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Relationship Between 25 (OH) Vitamin D level and Subclinical Atherosclerosis in Type 1 Diabetic Children

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ABSTRACT

Background: Hypovitaminosis D is associated with increasing risk of macrovascular complications in patients with type 1 diabetes mellitus. **Aim**: early prediction of risk factors of cardiovascular complication of type 1 diabetes mellitus to decrease the morbidity and mortality of type 1 diabetes mellitus. **Patients and Methods:** This case-control study included 88 children between 12 and 15 years old who were classified into two groups. Group I: 50 patients who had already been diabetics for 5 years or more and they were 20 males (40%) and 30 females (60%).Group II: 38 apparently healthy subjects, matched to the diseased group. They were 14 males (37%) and 24 females (63%) According to diabetic control and HbA1c % level, we divided the diabetic group into; group Ia (well controlled): they were 19 patients, and their HbA1c level was up to 7.5 % and Group Ib (poorly controlled): 31 patients, and their HbA1c level was more than 7.5 %. The studied groups were subjected to the following: thorough history taking, clinical examination and laboratory investigations including: lipid profile,HbA1c,vitamin D and radiological aortic intima media thickness (aIMT) measurement using B mode ultrasonography. **Results:** There were significant Vitamin D deficiency in diabetic group in comparison to healthy controls.Our study also reported a significant positive correlation between aIMT and HbA1C ($P < 0.001$). AIMT increased significantly as HbA1C increased. We also noted a significant reversed correlation between vitamin D and the increase of aortic IMT ($P < 0.001$ each). **Conclusions:** We concluded that conventional cardiovascular risk factors are linked to the increased IMT and Vitamin D is a significant determinant of an increase in IMT in type 1 diabetics. This process is likely an early stage of atherosclerosis. The significant association might point to a link in the pathogenesis of atherosclerosis.

KEYWORDS: Vit D, subclinical atherosclerosis, type 1 DM

INTRODUCTION

Type 1 diabetes mellitus, a disease with genetic predisposition and autoimmune pathogenesis, predominantly affects children and young adults. It is characterized by autoimmune destruction of insulin producing beta-cells in the pancreas. [1]

Diabetes continues to be a public health concern. The global number of individuals with diabetes 347 million people worldwide [2]. It has been estimated that 6.5% would be affected with diabetes worldwide by the year 2025.The incidence of type 1 diabetes mellitus in Egypt is 8/100 000 per year. [3,4]

Diabetes has many complications such as cardiovascular disease, renal impairment, and peripheral neuropathies. Cardiovascular complication is the leading cause of mortality in diabetic patients. Although cardiovascular disease is not specific to diabetes, it is more prevalent among patients with type 1 or type 2 diabetes than among those without diabetes. Type 1 diabetes is associated with at least a 10-fold increase in cardiovascular disease as compared with an age-matched nondiabetic population. Individuals with diabetes mellitus have 2-fold to 4-fold increased risk of developing atherosclerotic diseases. [5]

The role of vitamin D in the pathogenesis and prevention of diabetes has sparked widespread interest. In peripheral insulin target tissues, vitamin D enhances insulin action via regulation of the calcium pool. Vitamin D also acts as a potent immunosuppressor. It tends to down-regulate the transcription of various proinflammatory cytokine genes. It promotes the induction of regulatory T-lymphocytes, the production of anti-inflammatory cytokines, and protects beta-cell from destruction. [6]

Serum 25(OH) vitamin D concentrations (Levels categorized into sufficient ≥ 30 ng/ml , insufficient 20-30ng/ml, deficient ≤ 20 ng/ml), which reflect both vitamin D intake and endogenous production. So, it is the best indicator of vitamin D body store levels, and it is measured as a marker of vitamin D status. The 25(OH) D is metabolized to its active form 1, 25-dihydroxyvitamin D (1, 25(OH) 2D) in the renal epithelium and in macrophages and other cells of the immune system. [7]

