Research Article

Evaluation the Effect of Vitamin D3 on Glycemic Indices on Iraqi Children with Type 1 DM.

Lubab Tarik Nafei[1], Kadhim Ali Kadhim[1], Ali Muaffaq Said [2]. Sadik Hameed Ghani[3]
[1]Department of clinical pharmacy, College of pharmacy, Al-Mustansiriyah University, Baghdad, Iraq.
[2]Collage of pharmacy/ University of AL-Yarmouk, Baghdad, Iraq.
[3]Child Center Teaching Hospital, department of pediatric endocrinology.
*Corresponding author's E-mail: lubab_alhamdany@yahoo.com

ABSTRACT

DM is not a single entity but rather a heterogeneous group of disorders in which there are specific genetic patterns as well as other etiologic and pathophysiologic mechanisms that lead to impairment of glucose tolerance. Vitamin D is not only necessary for maintaining bone health, but it also may plays an important role in several other biochemical mechanisms within the body which it is started by its binding to vitamin D receptors found in most tissues such as pancreatic β-cells. The study in new-onset type 1 diabetic pediatrics established the effect of vitamin D3 on people with lower serum concentration of this vitamin, and evaluated its effect on the decline of residual β-cell function. These mechanisms suggested that vitamin D3 deficiency impairs insulin secretion through regulation of calcium homeostasis and directly or indirectly affects glucose intolerance. The present study was designed to evaluate the possible correlation between serum vitamin D3 (cholecalciferol) levels with serum fasting blood glucose, serum (HbA1c), serum insulin levels, serum C-peptide levels related to newly diagnosed pediatric patients with type 1 diabetes mellitus. The patients were treated with oral vitamin D3 depending on patient`s condition and physician`s opinion, where they were randomized into three groups: the first group includes: 25 newly diagnosed pediatric patients with an age range of (8.78±0.53), treated with vitamin D3 (2000IU/day) combined with daily insulin regimen, the second group includes: 25 newly diagnosed pediatric patients with an age range of (8.16±0.54), treated with insulin daily regimen only, and the third group included:25 healthy pediatrics with an age range of (6.77±0.49).All patients received their treatment for 3 months duration, and blood samples were collected from them at the beginning of the study (baseline) and after 45 days and 90 days of starting vitamin D3 treatment to measure the possible changes in the following parameters; FSG, glycemic control (HbA1c), serum C-peptide, serum insulin, serum vitamin D3.The results showed that FSG, HbA1c, were significantly decreased in all vitamin D3 treated group`s patients, while serum vitamin D3, serum insulin, C-peptide, were significantly increased in the all vitamin D3 treated group`s patients after 45 and 90dayscompared to baseline values where (P>0.05). The use of 2000 IU/day dose of vitamin D3 as supplementary treatment with the daily insulin regimen for newly diagnosed type 1 diabetic pediatric patients who reveal a significant correlation between serum vitamin D3 levels and an improvement efficacy.

Keywords: Beta-cells of pancreas, Body Mass Index, FBG, type 2 Diabetes Mellitus, vitamin D3.

INTRODUCTION

Diabetes mellitus mentions to a number of metabolic diseases regarded with persistent hyperglycemia following from defects in insulin secretion, insulin action, or both. This prolonged hyperglycemia of diabetes result in long-term damage and loss of functions of many organs especially the eyes, kidneys, and nerves.[2] Worldwide, the incidence of DM for all ages is expected to be increase to 4.4% by the year 2030. Around 5% to 10% of the diagnosed cases of diabetic have T1DM.[3]

The interactions of genetic and environmental factors that are in the end can cause destruction of the pancreatic β-cells and insulin deficiency in T1DM. Mostly this process results from autoimmune β-cell destruction, although not all cases have the evidence of islet directed autoimmunity.[4] The rate of decline in β-cell mass may be varies broadly among individuals from rapidly progress to slow progress rate. Generally the characters of diabetes do not become marked until a majority of β-cells are

destroyed [about 80%].[4, 5] At this moment, the residual functional β-cells still present but not enough in number and action to maintain glucose tolerance.[4] There were many risk environmental agents that start islet destruction include dietary components (such as cereals), infections (enteroviruses, chemicals, seasonality and geographic positions could affect incidence of T1DM in different individuals.[6] Vitamin D (calciferol) is a basic name for a group contains a large number of fat steroids and the two major forms are: vitamin (D2) called ergocalciferol and vitamin (D3)called cholecalciferol. The natural source of cholecalciferol is created in the skin from the action of short wavelength ultraviolet light from the sun and also in some types of foods.[7]

Vitamin D has characteristic features of a hormone, and accordingly vitamin D is a pro-hormone, rather than a true vitamin .The active form of vitamin D is binding to VDR then started its main action inside body.[8, 9] It has been suggested that vitamin Deficiency be defined as a vitamin D of [< 20 ng/mL], while the insufficiency as a

International Journal of Pharmaceutical Sciences Review and Research
Available online at www.globalresearchonline.net
134

vitamin D of [21 – 29 ng/mL].The sufficiency as a vitamin D of [30 – 100 ng/mL].[10-13]

Role of vitamin D3 in T1DM

There is increasing evidence that vitD3 affects in the pathogenesis, risks and complications of DM. The studies shown that vitD3 supplementation in infancy diminishes the risk of developing T1DM during early adulthood, with the predictable pancreatic receptor on the islet cells to the active metabolite of vitD3, that giving vitD3 an important role in the homeostasis of glucose metabolism.[14]

It has been reported that exposition of human β-cell to vitD3 protects them from death.[15] Supplementation of vitD3 is beneficial and nontoxic only in people whose biological concentration of the vitamin is less than optimum. But also the new suggestion predicted that all infants should receive at least the amount of vitD3 indicated in the current references.[16] VitD3 deficiency impairs insulin secretion, induces glucose intolerance and also increases the risk of diabetes associated complications. As a major regulator for calcium homeostasis, vitD3 directly and or indirectly improves insulin exocytosis [17] via activating of calcium-dependent endopeptidases and normalization of extracellular calcium, ensuring that normal calcium flux through cell membrane then correct glucose intolerance.

