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Is Vitamin D Deficiency Risk Factor for Type II Diabetes Mellitus?

[*]Fawzy A. Elmessallamy, MD, [*] Mohamed S. S. Saad, MD, *Hatem M. Salem, **Ahmad Baraka MD

Internal Medicine [*] and Clinical Pathology** Departments, Faculty of Medicine, Zagazig University Hospitals

Abstract: ***Introduction: Vitamin D deficiency causes reduced insulin secretion in rats and human it may predispose to glucose intolerance, altered insulin secretion and type II diabetes mellitus. The Aim of the study: To study the association between vitamin D status and type II diabetes mellitus and to assess the effects of vitamin D and calcium supplementation on glycemic control. Subjects: The current study included two groups the first group included 69 male diabetic patients suffering from type II diabetes mellitus and second group included 45 age and sex matched healthy persons as control group and each of this group was subdivided into 3 subgroups according treatment protocol first subgroup of each group (diabetic and control) did not receive calcium nor vit D supplementation, second subgroup of both groups receive calcium supplementation alone, third subgroup of both groups received both calcium and vitamin D supplementation. Methods: all subjects of the study was subjected to careful history taking, thorough clinical examination, laboratory investigation including fasting and two hours postprandial blood sugar, Fructosamine, Fasting Insulin, & HOMA-IR in addition to Vitamin D assessment by ELIZA in the beginning and after one month of starting treatment protocol. Results: Serum Vitamin D and fasting insulin levels were statically higher among control group than among diabetic patients as whole while mean values of other parameters were statically higher compared to controls. Statistically significant decrease of serum vitamin D and fasting insulin levels and statistically significant increase of FBG, PPBG, serum fructosamin and HOMA.IR were found in diabetic group as compared to control group as a whole in the beginning of study and after one month of supplement of calcium and vitamin D in 2[nd] and 3[rd] subgroups of both group, there was statistically significant decrease of FBG, PPBG, serum fractosamin and HOMA.IR and significant increase of serum insulin level in the 2[nd] and 3[rd] subgroups of diabetic patients after one month of treatment protocol as compared to before treatment, while serum vitamin D was significant increase in subgroup III only after treatment with calcium and vitamin D. Significant negative correlation between vitamin D and each of FBS, PPBG, serum fractosamin and HOMA IR and significant positive correlation between vitamin D and serum fasting insulin in diabetic subgroup III. Conclusion: vitamin D deficiency may play role in development of type II diabetes in susceptible individuals and its supplementation to those subjects improve glycemic status thus correction of vitamin D deficiency of those subjects may delay or prevent occurrence of type II diabetes and help to improve glycemic control of type II diabetes but our understanding of the exact mechanisms by which vitamin D and calcium may promote beta cell function, or ameliorate insulin resistance and systemic inflammation is in need for more investigation.***

Keywords: Insulin secretion, Calcium, Vitamin D, Type II diabetes mellitus and HOMA.IR

1. Introduction

Vitamin D insufficiency has long been suspected as a risk factor for type I diabetes based on animal and human observational studies. More recently, there is accumulating evidence to suggest that altered vitamin D and calcium homeostasis may play also a role in the development of type II diabetes mellitus **(Badenhoop et al., 2005)**.

Altered vitamin D and calcium homeostasis may play a role in the development of type 2 diabetes mellitus as vitamin D and calcium insufficiency may negatively influence glycemia whereas, combined supplementation with both nutrients may be beneficial in optimizing glucose metabolism **(Marks et al., 2003)**.

The major and most well known function of vitamin D is to maintain calcium and phosphorus homeostasis and promote bone mineralization. However, recent evidence suggests that vitamin D and calcium homeostasis may also be important for a variety of non-skeletal outcomes including their actions as modifiers of diabetes risk **(Dawson-Hughes et al., 2006).**

There are many evidence that there is a role for vitamin D in pancreatic ß-cell function in which the direct effect of vitamin D on pancreatic ß-Cells may be mediated by binding of its circulating active form, 1.25 OHD, to the ß-cell vitamin D receptor whereas, the indirect effects of vitamin D may be mediated via its important and well recognized role in regulating extracellular calcium and calcium flux through ß-cell **(Hewison et al., 2004)**.