Several epidemiological studies have shown an association between low serum 25 hydroxyvitamin D [25(OH) D] levels and increased risk for cardiovascular diseases (CVD), hypertension, stroke, and hyperglycemia , in which hypovitaminosis D reaches a prevalence of up to 75% [8]

Vitamin D deficiency should not be considered only as a feature of osteo-mineral disorders, but also as a biomarker and a risk factor for metabolic derangements as well as CVD. This study aims to examine and analyze the effects of hypovitaminosis D as a risk factor for CVD in type 1 diabetic children. [9]

High-resolution ultrasound is a reliable, noninvasive method for detecting early structural and functional atherosclerotic changes in the arterial wall. Increased aortic intima-media thickness (IMT) is a structural marker of early atherosclerosis that correlates with vascular risk factors, relates to the severity and extent of coronary artery disease, and predicts the likelihood of cardiovascular complications.[10,43]

Methods:

This case-control study included 88 children between 12 and 15 years old who were classified into two groups:

Group I: 50 patients who had already been diagnosed as diabetic patients according to the standard ADA criteria and had regular follow up in pediatric endocrinology outpatients' clinic, Ismailia Health Insurance Hospital, Egypt.

They fulfilled the following criteria:

Children (12-15years) suffering from type 1 diabetes mellitus and duration of diabetes more than 5 years.

Group II: 38 apparently healthy subjects, age and sex matched to the diseased group. They were collected during the period from September 2014 to March 2015.

According to diabetic control and HbA1c % level, we divided the diabetic group into; group Ia (well controlled): and their HbA1c level was up to 7.5 % and Group Ib (poorly controlled): and their HbA1c level was more than 7.5 %. [10]

Patients presenting with any of the following were not included in the study:

-Patients suffering from any chronic illness

-Active smoker patients.

-Hypertensive Patients: blood pressure values greater than 95th percentile for age, height and sex on three different occasions diagnosed as hypertension according to International Pediatric Hypertension Association 2006.

-Patients having abnormal lipid profile.

-Obese patients: Obesity is defined as a BMI at or above the 95th percentile for children of the same age and sex. [11]

-patient having microalbuminuria

Microalbuminuria defined as albumin/creatinine ratio of 30-300 mg/gm

All patients were subjected to:

Medical history including :

-personal history (Socio-demographic data)

-detailed present history of diabetic children:

(onset of diagnosis, current and previous medications, duration of treatment , complications, frequency of follow up and hospital admission)

-Past medical history specially history of vitamin D administration .

*Clinical examinations w*ith emphasis on:

-Blood pressure.

Using the "gold standard" technique for BP measurement in children auscultation with sphygmomanometer containing a mercury column, using the stethoscope placed over the brachial artery pulse, proximal and medial to the antecubital fossa and below the bottom edge of the cuff (about 2 cm above the cubital fossa). The auscultatory method relies on the deduction of Korotkoff sounds for determining systolic and diastolic BP

values. With use the appropriate cuff size, measure BP in controlled environment; allow 3-5 min of rest in the seated position, the anticubital fossa must be supported at heart level. Then put BP level on the percentile as blood pressure values greater than 95th percentile for age, height and sex on three different occasions diagnosed hypertensive according to International Pediatric Hypertension Association 2006.

-Weight, Height, and Body mass index (BMI) were calculated as = weight (kg) \ height (m^2), according to the Egyptian growth curves.

-waist circumference

Radiological assessment :

The entire study patients were subjected to;

High resolution beta mode ultrasonography:

The procedure was performed and interpreted by a single radiologist on the same ultrasound machine (Philips medical system/HD11 with a 10-MHztransducer linear array probe). The aorta was scanned, with the subject in supine position. Intima-media thickness was measured from end-diastolic M-mode images (minimum vessel distension) after a 10-minute rest. Plaques, which were defined as focal thickening > 1.2-1.5 mm were avoided because they had different implications. The distance between lumen-intima and media-adventitia interface was measured. The largest thickness was subjectively chosen (IMT max). The far wall was used for assessment because the accuracy of the near wall is less than that of the far wall because of technical considerations. [12]

Laboratory investigation:

-Glycated hemoglobin (HbA1c) level measured by quantitative colorimetric determination of glycohemoglobinin whole blood.