VitD3 mediates the activity of β-cell calcium-dependent endopeptidases promotes conversion of proinsulin to insulin and increases insulin output. In peripheral insulin target tissues, vitD3 improves insulin action through regulation of the calcium pool. The studies discover that pancreatic β-cells that secretes insulin and cells of the immune system has been shown to contain VDRs[receptors for vitD3] as well as the 1 alpha hydroxylase enzyme[18]. Evidence indicates that vitD3 treatment improves glucose tolerance, so vitD3 deficiency leads to reduced insulin secretion.[19, 20] Other potential mechanisms of vitD3 in diabetes include improving insulin action by enhancing expression of the insulin receptor, and improving insulin reaction for glucose transport. [21] With few exceptions, dose of vitD3 less than 1,200 IU/day have not been shown to be as effective as doses of 2,000 IU/day on decreasing serum blood sugar, HbA1c, and other disease markers in diabetic patients. [22]

MATERIALS AND METHODS

This is a prospective randomized controlled open label study carried out in Child Central Teaching Hospital for the out-patients clinic in endocrinology department during the period from 1st April 2015 to 15th May 2016.Ethical Approval was obtained from Ethics Committee by Pharmacy College/ University of AL-Mustansyriah. The study was conducted on 75 Iraqi child newly diagnosed T1DM patients [not more than 1year duration of disease] and whose ages were between [4-12] years. The patients chosen to participate in this study were classified by physician according to Wagner classification and informed consent taken from the patient to make the study and to follow restricted diet and asked to monitor their blood glucose levels at the initial visit to the center. The patient's records were maintained for the next three month after their initial visit to hospital; they were observed for BMI, vitD3, insulin level, C-peptide, FBG, were measured before, 6 weeks, and after 12 weeks of treatment. Only Serum HbA1c was measured before and after starting drug treatment. All the patients were on the same treatment and dose of vitD3, as well as their standard medications for DM. Also medical and drug history was taken from the newly diagnosed patients using the data sheet charts. Only patients with T2DM, T1DM with history of autoimmune or chronic inflammatory diseases, Patients with CRF or hepatic disease, Patient with diabetic complications or uncontrolled diabetes, Patient with any type of cancers or taking chemotherapy or any other drugs were excluded from the study. The patients were randomized into three groups: group 1/ 25 patients receive 2000 IU vit.D3 once daily only in addition to the normal insulin regimen, group 2/25 patients receive insulin (soluble and Lente) twice daily and group 3/25 apparently healthy subjects, consider as control group. From each patient and control subject, blood samples were collected after 12 hours of fasting. 10 milliliters was taken before starting the treatment [as baseline], 6 weeks later and then after 12 weeks from baseline reading to follow the changes in the studied parameters for analysis of (FBG, HbA1c, SerumvitD3, Serum insulin, and C-peptide).

Statistical analysis

Analysis of data was carried out using the available statistical package of SPSS-22. Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range. Pre- and post-treatment values were statistically analyzed using students-t-test for difference between two independent means or Paired-t-test for difference of paired observations (or two dependent means), or ANOVA test for difference among more than two independent means. Pearson correlation was calculated for the correlation between two quantitative variables with its t-test for testing the significance of correlation. The correlation coefficient value (r) either positive or negative with value <0.3 represent no correlation, 0.3-<0.5 represent weak correlation, 0.5-<0.7 moderate strength, >0.7 strong correlation. In addition to correlation the r2 was calculated (The coefficient of determination), i.e. when value of r=0.58, then r2=0.34, this means that 34% of the variation in the values of y may be accounted for by knowing values of x or vice versa. Statistical significance was considered whenever the P value was equal or less than 0.05.

RESULTS

Effect of treatment with vitamin D3 on serum vitamin D3 in type 1 DM pediatric patients

The means±SE and the efficacy of vitD3 therapy in the patients with T1DM, group1 comparing with patients in group2 and with the group3 on baseline, after 45 days of treatment and after 90 days of treatment are shown in Table and Figure (1). There was highly significant difference among three independent means [group1 x group 2 x group 3] at every period and the *P* value was (<0.01). Also there was significant difference between two dependent means [Pre x after 45, Pre x After 90 or After 45 x 90] for group1.

Table 1: Effect of vitD3 on serum vitD3 level in pediatric patients with T1DM.

Variable	The study groups		
	Group 1	Group 2	Group 3
Pre VitD3 level (ng/ml)	11.05±0.992 (5.60-24.50)	15.00±1.565 (5.02-30.60)	26.67±2.201 (11.90-50.05)
After 45 days VitD3 level	18.22±1.081 (8.10-28.80)	14.14±1.051 (6.10-29.30)	27.50±2.075 (12.50-56.62)
After 90 days VitD3 level	26.41±1.796 (12.80-58.80)	10.52±0.808 (4.90-22.89)	29.83±2.317 (12.50-50.90)
P(values)			
Pre compared to group3	0.038*	0.0001**	-
Pre compared to group2	0.0001**	-	-
Comparing ALL	0.0001#,**	-	-
45 compared to group3	0.009*	0.0001**	-
45 compared to group2	0.0001**	-	-
Comparing ALL	0.0001#,**	-	-
90 compared to group3	0.0001**	0.249^{ns}	-
90 compared to group2	0.0001**	-	-
Comparing ALL	0.0001#,**	-	-
P value Pre x After 45	0.0001**	0.502^{ns}	0.248^{ns}
P value Pre x After 90	0.0001**	0.002*	0.001*
P value After 45xAfter 90	0.0001**	0.0001**	0.023*

Data were presented as Mean±SEM (Range) where

*Significant: difference between two independent means (group1x group2, group1 x group3, or group2 x group3) at every period, OR significant difference between two dependent means (Pre x after 45, Pre x After 90, or After 45 x 90) for every group.

