms of socio-economic variables (ages in years, sex, education, occupation and monthly income in BDT).

Table 2 Stress related Information

Characteristics	Total(N=124)	Treatment(N=61)	Placebo(N=63)	p-value
BloodPressure(systolic)				
<120 mmHg	45(36.3)	14(23.0)	31(49.2)	
≥120mmHg	79(63.7)	47(77.0)	32(50.8)	P=.002
BloodPressure(Diastolic)				
<80mmHg	64(51.6)	30(49.2)	34(54.0)	
≥80mmHg	60(48.4)	31(50.8)	29(46.0)	P=.594
Havingstress				
Yes	67(54.0)	38(62.3)	29(46.0)	
No	57(46.0)	23(37.7)	34(54.0)	P=.069
Reasonsfor stress				
Economic	48(38.7)	28(45.9)	20(31.7)	
Health	37(29.8)	17(27.9)	20(31.7)	P=.246
Sleep latelyatnight				
Yes	51(41.1)	24(39.3)	27(42.9)	
No	36(29.0)	19(31.2)	17(27.0)	P=.868
Sometimes	37(29.8)	18(29.5)	19(30.1)	

Table2 outlines the changes of non-biochemical variables showed no significant differences(P>0.05) were observed for blood Pressure levels (both systolic and diastolic) between baseline and end line in treatment group. Similar results were also found for placebo. It is important to notice that 'systolic blood pressure 'showed significant differences(P<0.05) at baseline between treatment and placebo group.

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Table 3Changes of different bio-chemical indices across three or two time-points following (3-months) vitamin D Supplementation

Mean Indices	Treatment (n=61)				Placebo (n=63)				P-value for Between-groups
	Baseline	6-weeks follow-up	End- line	P-value for Within-Treatments groups	Baseline	6-weeks follow-up	End-line	P-value for Within placebos groups	
Vitamin D (25-OH)$_2$(ng/ml)	14.5±6.1	-	35.8±7.5	P=.000	19.4±8.8	-	20.5±5.2	P=0. 965	P=.001
Fasting Blood Glucose(mmol/L)	10.9±3.5	9.98±3.3	8.42±1.7	P<0.001 (All pairs)	10.6±2.4	9.1±3.6	11.5±2.3	P<.001 (All pairs)	P=000 (End-line)
Malonaldehyde (µm/ml)	2.0±0.41	-	1.93±0.42	P=.270	1.95±0.16	-	2.23±0.4	P=.000	P=.000 (End-line)
Super-Oxide-Dismutase (U/ml)	4.42±0.97	-	5.8±1.17	P=.000	4.6±0.68	-	4.6±0.87	P=.644	P=.000 (End-line)

In Table-3 showed -2 timelines (baseline and end line) for vitamin D, MDA and SOD and FBS had 3 timelines (baseline, follow-up and end line).While considering comparison among 'within time variant' treatment groups FBG, vitamin D and SOD were significantly different (P<0.05) except MDA. While considering comparison "between groups" vitamin D and SOD increased (P<0.05) and FBG and MDA decreased significantly (P<0.05) in treatment group as compared to placebo.

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Table 4 : "Fixed Effect Multiple Regression Model" Describing the association of glycemic indices and other important biochemical parameters with vitamin D (ng/ml) by R2-changes across timelines.

Bio-chemical Variables	**β**-Coefficient (Unstandardized)	Standard error	P-value	R^2-change**	Interpretation (One-unit change in vitamin D, decreases/Increase)
FBG (mmol/L)	-0.650	.447	0.010	Only treatment group =6.2%	↓ FBS by 0 .650 unit
MDA(µm/ml)	-3.695	1.368	0.007	Time-varying Changes =47.3%	↓MDA by 3.695 unit
SOD(u/ml)	1.213	.502	0.016		↑SOD by 1.213 unit

Table 4 outlines that FBG (**β**= -.650, Std. error =.447, p<.05) and MDA (**β** = -3.695, Std. error =1.368, p<.01) are significant negative predictors (one unit increase of vitamin D level decreased these variables significantly) of vitamin D status. Inversely, SOD (**β** =1.213, Std. error =.502, p=.016) showed significant positive predictors (one-unit increase of vitamin D level increased these variables significantly as compared to placebo) of Changing Vitamin D level over 3-months intervention.