Insulin secretion is a calcium dependent process; therefore, alterations in calcium flux can have adverse effects on ß-cell secretory function **(Milner et al., 1987).**

Inadequate calcium intake or vitamin D insufficiency may later affect the balance between extracellular and intracellular ß-cell calcium pools, which may interfere with normal insulin release especially in response to a glucose load **(Milner et al., 1987).**

Associations between low vitamin D level and decreased insulin sensitivity have been reported in cross-sectional studies **(Bell et al., 2004).**

Vitamin D may improve insulin sensitivity and promote ß-cell survival by directly modulating the generation and effects of cytokines which may play a role in ß-cell dysfunction by triggering ß-cell apoptosis **(Boucher et al., 2002).**

2. Objectives

- To study the association between vitamin D status and development of type II diabetes mellitus.
- To assess the effects of vitamin D and calcium supplementation on glycemic control of those subject.

3. Subjects and Methods

The current cohort study was conducted in the period between June 2014 and June 2015 in Internal Medicine Department of Zagazig University Hospitals and included 69 male diabetic patients suffering from type II diabetes mellitus (group I) & 45 healthy male age matched persons served as control group (group II).

Inclusion Criteria:

1) **Age:** Between 30-50 years old.
2) All patients are suffering from type II diabetes mellitus diagnosed according to ADA diagnostic criteria 2014. The duration of their diabetes ranged from 6-20 years with a mean value ± SD of (12.7 ± 3.6).

Exclusion Criteria:

1) Patients below 30 years or above 50 years old and female.
2) Patients suffering from malabsorption syndrome or GIT troubles affecting vitamin D absorption.
3) Patients suffering from clinical osteoporosis or osteomalacia.

The subjects of this study were divided into two groups:

(I) Patients group:

Include 69 diabetic patients suffering from type II diabetes mellitus are under observation for 1 month and divided into 3 subgroups according to treatment protocol:

1) **Subgroup Ia**: 23 patients suffering from type II diabetes middle aged not supplemented with vit D or Ca^{++}.
2) Subgroup Ib: 23 patients with type II diabetes, middle aged, supplemented with Ca^{++}.
3) Subgroup Ic: 23 patients of type II diabetes, middle aged, supplemented with vit D and Ca^{++} with a for 1 month.

(II) Control group:

Include 45 normal persons divided into 3 subgroups according to treatment protocol:

1) **Subgroup IIa** contains 15 normal persons not suffering from diabetes mellitus with no supplementation of calcium ± vitamin D.
2) **Subgroup IIb** contains 15 normal persons supplemented for 1 month with calcium.
3) **Subgroup IIc** contains 15 normal persons supplemented for 1 month with calcium and vitamin D.

Methods:

All subjects were subjected to the following:

- A careful history taking regarding disease history and associated symptoms and personal history especially age, which must be between 30-50 years old to exclude osteoporosis and osteomalacia as much as possible.
- Thorough clinical examination with special stress to exclude any skeletal deformities or malformations and to search for any systemic manifestations or signs of malabsorption syndromes
- The laboratory investigations which done for all persons in clinical pathology department protocol of Zagzaig University Hospital including:

1) Fasting blood sugar.
2) 2 hours postprandial blood sugar.
3) Serum Fructosamine.
4) Serum Fasting Insulin
5) HOMA-IR (Homeostatic model assessment for Insulin resistance) was calculated by multiplying fasting serum insulin in fasting Blood sugar (by mmol/L) then divided by 22.5. To obtain fasting blood sugar by mmol/L we divide its level obtained in mg/dl by 18.
6) Vitamin D assessment is done by measuring 25 hydroxyvitamin D in serum.The active part of vitamin D that can be measured in serum is 25 (OH) vit D which was measured in our study by ELISA in the beginning of study and after one month.

- Treatment protocol:

First subgroup of each group (diabetic and control) did not receive calcium nor vit D supplementation, second subgroup of both groups receive calcium supplementation (500 mg once daily for one month) alone, third subgroup of both groups received both calcium(500 mg once daily) and vitamin D (400 IU once daily) for one month.

All control and patients in the six previous subgroups remained under observation aiming at measuring the needed investigations before and after one month for each person.

All of patients must continue their original treatment for diabetes mellitus either with insulin or oral drugs with the same described dose for them from their consultants and continue on their prescribed diet.

Ethical Clearance:

Approvals were obtained from governmental departments, ethical committee in faculty and from patients included in the study or their 1st degree, relatives.

Statistical Analysis:

Statistical analysis was performed using spss software version 10.0 under Microsoft windows® XP©.

Continuous data was expressed in the form of mean ±SD.

Student test was used to compare such variable chi-square test was used to compare categorical data.

Pearson's correlation coefficient was used to correlate variables.