Significant: difference among three independent means (group1 x group2 x group3) at every period. **: highly significant :(< 0.01).NS: non-significant (>0.05).
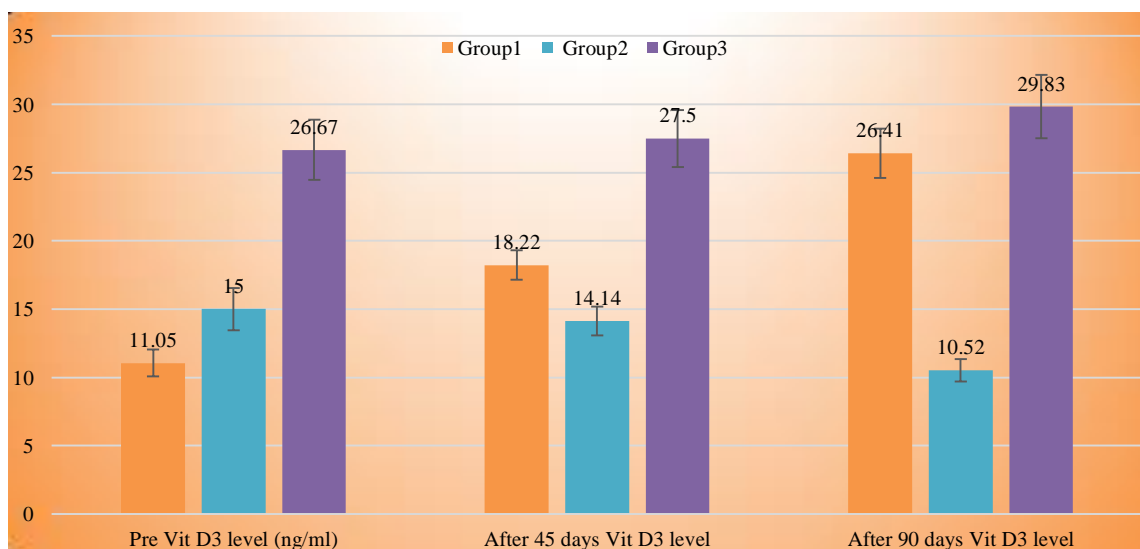

Figure (1): Effect of vitD3 on serum vitD3 level in pediatric patients with T1DM.

Effect of treatment with vitamin D3 on serum insulin levels in pediatric patients with T1 DM

The results of the study presented that treatment with vitD3 [2000UI /daily] affect significantly serum insulin levels compared to baseline after 3 months of treatment [P value Pre x After 90: = 0.001], while for group2 and group3 P value were non- significant (0.188, 0.134 respectively). Also there was significant difference among three independent means [group1x group2 x group3] at every period of treatment (where P value was >0.05).

Moreover, Table and Figure (2) showed the (means±SE) for each group and periods included in the study. The treatment with vitD3 produced the highest increasing in this parameter after 45 days then after 90 days compared to baseline values. However, no significant differences were reported between the effects of vitD3for group1 and group3 compared to group2: P value [After 45 x after 90] for group1 (0.217), for group2 (0.001), while for group3 where P value 0.193 (P>0.05).

Table 2: Effect of vitD3 on serum insulin level in pediatric patients with T1DM.

variable	The study groups		
	Group1	Group2	Group3
Pre Insulin level (Mu/ml)	27.58±5.277 (0.20-91.70)	11.84±3.224 (0.12-63.38)	17.98±2.150 (2.34-43.60)
After 45 days Insulin level	35.48±6.103 (0.78-101.6)	35.80±5.264 (9.50-99.60)	18.26±2.059 (3.10-39.10)
After 90 days Insulin level	41.46±5.733 (10.0-99.30)	14.13±2.582 (2.56-51.70)	18.63±1.943 (2.85-36.20)
P(values)			
Pre compared to group3	0.014*	0.099[ns]	-
Pre compared to group2	0.120[ns]	-	-
Comparing ALL	0.016#	-	-
45 compared to group3	0.969[ns]	0.010*	-
45 compared to group2	0.003*	-	-
Comparing ALL	0.016#	-	-
90 compared to group3	0.0001*	0.0001*	-
90 compared to group2	0.170[ns]	-	-
Comparing ALL	0.0001#	-	-
P value Pre x After 45	0.090[ns]	0.0001*	0.389[ns]
P value Pre x After 90	0.001*	0.188[ns]	0.134[ns]
P value After 45xAfter 90	0.217[ns]	0.001*	0.193[ns]

Data were presented as Mean±SEM (Range) where

*Significant: difference between two independent means (group1x group2, group1 x group3, or group2 x group3) at every period, OR significant difference between two dependent means (Pre x after 45, Pre x After 90, or After 45 x 90) for every group.

Significant: difference among three independent means (group1 x group2 x group3) at every period. **: highly significant :(< 0.01).NS: non-significant (>0.05).

Effect of treatment with vitamin D3 on serum HbA1c in pediatric patients with T1DM

The means ±SE for study results for the different groups at each period are shown in table and figure (3). Also the table showed that all DM patients treated with vitD3 revealed highly significant decrease in HbA1c levels after 3 months of treatment (P>0.01) compared with pre-treatment values.

Meanwhile, Table and Figure (3) showed that treatment with vitD3 produced the high reduction in this parameter after 3 [P value Pre x After 9 days for the group1] (P value 0.0001) compared to group2 (P value0.688) and group3 (P value 0.034), this revealed no significant difference between these patients how where not treated with vitD3 (P>0.05).

Data were presented as Mean±SEM (Range) where

*Significant: difference between two independent means (group1x group2, group1 x group3, or group2 x group3) at every period, OR significant difference between two dependent means (Pre x after 45, Pre x After 90, or After 45 x 90) for every group.