-lipid profile measured by enzymatic colorimetric method, venous blood sample was withdrawn in the morning after at least 10 hours fasting.

-25-OH vitamin D level was measured by ELISA kits.Levels categorized into Deficient ≤ 25 nmol/l, Insufficient >25 till 50 nmol/l and optimal >50 nmol/l Vitamin D)[13]

Data management and statistical analysis:

All data were coded, computerized, they were presented in order of frequency and percentage and tabulated in graphs and tables by Excel 2003 for windows. Chi-square test was used for qualitative data to find out the difference between variables and to detect significant associations of data. T-test was used for detection of difference quantitative data. Data was summarized as mean ± standard deviation. Pearson correlation was done for correlation between variables, P-value fixed at 5% level where, $p>0.05$:non-significant, $p<0.05$:significant difference, $p<0.001$:highly significant difference.

Ethical considerations:

We received a consent from parents of all individuals participating in our research and were informed about the objectives of the study and details of study steps. Confidentiality of the information was guaranteed, no personal data was published. Agreements from the responsible authorities was obtained, from ethical committee of faculty of medicine Suez Canal University Institute. The subjects did not pay for this research and did not pay for the investigations, they had the right to withdraw at any time from the study. All left over samples if any were discarded at once and not used in any other research.

Results:

This case-control study included 88 children between 12 and 15 years old who were classified into two groups:

The diabetic group included twenty males (40%) and thirty females (60%) while control group included fourteen males (37%) and twenty four females (63 %) (Figure 1).

The comparison between diabetic children (group I) and their healthy matched controls (Group II) showed that the mean age for diabetic children was 13.9±1.11 and ranged from (12-15 years) while that of controls was 13.5±1.01 and also ranged from (12-15 years). (Table 1).

The diabetic children were significantly shorter than the control group, with mean height (158.58±12.56) and (161.66±5.55) respectively (p-value <0.001).The BMI and weight were also significantly higher in the diabetic group (p – values <0.001).The BMI was (20.03±2.52) in diabetic children , in comparison to (19.01±1.32) in the healthy controls, while weight was (45.10±11.34) in diabetic children , and (39.39±3.93) in healthy controls. (Table 1)

There were also significant increase in waist circumference and waist/hip ratio in diabetic children (p-value <0.001). (Table 1)

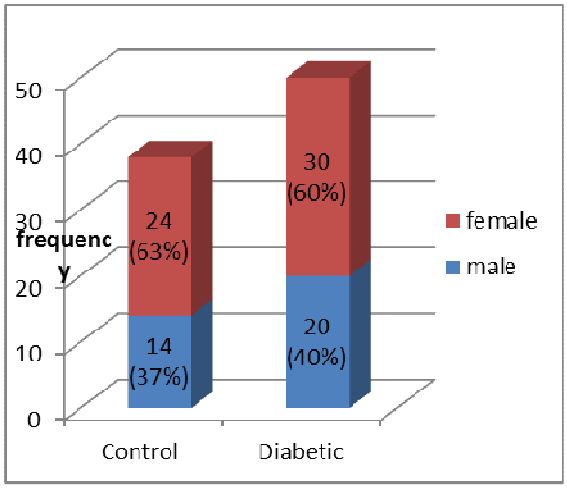

Fig. 1: sex distribution among studied groups

Table 1: Comparison between the diabetic children and controls as regard some clinical parameters.