This statistical analysis was done with the help of Community Department Professors of Faculty of Medicine in Zagazig University

4. Results

Table 1: Comparison of mean values ± SD of age (years) between the studied subgroups

Demographic data	*Cases [(N=23) for each group]*	*Controls [(N=15) for each group]*	*t-test*	*P-value*
Age (Years) X±SD				
Subgroup I	44.3±4.9	41.6±7.3	1.3	NS
Subgroup II	45.7±4.4	41±7.5	1.4	NS
Subgroup III	44.4±5.6	43±5.0	1.02	NS

Mean values of age among cases of group I, II and III are Non Statistically among controls.

Table 2: Comparison of the baseline characteristics between the studied groups as a whole

Laboratory parameters	*Cases (N=69)*	*Controls (N=45)*	*t-test*	*P-value*
Serum Vit. D (IU)				
X±SD	70.9±25.8	92.4±16.3	-2.8	0.01**
Fasting blood sugar (mg/dl)				
X±SD	181.7±124.5	85.2±9.3	3.0	0.005**
Two hours post prandial blood sugar (mg/dl)				
X±SD	234.8±115.2	115.0±9.5	4.0	0.000***
Serum Fructosamine (mg/dl)				
X±SD	427.5. ± 71.0	227.4±18.4	10.6	0.000***
Serum Fasting insulin (mIU/L)				
X±SD	4.2±1.0	6.8±0.9	-7.8	0.000***
HOMA IR				
X±SD	1.6±0.6	1.4±0.1	1.6	0.1

Mean values of vitamin D and fasting insulin are statistically higher among controls than among cases while mean values of other parameters are statistically higher in cases compared to controls.

Table 3: Comparison of the different parameters of the study between subgroups II of cases and control after supplementation with Ca^{++} for 1 month

Laboratory parameters	*Cases Subgroup II (N=23)*	*Controls Subgroup II (N=15)*	*t-test*	*P-value*
Serum Vit. D (IU)				
X±SD	67.1±24.6	85.3±22.4	-2.3	0.02**
Fasting blood sugar (mg/dl)				
X±SD	254.8±163.3	83.5±8.9	4.0	0.000***
Two hours post prandial blood sugar (mg/dl)				
X±SD	300.1±167.4	116.4±11.4	4.2	0.000***
Serum Fructosamine (mg/dl)				
X±SD	368.9±132.2	214.8±15.6	4.5	0.000***
Serum Fasting insulin (mIU/L)				
X±SD	3.9±0.8	6.1±0.8	-7.6	0.000***
HOMA IR				
X±SD	2.2±0.8	1.2±0.1	4.9	0.000***

Mean values of vitamin D and fasting insulin are statistically higher among controls than among cases while mean values of other parameters are statistically higher in cases than among controls.

Table 4: Comparison of the different parameters of the study between Subgroup III of case and control after Ca^{++} and vitamin D supplementations for 1 month

Laboratory parameters	*Cases Subgroup III (N=23)*	*Controls Subgroup III (N=15)*	*t-test*	*P-value*
Serum Vit. D(IU)				
X±SD	63.5±31.3	96.9±16.2	-3.8	0.000***
Fasting blood sugar(mg/dl)				
X±SD	237.5±84.6	79.8±6.5	7.2	0.000***
Two hours post prandial blood sugar (mg/dl)				
X±SD	284.8±89.4	113.1±8.0	7.4	0.000***
Serum Fructosamine (mg/dl)				
X±SD	435.3±81.7	208.0±7.6	10.7	0.000***
Serum Fasting insulin (mIU/L)				
X±SD	3.7±0.8	6.3±0.3	-10.0	0.000***
HOMA IR				
X±SD	2.0±0.3	1.2±0.1	9.5	0.000***

Mean values of vitamin D and fasting insulin are statistically higher among controls than among cases while mean values of other parameters are statistically higher in cases than among controls.