Significant: difference among three independent means (group1 x group2 x group3) at every period. **: highly significant :(< 0.01).NS: non-significant (>0.05).
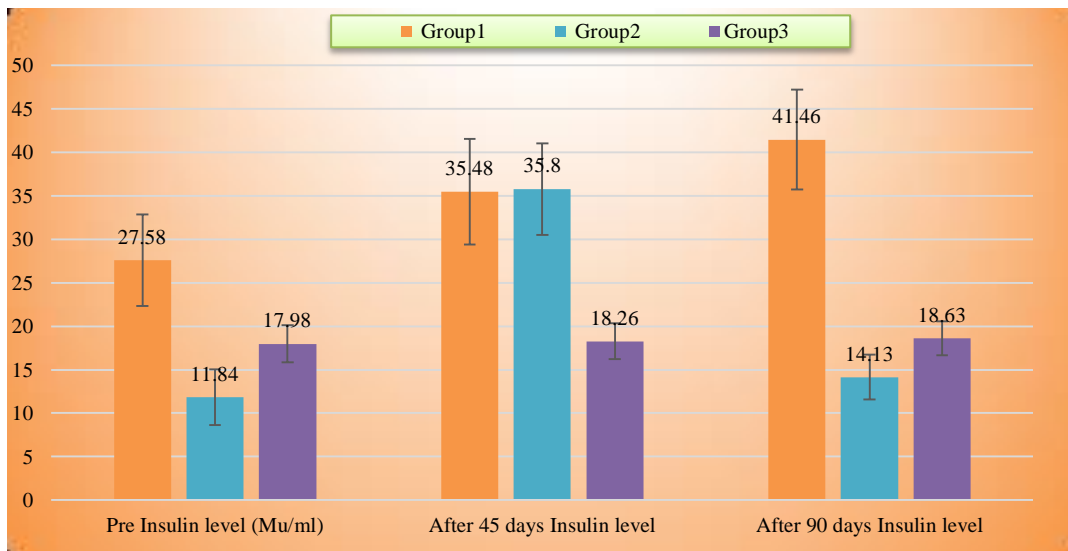
Figure 2: Serum insulin levels in pediatric patients with T1DM after treatment with vitD3.

Table 3: Effect of treatment with vitD3 on HbA1c in pediatric patients with T1DM.

| variable	The study groups		
	Group1	**Group2**	**Group3**
Pre HBA1c%	11.85±0.344 (8.20-15.0)	10.24±0.560 (1.30-15.0)	4.33±0.217 (2.00-6.20)
After 90 days HBA1c%	7.76±0.308 (5.0-10.0)	10.01±0.418 (6.50-14.0)	4.09±0.196 (2.00-5.98)
P values			
Pre *P* value compared to group3	0.018*	0.0001*	-
P value compared to group2	0.0001*	-	-
P value compare ALL	0.0001#	-	-
90 *P* value compared to group3	0.0001*	0.0001*	-
P value compared to group2	0.0001*	-	-
P value compare ALL	0.0001#	-	-
P value Pre x After 90	0.0001*	0.688^{ns}	0.034*
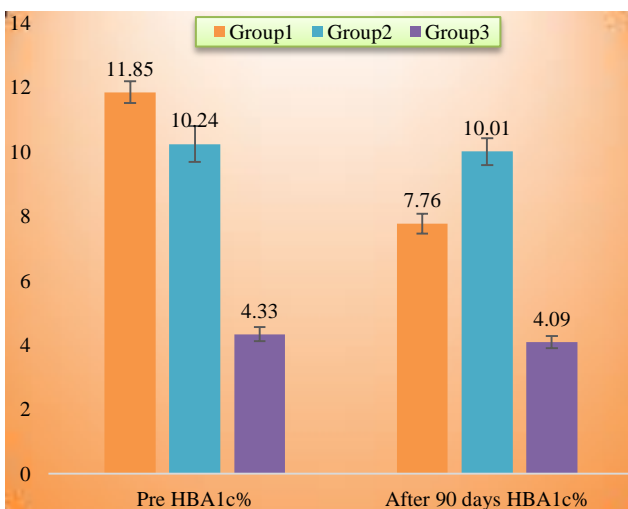
Figure (3): Effect of treatment with vitD3 on HbA1c in pediatric patients with T1DM.

The effect of treatment with vitamin D3 on FBG in pediatric patients with T1DM

The (means±SE) for study results for all groups and at every period involved in the study are shown in Table and Figure (4). Also the results demonstrated that there is a significant decrease in FBG within patients of group1 after 90 days (0.004) treating with vitD3 (*P*<0.05) compared with baseline values and with 45 days after treatment within the other groups of the study [0.013, 0.437, represent *P* value for group2 and group3 after 90 days of treatment].

Moreover, Table and Figure (4) showed that treatment with vitD3 produced a higher percent reduction in this parameter after 3 compared with base line values, rather than the effect of treatment with vitD3 after 45 days of treatment. There is a significant difference among the three groups treated with vitD3 after 3 months (*P*<0.05), but non-significant after 45 days (*P*>0.05). Also there was highly significant difference among three independent means [group1 x group2 x group3] at every period (*P*<0.01).