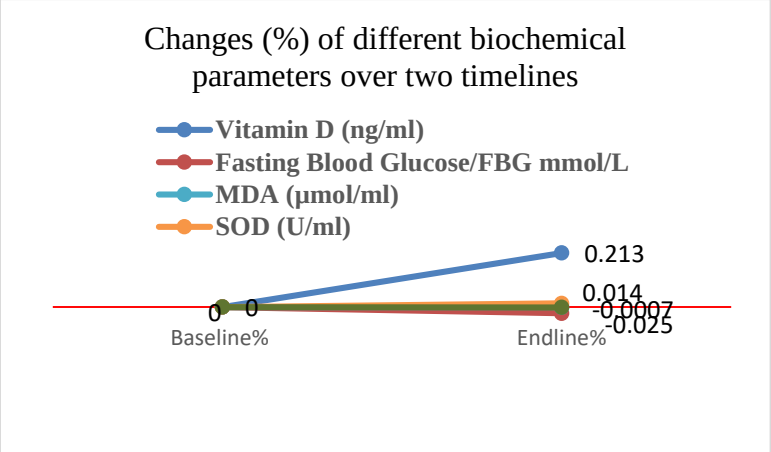

Figure 1 showed percent (%) changes of different biochemical parameters among treatment group from baseline to the end line. The highest changes of variation were observed in Vitamin D (21.3%) followed by SOD(1.4%).

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DISCUSSION

According to Endocrine society vitamin D can be define as (i.e. deficient=< 30 ng/ml, sufficient ≥30 ng/ml)(Holick et al., 2011;Waterbury, 2018).[9,10] This study found that 20,000 IU 25-hydroxy cholecalciferol (vitamin D3) supplementation at every 5th day for 12 weeks effectively (P=.000) increased the 25 (OH) D3 level from baseline to end line(14.5±6.1 ng/mL to 35.8±7.5 ng/mL). Moreover, end line 25-hydroxyvitamin D levels were significantly higher in the treatment group as compared to placebo (treatment: 35.8 ±7.5 ng/mL and placebo: 20.05±5.2 ng/mL, p=0.001).Several studies also showed similar results by Tang H etal(2018) [11](baseline: 41.16 nmol/L versus end line: 82.22 nmol/L); Ryu et al.[12] (35.4 ± 8.5 ng/mL vs. 18.4 ± 7.3 ng/mL, p < 0.001); Anyanwu A C[13]. Mean FBG gradually decreased (P<0.001) from baseline 10.9 ng/ml (±3.5) to the end line 8.42 (±1.7).

In case of diabetes SOD is an important antioxidant enzyme in the regulation of oxidative stress. To reduce oxidative stress, it acts as a first line defense against reactive species also reduces the risk of cellular and histological injury as well. Another stress marker like MDA levels if elevated in plasma, serum, and other tissues indicate that peroxidative injury may be involved in the development of diabetes complications. Results from the bivariate analysis of this study revealed that two biomarkers of free radicaloxidative stress are plasma superoxide dismutase (SOD) and malondialdehyde (MDA).[3]In Bivariate analysis showed insignificant reduction of mean MDA level from baseline(2.0±0.41 µmol/ml) to the end line (1.93±0.42) after vitamin D supplementation while the placebo group had significant (P<0.001) increment of MDA level in end line (2.23±0.04 µmol/ml) than in baseline (1.95±0.2). In contrast, treatment group showed significantly difference (p=0.000) of SOD level from baseline to end line (4.42±0.97 U/ml to 5.8±1.17U/ml) compared to placebo.

Overall R2-change in multivariate analysis (table 4) showed 44.4% variation for different biochemical predictors of vitamin D and revealed that MDA (P<.05) is inversely associated with vitamin D levels of T2DM patients. In contrast, SOD have positive associations of changing Vitamin D level over 3-months intervention. Non-significant changes in the mean FBS level after 12 weeks of supplementation in the treatment group compared to the placebo also reported in other studies by Anyanwu et al., 2017; Rashidi et al., 2016.[13,14]

Both SOD and MDA have been considered as biological markers of oxidative stress. Systemic inflammation has been linked to oxidative stress. Impaired oxidative balance and increased ROS production result in activation of nuclear factor κB (NFκB) which plays a critical regulatory role in immunity and inflammatory responses. Malondialdehyde (MDA) is a stable end product of lipid peroxidation and therefore can be used as an indirect measure of the cumulative lipid peroxidation. Oxidative stress plays a vital role in systemic inflammation, development of type 2 diabetes and its related complications.[15] Increased activity of SOD was

independently associated with lower all-cause mortality in older women but not in men reported in a recent study.[16]and physical activity significantly reduced MDA level also reported in an earlier study.[17]

CONCLUSION

Chronic Diabetes Mellitus is responsible for altering the glucose metabolism and the immune response that is disruption of homeostasis between radical species and defense system enzymatic antioxidant which leads to development of diabetes-related complication resultingmorbidity and mortality. In the current study, it was observed the beneficial impact of 12 weeks' vitamin D supplementation to reduce oxidative stress among those who were vitamin D deficient diabetic patients.

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