Table 5: Comparison of the different parameters of the study between Subgroup II of Cases before and after Ca^{++} supplementation for 1 month

Laboratory parameters	*Cases before the month (Subgroup II) (N=23)*	*Cases after the month (Subgroup II) (N=23)*	*t-test*	*P-value*
Vit. D (IU)				
$\bar{X}$±SD	67.1±24.6	68.5±24.0	-1.1	0.3
Fasting blood sugar(mg/dl)				
$\bar{X}$±SD	254.8±163.3	220.1±157.8	2.5	0.02*
Two hours post prandial blood sugar (mg/dl)				
$\bar{X}$±SD	300.1±167.4	229.1±77.9	2.8	0.01**
Serum Fructosamine (mg/dl)				
$\bar{X}$±SD	368.9±132.2	318.3±67.0	2.6	0.01**
Serum Fasting insulin (mIU/L)				
$\bar{X}$±SD	3.96±0.8	4.2±0.7	-2.6	0.01**
HOMA IR				
$\bar{X}$±SD	2.2±0.8	1.9±0.5	2.3	0.03*

Mean values of fasting insulin are statistically higher among cases after supplementation than among cases before while mean values of other parameters are statistically higher in cases before than among cases after.

Table 6: Comparison of the different parameters of the study between Subgroup III of Cases before and after Ca^{++} & vitamin D supplementations for 1 month

Laboratory parameters	*Cases before the month (group III) (N=23)*	*Cases after the month (group III) (N=23)*	*t-test*	*P-value*
Vit. D (IU)				
$\bar{X}$±SD	63.5±31.3	75.8±25.6	-6.9	0.000***
Fasting blood sugar (mg/dl)				
$\bar{X}$±SD	237.5±84.6	185.5±41.4	3.3	0.003**
Two hours post prandial blood sugar (mg/dl)				
$\bar{X}$±SD	284.8±89.4	229.0±43.5	3.3	0.003**
Serum Fructosamine (mg/dl)				
$\bar{X}$±SD	435.3±81.6	368.47±52.2	3.4	0.003**
Serum Fasting insulin (mIU/L)				
$\bar{X}$±SD	3.7±0.8	3.9±0.6	-2.0	0.05*
HOMA IR				
$\bar{X}$±SD	2.0±0.3	1.7±0.3	3.2	0.004**

Mean values of vitamin D and fasting insulin are statistically higher among cases after supplementation than among cases before while mean values of other parameters are statistically higher among cases before than among cases after.

Table 7: Correlation coefficient between vitamin D and other parameter of the study in subgroup IIa and IIIa

	Subgroup IIa		*Subgroup IIIa*	
	r	*p*	*r*	*p*
Fasting blood sugar (mg/dl)	0.123	NS	-0.451	<0.03
Two hour post-prandial blood sugar (mg/dl)	0.165	NS	-0.483	<0.02
Serum fractosamin (mg/dl)	0.091	NS	-0.682	<0.01
Serum fasting insulin level mIU/L)	0.201	NS	+0.573	<0.01
HOMA IR	-0.185	NS	-0.601	<0.01

Significant negative correlation between vitamin D and each of FBS, PPBG, serum fractosamin and HOMA IR and significant positive correlation between vitamin D and serum fasting insulin in subgroup IIIa