Table (4):-Effect of treatment with vitD3 on FBG in pediatric patients with T1DM.

variable	Study groups		
	Group1	Group2	Group3
Pre FBG (mg/dL)	171.04±13.289 (54.0-308.0)	172.24±15.499 (90.0-353.0)	77.49±2.984 (49.99-100.10)
After 45 days FBG	153.28±15.247 (75.0-400.0)	196.36±16.062 (90.50-350.0)	78.51±4.056 (45.0-115.0)
After 90 days FBG	122.29±10.292 (73.0-300.0)	217.10±16.457 (113.0-371.0)	73.60±3.285 (43.50-100.0)
P(values)			
Pre compared to group3	0.953^{ns}	0.0001*	-
Pre compared to group2	0.0001*	-	-
Comparing ALL	0.0001#	-	-
45 compared to group3	0.058^{ns}	0.0001*	-
45 compared to group2	0.0001*	-	-
Comparing ALL	0.0001#	-	-
90 compared to group3	0.0001*	0.0001*	-
90 compared to group2	0.0001*	-	-
Comparing ALL	0.0001#	-	-
P value Pre x After 45	0.336^{ns}	0.150^{ns}	0.823^{ns}
P value Pre x After 90	0.004*	0.013*	0.437^{ns}
P value After 45xAfter 90	0.051*	0.183^{ns}	0.207^{ns}

Data were presented as Mean±SEM (Range) where

*Significant: difference between two independent means (group 1 x group 2, group 1 x group 3, or group 2 x group 3) at every period, OR significant difference between two dependent means (Pre x after 45, Pre x After 90, or After 45 x 90) for every group.

Significant: difference among three independent means (group 1 x group 2 x group 3) at every period.**: highly significant :(< 0.01).NS: non-significant (>0.05).
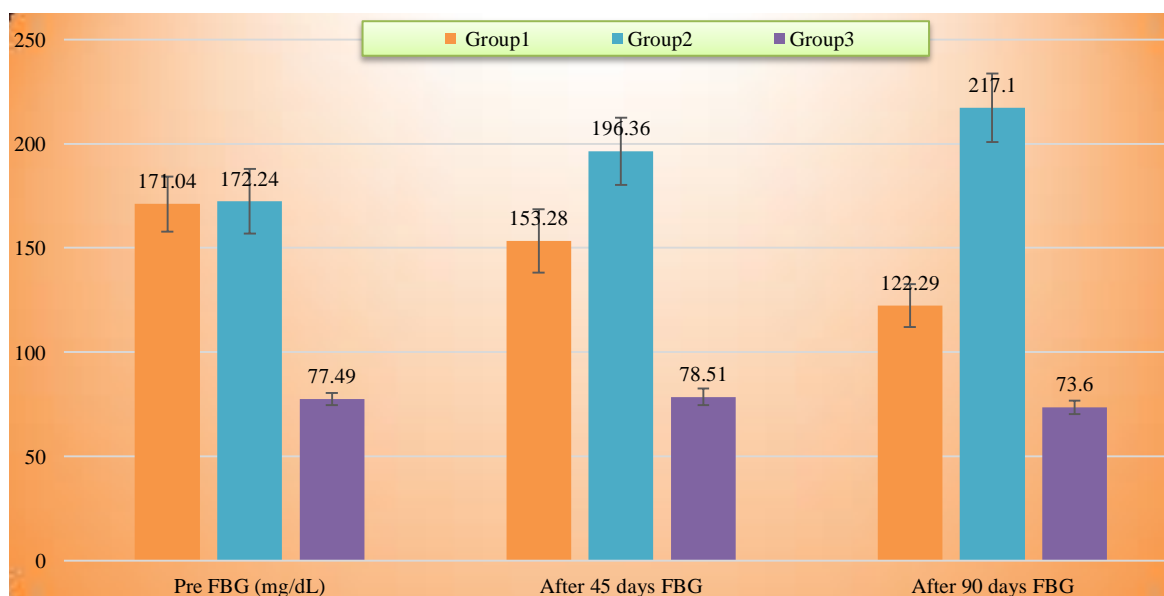

Figure 4: Effect of treatment with vitD3 on FBG in pediatric patients with T1DM.

Effect of treatment with vitamin D3 on serum C-peptide in pediatric patients with T1DM

The (means±SE) for study results for all groups and at each single period are shown in Table and Figure (5).Furthermore there was highly significant difference among three independent means [group1 x group2x group3] at every period during treatment. Also there was highly significant reduction in serum C-peptide within group1 compared to other groups of study after 45, 90 days of treatment ($p<0.01$).

Table (5):- Effect of treatment with vitD3 on serum C-peptide in pediatric patients with T1DM.

variable	The study groups		
	Group1	Group2	Group3
Pre Serum C-peptide	0.60±0.091 (0.01-1.60)	0.68±0.127 (0.03-2.50)	2.86±0.238 (1.01-5.10)
After 45 days Serum C-peptide	0.98±0.084 (0.05-1.70)	0.69±0.141 (0.08-3.20)	2.78±0.241 (1.00-4.90)
After 90 days Serum C-peptide	1.21±0.094 (0.32-2.10)	0.47±0.107 (0.01-1.98)	2.91±0.252 (0.70-4.95)
P(values)			
Pre compared to group3	0.593[ns]	0.0001**	-
Pre compared to group2	0.0001**	-	-
Comparing ALL	0.0001#	-	-
45 compared to group3	0.088[ns]	0.0001*	-
45 compared to group2	0.0001*	-	-
Comparing ALL	0.0001#	-	-
90 compared to group3	0.0001*	0.0001*	-
90 compared to group2	0.0001*	-	-
Comparing ALL	0.0001#	-	-
P value Pre x After 45	0.0001**	0.908[ns]	0.272[ns]
P value Pre x After 90	0.0001**	0.009*	0.683[ns]
P value After 45xAfter 90	0.007*	0.024*	0.257[ns]

Data were presented as Mean±SEM (Range) where:

*Significant: difference between two independent means (group1x group2, group1 x group3, or group2 x group3) at every period, OR significant difference between two dependent means (Pre x after 45, Pre x After 90, or After 45 x 90) for every group.