Clinical Parameter	Group I(Diabetic children)(N=50)	Group II(Control)(N=38)	P-Value
Age:(year) (Mean±SD)	13.9±1.11	13.5±1.01	0.085
Weight (kg) (Mean±SD)	45.10±11.34	39.39±3.93	<0.001*
Height (cm) (Mean±SD)	158.58±12.56	161.66±5.55	<0.001*
BMI (kg/m^2)(Mean±SD)	20.03±2.52	19.01±1.32	<0.001*
Waist circumference (cm) (Mean±SD)	67.65±7.59	58.28±5.13	<0.001*
Waist /hip ratio	0.83±0.044	0.80±0.069	0.014*

*significant

Table 2: Comparison between the diabetic children and controls as regard some Laboratory parameters.

Laboratory parameter	Group I(Diabetic children)(N=50) (Mean±SD)	Group II(Control)(N=38) (Mean±SD)	P-Value
cholesterol	128.14 ± 39.98	131.97 ± 38.26	0.651
Triglycerides	178.74 ± 43.18	191.92 ± 49.43	0.186
LDL	81.78 ± 27.64	84.13 ± 30.83	0.708
HDL	124.66 ± 35.70	119.29 ± 38.56	0.501
HbA1c (%)	9.39 ± 2.52	4.47 ± 0.85	<0.001*
25-hydroxyvitaminD (nmol/l)	30.34 ± 15.20	48.53 ± 20.26	<0.001*

*significant

As regard some laboratory parameters, The HbA1c was significantly higher in the diabetic group with mean (9.39 ± 2.52 gm/dl) in comparison to healthy controls (4.47 ± 0.85 gm/dl) , (p –value <0.001) . **(table 2)**

Vitamin D level was significantly lower in diabetic group with mean (30.34 ± 15.20 nmol/l) in comparison to healthy controls with mean (48.53 ± 20.26 nmol/l) , (p –value <0.001).There was no significant difference between lipid profile in both groups.(table2)

Table 3: Comparison between the diabetic children and controls as regard aIMT(aortic intima media thickness).

parameter	Group I(Diabetic children)(N=50) (Mean±SD)	Group II(Control)(N=38) (Mean±SD)	P-Value
aIMT (cm)	0.059 ± .0178	0.039± .006	<0.001*

*significant

Table 3 shows the a IMT (aortic intima media thickness) was significantly (p-value <0.001) higher in diabetic group with mean (0.059 ± .0178) in comparison to healthy controls with mean (0.39± .006).

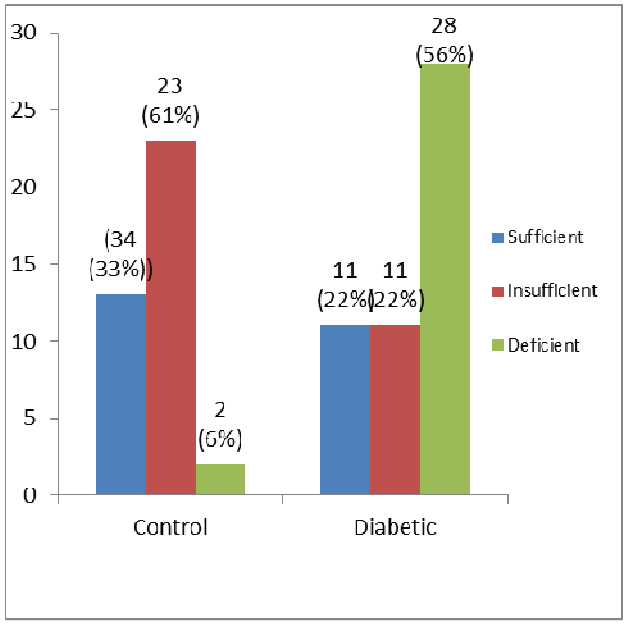

Fig. 2: 25-hydroxyvitD levels among studied groups

Concerning 25-hydroxyvitD levels in diabetic patients, the current study found that 56 % of the studied diabetic group had deficient 25-hydroxyvitD levels while 22 % had insufficient 25-hydroxyvitD levels and 22% had normal 25-hydroxyvitD levels. Compared to healthy controls, we found that only 6% were 25-hydroxyvitD deficient and 61 % were 25-hydroxyvitD insufficient while 34% had normal levels.(Figure 2)