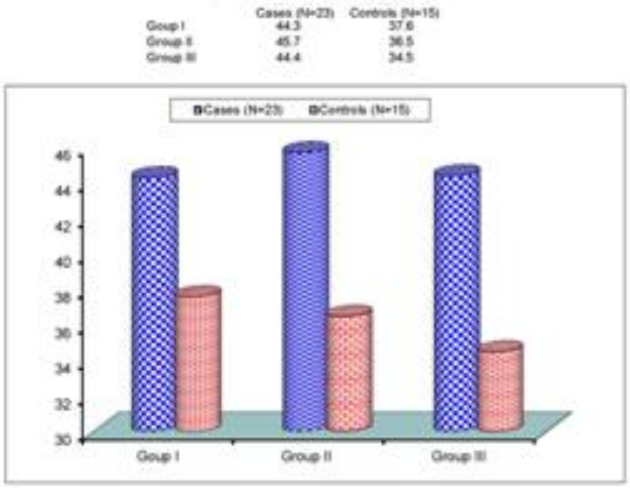

Diagram 1: Sociodemographic data of the studied groups

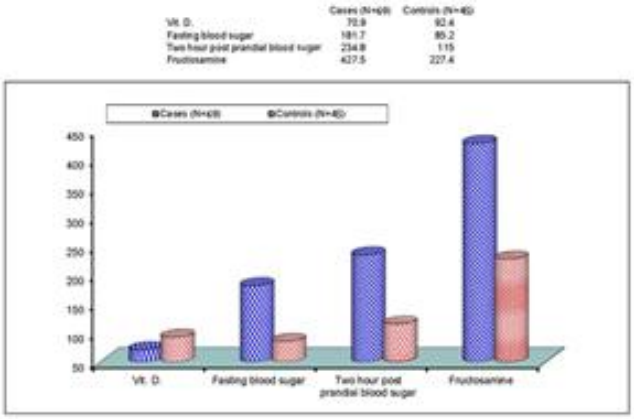

Diagram 2: Baseline characteristics of the studied patients and controls

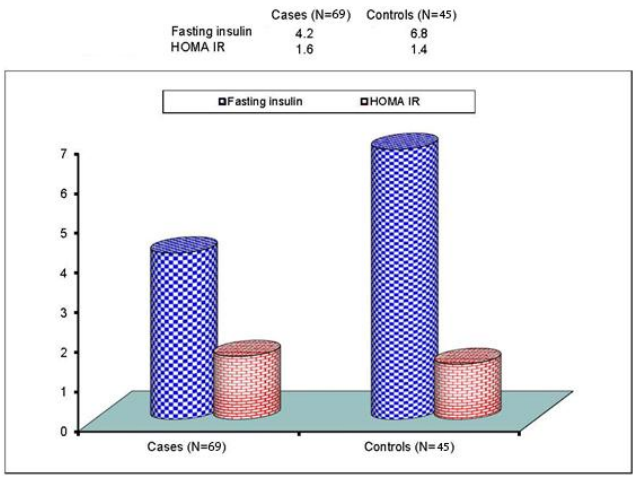

Diagram 3: Baseline characteristics of the studied patients and controls (continue)

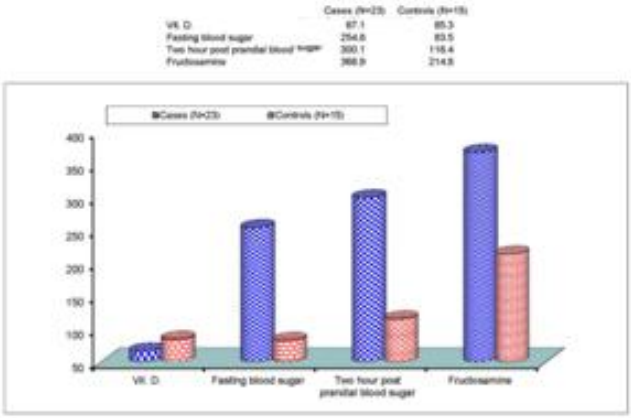

Diagram 4: Cases and controls after supplementation with Ca^{++} for 1 month

5. Discussion

Vitamin D status is lower in individuals with obesity and with type 2 diabetes, but the causality of this relationship is unknown. In nearly all human studies, obesity is associated with low 25(OH) D concentrations **(Ozfirat Z, Chowdhury TAet al., 2010).**

There is limited evidence of an effect of calcium supplementation on diabetes-related parameters from trials that have examined the effects of calcium either alone or as a component of dairy products.

Trials with small numbers of non-diabetic participants that have examined the effects of calcium supplementation as a component of dairy products in relation to glycemia or insulin resistance have shown conflicting results but most studies show a neutral effect **(Thompson et al., 2005)**.

Among participants with impaired fasting glucose at baseline, those who took combined vitamin D and calcium supplements had a significantly lower rise in fasting glycemia and insulin resistance **(Pittas, 2007).**

Therefore, given the potential link between vitamin D, calcium and diabetes, it is plausible that the rising incidence of type II diabetes mellitus may, at least in part, be due to suboptimal vitamin D and calcium status. Furthermore, certain

determinants of adequate vitamin D and calcium status (aging, physical inactivity dark skin and obesity) are also strong risk factors for type II diabetes. Although this may simply reflect confounding, the link between these risk factors and type II diabetes mellitus may, at least partially, be mediated by vitamin D and calcium insufficiency **(Pittas et al., 2006)**.

As shown in the results either in statistics or in charts, there is very minimal effect of supplementation with calcium and vitamin D or calcium alone on the glycemic state of patients suffering from type II diabetes mellitus and having normal serum 25(OH) vitamin D levels while the most effective and acceptable results obtained from supplementations, mainly with calcium and vitamin D, were obtained in type 2 diabetic patients with low levels of serum 25 (OH) vit. D.

The baseline characteristics of the studied patients show that mean values of vitamin D and fasting insulin are statistically higher among controls than among cases while mean values of other parameters are statistically higher cases than among controls. In several cross-sectional and prospective cohort studies, type 2 diabetes and conditions known to be part of the metabolic syndrome were associated with a poor vitamin D status **Liu E, Meigs JB, Pittas AG, et al.(2010**)After supplementation with calcium, the mean values of vitamin D and fasting insulin are statistically higher among controls than among cases while mean values of other parameters are statistically higher in cases than among controls. After supplementation with calcium and vitamin D, the mean values of vitamin D and fasting insulin are statistically higher among controls than among cases while mean values of other parameters are statistically higher in cases than among controls.