Significant: difference among three independent means (group1 x group2 x group3) at every period. **: highly significant :(< 0.01).NS: non-significant (>0.05).
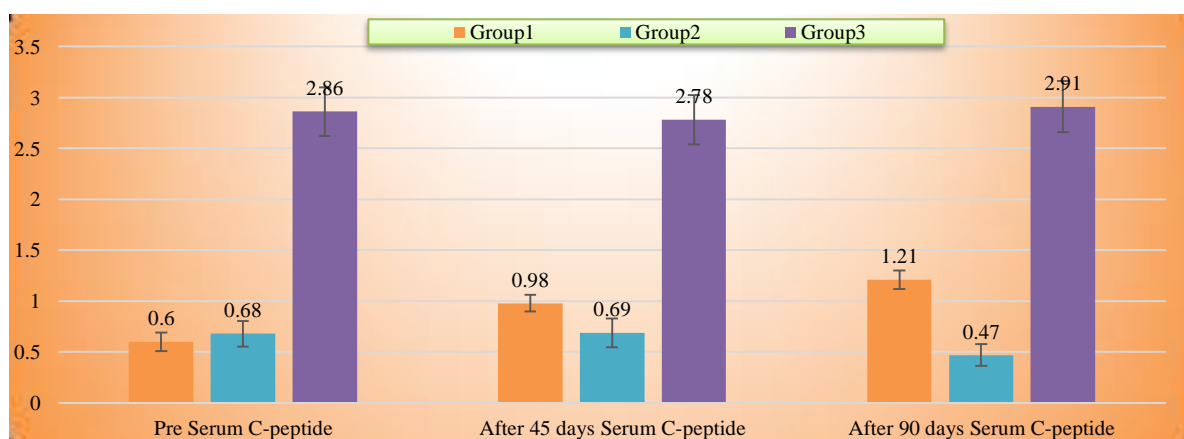
Figure (5): Effect of treatment with vitD3 on serum C-peptide in pediatric patients with T1DM.

DISCUSSION

In the present study, T1DM pediatric patients appeared to be low serum levels of vitD3. Those patients received vitD3 in addition to their daily insulin routine for 3 months showed a highly significant results for group1 compared with the other groups at periods [45, 90 days] after treatment where [*P*<0.01]. Also highly significant difference for group 1 if a comparison made between [45, and 90 days] after treatment where [*P*<0.05], which

showed an improvement in the serum vitD3 as showed in table and figure (1).The results compatible with Li *et al* study which noted lower vitD3 levels in T1DM patients compared with healthy controls and also found that vitD3 levels were much lower in individuals with T1DM or whom T1DM with complications.[23] The study demonstrates that delivery of 2,000 IU /daily vitD3 yield a good outcome among patients with low serum levels of vitD3 in a short-term treatment, otherwise the appropriate method of treatment should be determined

for a given patient to ensure compliance with a suitable efficacy and safety. Finally, the use of the current relatively high doses of vitamin D for the long-term treatment of low serum levels of vitD3 in infants and young children was not definite yet. [24]

The present study showed that treatment with vitD3 offered highly significant effect on serum insulin levels for group1 after 3 months of treatment compared to baseline [*P*-value pre-treatment against after 90 days of treatment: *P* was<0.01] with their baseline values, while for other groups *P*- value wasnon-significant (*P*>0.05). Also *P*-value for group1 against [group 2 and group3] showed highly significant difference at the end of treatment period, that's have a good influence on serum insulin (increase serum insulin levels) specifically for group1 patients as showed in Table and Figure (2). Moreover this present study compatible with Giulietti *et al* study around vitD3 deficiency that could leads to β-cell dysfunction and to decrease in insulin synthesis, insulin secretion and even to a clear insulin deficiency in vivo. [25] But, almost Mathieu and Baden hoop *et al* related studies found that vitD3 is essential for normal insulin secretion, impaired oral glucose tolerance, and expression of the gene encoding insulin. Thus any decrease in insulin secretion can be corrected by vitD3 supplementation. [26]

Because of the strong correlation between vitD3 and T1DM, the present study agreement with other studies of Pitocco *et al* and Li *et al*. Both demonstrated that vitD3 had a protective effect on maintaining β-cell function [27,] although the effect was not so clear and vitD3 supplementation could only momentarily reduce the insulin dose, if vitD3 dose was small dose to be administered in T1DM. While the Li's study, confirmed that the insulin plus vitD3 treatment [vitamin D3; 0.5 μg/day] group developed no β-cell failure, while 27.8 % in the control group developed β-cell failure [28.] The present study showed that patients in group1 who treated with vitD3 revealed highly significant decrease in HbA1c levels after 3 months of treatment (*P*>0.01) compared with pre-treatment values and compared with other groups involved in this study [results with non-significant *P* values where *P* value>0.05]. These results are compatible with a study demonstrated that the hypoglycemic activity of vitD3 on glycemic control (especially %HbA1c) in diabetic patients and it's related to vitaD3 level.If it was [above 30 ng/ml], the patients presented with much lower HbA1c levels than those patients who remained with vitD3levels [below 30 ng/ml]. This means that those people with the highest serum levels of vitD3 showed a good glucose control than those who were with lowest levels of vitD3. [29] Moreover, the present study agreed with Aljabri and Bokhari *et al* study on this field showed that treatment with maximum dose of vitD3 (2000IU) produced a good significant reduction in this parameter after 3 months for group1 patients rather than poor significant reduction for the other groups [group2 and group3

patients] if the final results values compared with the baseline values as showed in Table and Figure (3). [30] On the other hand, the Nikooyeh *et al* study discovered an inverse relationship concerning changes in vitD3 concentration and changes in serum insulin, and HbA1c. [31] And HbA1c change for better by 1%–1.5% in diabetic patients with vitamin D deficiency that was complete their treatment with vitD3. [32, 33]