(N.B: Deficient ≤ 25 nmol/l, Insufficient >25 till 50 nmol/l and optimal >50 nmol/l Vitamin D) (Thacher TD, 2011)

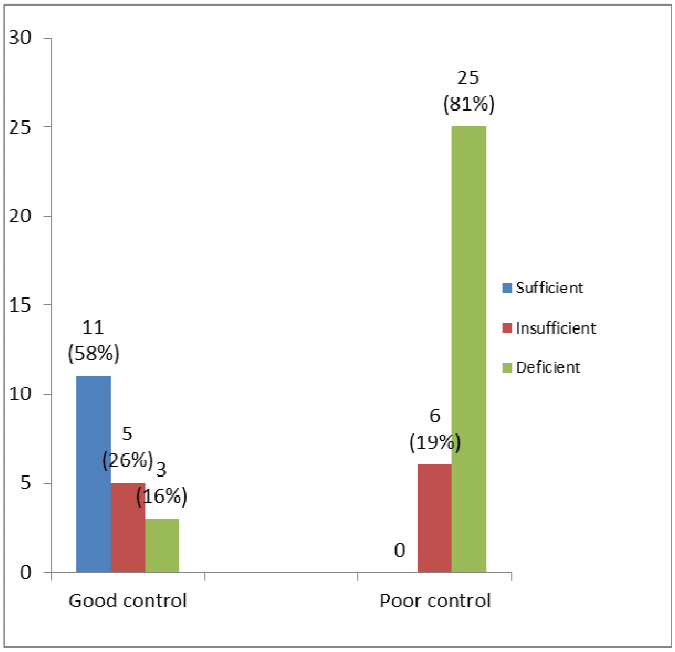

Fig. 3: Comparison between 25-hydroxyvitD levels between good and poor controlled diabetics.

Figure 3 showed that 3 patients with good glycemic controlled had deficient 25-hydroxyvitD versus 25 patients with poor glycemic control while 5 patients with good glycemic controlled had insufficient levels versus 6 patients with poor glycemic control.

Table 4 shows there were significant strong negative correlation between 25-hydroxyvitamin D and HbA1c % ($r = -0.832$, $p<0.001$) and a strong negative correlation between 25-hydroxyvitamin D and aIMT ($r = -0.894$,

p<0.001) . On contrary, there were insignificant correlations between 25-hydroxyvitamin D and duration of diabetes, BMI and lipid profile.

Table 4: Correlations between 25-hydroxyvitamin D and studied parameters

Vitamin D	correlation	p-value
Sex	-0.161	0.265
Age	0.017	0.909
Duration of diabetes	0.035	0.807
BMI	0.198	0.168
Weight (kg)	0.166	0.248
Height (cm)	0.133	0.358
Waist circumference	-0.049	0.736
Waist /hip ratio	-0.147	0.307
Cholesterol	-0.121	0.404
Triglycerides	-0.055	0.705
LDL	0.026	0.855
HDL	0.039	0.789
HbA1C	-0.832	<0.001*
aIMT (cm)	-0.894	<0.001*

Table 5: Comparison between good and poor glycemic controlled diabetic children as regard some clinical parameters.

Parameter	Good controlled No=19 (Mean±SD)	Poor controlled No=31 (Mean±SD)	P- Value
Age (years)	13.68 ±1.11	14.03 ± 1.11	0.287
duration of diabetes(years)	6.58 ± 2.16	6.35 ± 2.02	0.713
BMI (kg/m^2)	19.9 ± 2.69	20.05 ± 2.45	0.940
weight (kg)	44.63 ± 11.75	45.39 ± 11.27	0.822
height (cm)	153.58 ± 13.33	150.58 ± 12.30	0.980
waist circumference(cm)	66.73 ± 8.25	68.21 ± 7.24	0.511
waist/hip ratio	0.831 ± .0388	0.833 ± .0475	0.836

Table 5 showed there were insignificant differences between good and poor controlled diabetic children as regard age, duration of DM, weight, height, BMI , waist circumference.