There are no statistical significant differences between cases before and after one month without any supplementation.

The statistics of cases before and after one month with calcium I supplementation show that the mean values of fasting insulin are statistically higher among cases after supplementation than among cases before while mean values of other parameters are statistically higher in cases before than among cases after.

The statistics of cases before and after one month with calcium and vitamin D supplementation show that the mean values of vitamin D and fasting insulin are statistically higher among cases after supplementation than among cases before while mean values of other parameters are statistically higher among cases before than among cases after.

We also found significant negative correlation between vitamin D and each of FBS, PPBG, serum fractosamin and HOMA IR and significant positive correlation between vitamin D and serum fasting insulin. Trial in severely vitamin D-deficient Asians living in New Zealand revealed a modest improvement of their insulin sensitivity after six months of vitamin D supplementation **Von Hurst PR, Stonehouse W, Coad J.(2010).**

6. Conclusion

Vitamin D deficiency may play role in development of type II diabetes in susceptible individual and its supplementation to those subjects improve glycemic status thus correction of vitamin D deficiency of those subjects may delay or prevent occurrence of type II diabetes and help to improve glycemic of type II diabetes but our understanding of the exact mechanisms by which vitamin D and calcium may promote beta cell function, or ameliorate insulin resistance and systemic inflammation is in need for more investigation.

References

[1] **Badenhoop, K. and Mathieu, C. (2005):** Vitamin D and type I diabetes mellitus, state of the art, Trends of Endocrinal metabolism; 16: 261-266.
[2] **Bell, C.; Scragg, R. and Sowers, M. (2004):** Serum 25 – hydroxyl vitamin D, diabetes and ethnicity in the third national health and nutrition examination survey diabetes care; 27: 2813- 2818.
[3] **Boucher, B.J.; Timms, P.M.; Mills, P.G. and Price, C.P. (2002):** Circulating MMpa, vitamin D and variation in the TiMP-1 response with VDR genotype: mechanism of inflammatory damage in chronic disorders; 95: 787-796.
[4] **Dawson-Hughes, B.; Bischoff-Ferrari, H.A. and Willett, W.C. (2006):** Estimation of optimal serum concentrations of 25-hydroxy vitamin D for multiple health outcomes; 84: 18-28.
[5] **Hewison, M.; Bland, R. and Hills, C.E. (2004):** Expression of 25 hydroxy vitamin Ds-la-hydroxylase in pancreatic islets; 90: 121-125.
[6] **Liu E, Meigs JB, Pittas AG, et al.(2010)** Predicted 25-hydroxyvitamin D score and incident type 2 diabetes in the Framingham Offspring Study. Am J Clin Nutr 2010; 91:1627.
[7] **Marks, J.S.; Mokdad, A.H. and Dietz, W.H. (2003):** Prevalance of obesity, diabetes and obesity-related health risk factors; 289: 76-79.
[8] **Milner, R.D. and Hales, C.N. (1987):** The role of calcium and magnesium in insulin secretion from rabbit pancreas studied in vitro; 3: 47-49.
[9] **Ozfirat Z, Chowdhury TA(2010).** Vitamin D deficiency and type 2 diabetes. Postgrad Med J 2010; 86:18.
[10] **Pittas, A.G.; Dawson-Hughes, B. and Li, T. (2006):** Vitamin D and Calcium intake in relation to type 2 diabetes mellitus in women; 29: 650-656.
[11] **Pittas, A.G.; Harris, S.S. and Stark, P.C. (2007):** The effects of calcium and vitamin D supplementations on blood glucose and markers of inflammation in non-diabetic adults; 27: 629- 633.
[12] **Thompson, W.G.; Rostad Holdman, N.; Janzow, D.J. and Morris, Kl. (2005):** Effects of energy-reduced diets high in dairy products and fiber on weight loss in obese adults; 13: 1344 - 1353.
[13] **Vimaleswaran KS, Berry DJ, Lu C, et al. (2013)**Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. PLoS Med 2013; 10:e1001383.
[14] **Von Hurst PR, Stonehouse W, Coad J.(2010)** Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient - a randomised, placebo-controlled trial. Br J Nutr 2010; 103:549.