T1DM is characterized by the loss of the insulin-producing β-cells, which eventually results in high levels of fasting glucose in the blood and also can be seen in T2DM [34.] In the present study compatible with Sárközy *et al* that use of vitD3 as a supplementary therapy with insulin routine could improve the diagnostic for type 1DM by markers of DM including FBG. [35] Also agreed with Dong *et al* trial which suggested that the use of vitD3 as supplementary therapy with daily insulin routine could slow the decline of residual β-cell function and improves in FBG. [36] Furthermore, it showed that the newly diagnosed T1DM patients in group1 had an obvious increase in the baseline levels of FBG in comparison with patients in group3 which agreed with Al-Khailani *et al* study on this parameter. [37] Thus, the present study demonstrated that there is a good decrease in FBG for group1 patients after 90 days of treatment with vitD3 (where *P*<0.05) compared with the only fair decrease in baseline values against 90 days after treatment values for group2 patients. In addition Table and Figure (3) showed that there was non-significant results within group 3 comparing baseline values against after 45, 90 days values. The treatment with vitD3 produced a higher reduction in this parameter after 90 days of treatment compared with base line values and after 45 days within group1 patients, rather than the poor significant effect of treatment with vitD3 after 45 days of treatment within group2 patients and group3 patients, or compared with the fair significant effect of treatment with vitD3 after 90 days of treatment within group3 patients.

All the results from the study matched up with Holick *et al* study that have suggested that impaired FBG is improved by increasing vitD3 [sometimes with addition of Ca] intake. [38] The rapid rate of β-cell destruction mainly in infants and children, then keto acidosis developed as the first manifestation of the disease, sometimes with modest fasting hyperglycemia. At this latter stage of the disease, there is slight or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide. [39] Moreover Table and Figure (5) which indicated that there was highly significant increase in serum C-peptide after treatment with daily dose of vitD3 for pediatric patients with T1DM [in the group1] compared to other patients who didn't receive any vitamin D3 supplement [in the group2 and group3] after 45,90 days of treatment where (*P*<0.01). In addition the results in this study are compatible with Amit and Vandana *et al* study in patients with new onset of T1DM, where the improvement in vitD3 level

lead to correct the decline of pancreatic function and improve the levels of C-peptide. [40] However new studies still need to ensure whether the administration of vitD3 would contribute to the preservation of adequate levels of C-peptide after diagnosis. [41]

CONCLUSION

In newly diagnosed T1DM pediatric patients, serum vitD3 levels are lower compared to healthy members with equaled age and BMI. Serum levels of vitD3 are increasing in treatment groups who treated with vitD3 after 3 months to levels equal to that reported in healthy controls. The current study in treatment group has shown the association of hypo-vitaminosis D with significantly improves the biological pointers (FPG, HbA1c, serum vitD3, serum insulin, and serum C-peptide) in newly identified pediatric patients having T1DM. Under the present clinical conditions, the use of 2000/IU/day tablet as complementary constituent in addition to the insulin schedule in pediatric patients with T1DM showed a fair link between serum vitD3 levels and decreased in daily insulin requirements for most patients and some of the investigated biochemical markers.

REFERENCES

1. American Diabetes Association, Standards of Medical Care in Diabetes, Diabetes Care, S1 (34), 2011 Jan, 11-61.

2. Jane K, National Diabetes Education Program CDC National Center for Chronic Disease Prevention and Health Promotion, Available from: www.cdc.gov/media/presskits/aahd/diabetes.pdf.

3. Mary Anne KK, Lloyd Yee Y, Brian KA, Robin LC,GuglielmoBJ, KradjanWA, Applied Therapeutics: The Clinical Use of Drugs, 9th eds, Lippincott Williams & Wilkins, 2009, Chapter 50 DM, 2-11.

4. Fausi AS, Kasper DL, Longo DL, Jameson JL, Hauser SL, Braunwald E, Harrisons Endocrinology,2nd eds, The McGraw-Hill Companies, USA,2010, Chapter 19 DM, 273-275.

5. Bluestone JA, Atkinson MA, Arvan P. The Pathogenesis and Natural History of Type 1 Diabetes. Cold Spring Harbor Laboratory, 2012; 2: 4-14.

6. Klinegman RM, Behrman RE, Jenson HB, Stanton BF, ChapmanIR, Adger JrH,Nelson Text book of Pediatrics, 18th ed., Elsevier Philadelphia, 2007, Chapter 590 (6) DM in children, 1-2.

7. Bikle D, Non-classic actions of vitamin D, J Clin Endocrinol Metab, 94(1), 2009, 26-34.

8. Truswell AS, Parick GW, Ciara EOR,ABC of nutrition,4th eds,BMJ Publishing Group London, 2003, Chapter 10Vitamins and some minerals, 65-67.

9. Report on Health & Social Subjects, Department of Health: Dietary reference values for food energy and nutrients for the United Kingdom, HMSO, London, 1991; 41.

10. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, An Endocrine Society Clinical Practice Guideline: Evaluation, treatment, and prevention of vitamin D deficiency, J Clin Endocrinol Metab, 96(7),2011, 1911-30.

11. Mathieu C, Gysemans C, Giulietti A, Bouillon R, Vitamin D and diabetes, Diabetologia. 48, 2005, 1247-1257.

12. Mohr SB, Garland CF, Gorham ED, Garland FC, The association between ultraviolet B irradiance, vitamin D status and incidence rates of type 1 diabetes in 51 regions worldwide, Diabetologia, 51,2008, 1391-1398.

13. Bandeira F, Bandeira C, Freese E, Occult vitamin D deficiency and its relationship with bone mineral density among postmenopausal women in Recife Brazil, J Bone Miner Res, 18(2), 2003, 407- 9.

14. Mathieu C, van Etten E, Decallonne B, Vitamin D and 1, 25-dihydroxyvitamin D3 as modulators in the immune system, J Steroid Biochem Mol Bio,2004, 449 -52.

15. Gabbay MA, Sato MN, Finazzo C, Duarte AJ, Dib SA, Effect of cholecalciferol as adjunctive therapy with insulin on protective immunologic profile and decline of residual β-cell function in new-onset type 1 diabetes mellitus, Arch Pediatr Adolesc Med, 166(7), 2012, 601-7.