Table 6: Comparison between good and poor glycemic controlled diabetic children as regard some laboratory parameters.

Parameter	Good controlled No=19 (Mean±SD)	Poor controlled No=31 (Mean±SD)	P- Value
Cholesterol	123.74 ± 38.11	130.84 ± 41.47	0.548
Triglycerides	164.21 ± 24.17	187.65 ± 49.79	0.062
LDL	75.00 ± 23.02	85.94 ± 29.71	0.177
HDL	124.05 ± 35.30	125.03 ± 36.52	0.926
vit D (nmol/l)	43.68 ± 13.65	22.16 ± 9.16	<0.001*

*significant

Regarding the glycemic control, the current study found that good glycemic controlled diabetic children had significantly higher 25-hydroxyvitaminD levels than the poor glycemic controlled diabetic children where P<0.001. There were insignificant differences between both groups as regard lipid profile.

Table 7: Comparison between good and poor glycemic controlled diabetic children as regard aIMT.

Parameter	Good controlled No=19 (Mean±SD)	Poor controlled No=31 (Mean±SD)	P- Value
aIMT (cm)	0.043 ± 0.014	0.070 ± 0.011	<0.001*

*significant

Table 7 shows that good glycemic controlled diabetic children had significantly decreased aIMT where p<0.001.

Table 8: Correlations between aIMT and some clinical and laboratory parameters

aIMT	correlation	p-value
Sex	0.159	0.270
Age	0.016	0.911
Duration of diabetes	0.019	0.896
BMI	-0.157	0.277
Weight	-0.128	0.376
Height	-0.124	0.391
Waist circumference	0.032	0.825
Waist /hip ratio	0.109	0.450

Cholesterol	0.098	0.497
Triglycerides	0.173	0.228
LDL	0.126	0.383
HDL	0.029	0.842
HbA1C	0.875	<0.001*
Vitamin D	-0.894	<0.001*

Table 8 shows Correlations between aIMT and some clinical and laboratory parameters show significant positive correlation between aIMT and both HbA1c (r = 0.875 , p-value <0.001) and a significant negative correlation between aIMT and 25-hydroxyvitamin D level (r = -0.894 , p <0.001).There was no significant correlation between aIMT and lipid profile, BMI, age and duration of diabetes.

Discussion:

Type 1 diabetes mellitus (T1D) is an autoimmune disease in which the pancreas is unable to respond to secretagogue stimulation with appropriate insulin secretion. Hyperglycemia develops when more than 70-90% of the insulin-producing beta cells are destroyed. An autoimmune destructive process, which plays a central role in the development of T1D, is facilitated by the subject's own genetic susceptibility and by non-genetic factors. Non-genetic factors include viral infections, toxic chemicals, and others [14]

Vitamin D is a steroid hormone produced in the skin, having specific regulatory or functional effects on other parts of the body. Recent studies suggest that 25(OH)D3 shows immunomodulatory effects on a cellular level in patients with T1D and healthy controls by shifting immunity to self-tolerance. Increased plasma levels of 25(OH)D3 may inhibit a proinflammatory cell milieu. These studies generate the hypothesis that the immunmodulatory effects may be influenced by genotypes of the VDR and CYP24A1 illustrating their functional role in T1D susceptibility, which is worth further investigation. [15]

Morbidity from diabetes is a consequence of both macrovascular (atherosclerosis) and microvascular (retinopathy, nephropathy, and neuropathy) complications and is related to glycemia, as measured by HbA1c; which remains a major focus of therapy [16]