16. Riachy R, Vandewalle B, Moerman E, Belaich S, Lukowiak B, Gmyr V, 1,25-Dihydroxyvitamin D3 protects human pancreatic islets against cytokine-induced apoptosis via down-regulation of the Fas receptor, Apoptosis, 11(2), 2006, 151-9.

17. Seshadri KG, Tamilselvan B, Rajendran A, Role of vitamin D in diabetes, J Endocrinol Metab, Elmer press, 1(2), 2011, 47-56 .

18. Parekh D, Sarathi V, Shivane VK, Bandgar TR, Menon PS, Shah NS, Pilot study to evaluate the effect of short-term improvement in vitamin D status on glucose tolerance in patients with type 2 diabetes, EndocrPract, 16,2010,600-608.

19. Von Hurst PR, Sonehouse W, Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient: a randomized placebo-controlled trial, Coad J Br J Nutr, 103,2010,549-555.

20. Pittas AG, Lau J, Hu FB, Dawson-Hughes B,The role of vitamin D and calcium in type 2 diabetes: a systematic review and meta-analysis, J Clin Endo Metab, 92, 2007, 2017-2029.

21. Mathieu C, Gysemans C, Giulietti A, Bouillon R, Vitamin D and diabetes, Diabetologia, 48(7), 2005, 1247-1257.

22. Aranow C, Vitamin D and the Immune System, J Investig Med, 59(6), 2011 Aug, 881-886.

23. Li J, Xiao B, Xiang Y, Immune Function of Vitamin D in Type 1 Diabetes Mellitus, Intern J of Bio Med, 4(2),2014, 67-71.

24. Gordon CM, Williams AL, Feldman HA, May J, Sinclair L, Vasquez A, Cox JE, Treatment of hypo-vitaminosis in

infants and toddlers, J ClinEndocrinolMetab,93(7),2008 Jul,2716 -2721.

25. Giulietti AC, Gysemans K, Stoffels E, van Etten B, Decallonne L, Overbergh R, Mathieu BC, Vitamin D deficiency in early life accelerates Type 1 diabetes in non-obese diabetic mice, Diabetologia, 47,2004,459-460.

26. Mathieu C, Badenhoop K, Vitamin D and type 1 diabetes mellitus: state of the art, Endocrinology and Metabolism,20(20),2005Mar,1-5.

27. Li X, Liao L, Yan X, Protective effects of 1-alpha-hydroxyvitamin D3 on residual beta-cell function in patients with adult-onset latent autoimmune diabetes (LADA),Diabetes Metab Res Rev,25,2009,411–416.

28. Yang CY, Leung PSC, Adamopoulos IE, Gershwin ME, The Implication of Vitamin D and Autoimmunity: a Comprehensive Review, Clinic Rev AllergImmunol. Springer, New York, 2013Jan29, 1-6.

29. Vitamin D council: Type 1DM, Updated in Feb 2014,https://www.vitamindcouncil.org/health-conditions/type-i-diabetes.

30. Aljabri KS, Bokhari SA, Khan MJ, Ann Saudi Med, Glycemic changes after vitamin D supplementation in patients with type 1 diabetes mellitus and vitamin D deficiency, PMC, 30(6), 2010 Nov-Dec, 454-458.

31. Nikooyeh, B, Neyestani TR, Farvid M, Alavi-Majd H, Houshiarrad A, Kalayi A, Shariatzadeh N, Gharavi A, Heravifard S, Tayebinejad N, Daily consumption of vitamin D or vitamin D + calcium-fortified yogurt drink improved glycemic control in patients with type 2 diabetes: a randomized clinical trial,Am. J. Clin. Nutr, 93, 2011, 764-771.

32. Schwalfen berg G, Vitamin D and diabetes; improvement of glycemic control with vitamin D3 repletion, Can. Fam. Physician, 54, 2008, 864-866.

33. Mohammadian S, FatahiN,Zaeri H, VaKili MA, Effect of Vitamin D3 Supplement in Glycemic Control of Pediatrics

with Type 1 Diabetes Mellitus and Vitamin D Deficiency, Journal of Clinical and Diagnostic Research,9(3),2015 Mar, 5-7.

34. Khalaf BH, Abdulridh MK, Kadhim AK, Hussain SA, influence of large daily doses of metformin on the expression of interleukin-1β and c-reactive protein in type2 Diabetes patients, International Journal of Pharmacy and Pharmaceutical Sciences,(6) 2, 2014 Mar,506-509.

35. Sárközy M, Szűcs G, Pipicz M, Zvara Á, Éder K, The effect of a preparation of minerals, vitamins and trace elements on the cardiac gene expression pattern in male diabetic rats, Cardiovascular Diabetology,14(85),2015,3.

36. Dong JY, Zhang W, Chen JJ, Zhang Z-Li, Han SF, Review: Vitamin D Intake and Risk of Type 1 Diabetes: A Meta-Analysis of Observational Studies, Nutrients, 5, 2013, 3558-3560.

37. Al-Khailani KAK, Correlation between serum metformin with clinical and biochemical markers in Newly Diagnosed Female Patients with Type2 Diabetic Mellitus [PhD thesis], Baghdad(Iraq): University of Al-mustansriayh, 2006.

38. Holick MF, Issues in the Nutritional Treatment of Diabetes, Diabetes and the Vitamin D Connection, Current Diabetes Reports, 8, 2008, 393-398.

39. Dabelea D, Mayer DEJ, Saydah S, Search for Diabetes in Youth Study. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009, JAMA, 311, 2014, 1778–1786.

40. Amit V, Vadana K, Neeraj K, PreetiK, Vitamin D and Diabetes: A New Horizon, Acta Medica International,1(2), 2014 Jul – Dec,136-168.

41. Griz LHM, Bandeiram F, Andrade M, Gabbay MAL, Dib AS, Carvalho EF, Vitamin D and Diabetes Mellitus: An Update 2013,ArquivosBrasileiros de Endocrinologia & Metabologia, 2014, 58: 1-8.