Macrovascular complications of diabetes include coronary artery disease, stroke and peripheral vascular disease. Risk factors include insulin resistance, hyperglycemia, hypertension, hyperlipidemia, cigarette smoking and obesity [17]

Endothelial dysfunction, increased systemic inflammation, circulating free fatty acids, oxidative stress and the accumulation of advanced glycation end products portend an increased risk for diabetic atherosclerotic disease [18]

The lesions of atherosclerosis represent a series of highly specific cellular and molecular responses that can best be described as an inflammatory disease. Their underlying pathogenesis involves an endothelial dysfunction [19]

High-resolution B-mode ultrasound imaging of intima-media thickness (IMT) of the aorta has been shown to reflect histopathologically verified atherosclerosis. Therefore, it is widely applied in studies of the occurrence, and risk factors of early atherosclerosis [20]

The aim of our study was to estimate the relationship between vitamin D and aortic intima-media thickness, as a marker of vascular wall properties, in children with T1D.

Results of our study showed that comparison between the diabetic children and the control group as regards some clinical parameters revealed that group I had higher weight and shorter height than group II. This result was in agreement with (Thon et al., 1992)and (Paulino et al.,2006) who found that diabetic children were higher in weight and shorter in comparison to healthy children. Concerning BMI and waist circumference, there were significant difference between group I and group II where P< 0.001. This result was in agreement with Mao et al.,2011[22,23,24]

Regarding some laboratory parameters, we showed that group I had significant higher HbA1c % than group II. This was in agreement with Ciechanowski PS et al,2002[25]

Concerning 25-hydroxyvitamin D, group I had significantly lower serum level than group II where P<0.001. This could be explained by that Vitamin D deficiency may promote beta cells destruction in humans. Moreover, the presence of T1D is related to low vitamin D concentration whilst the lowering of 25-hydroxy vit D levels during the years after diagnosis is a consequence of disturbed metabolism due to diabetes mellitus. Indeed, this may be explained why bone density is lower in T1D than in T2D [26]

In animal (mice) study, a vitamin D analogue had been shown to down regulate the production of proinflammatory chemokines , thereby inhibiting T-cell recruitment and the development of T1D [27]

Another possible mechanism is that vitamin D may have direct effects on B-cells, including improving insulin secretion, enhancing expression of vitamin D receptors and improving islet morphology This result was in agreement with a study conducted in Egypt, by Soliman et al at Minia university hospital, they found that 15.1 % of the studied diabetic group had deficient 25-hydroxyvitD levels while 84.9 % had insufficient 25-hydroxyvitD levels [28,29]

This agrees also with (Bin Abbas et al, 2011) who found that 84% of the T1DM children were vitamin D deficient. The study included 100 Saudi children below 18 years old with T1DM attending the Pediatric Endocrinology and Diabetes Clinics. The study was conducted over a period from June to September 2010.[30]

Also, agrees with (Bener et al,2009) who found that vitamin D deficiency was considerably higher in T1DM children (90.6%). This study is based on the 170 T1DM cases in young Qatari population below 16 years of age. The survey was conducted over a period from 6 August to 25December 2007 .[31]

This result was also in agreement with (Littorin et al.,2006) who found that 25-hydroxyvitD was lower in patients with T1DM compared with control subjects whether they are recently diagnosed or after years of diagnosis .[32]

This finding may support the idea that vitamin D deficiency may be an important factor behind the development of T1D, perhaps with an immunological background (Szanya et al., 2002) and (Zemunik et al .,2005) Also, it was lower after years of diagnosis of T1D and this was in agreement with Svoren and his colleges.[33,34,39]

We showed that 22 % of T1D patients were 25-hydroxyvitD insufficient and 56 % were deficient. In comparison to our result,(Bener et al.,2009) found 90.6 % of diabetics versus 85.3 % of nondiabetics had vitamin D deficiency and in northeastern US , it had been found that 15 % of T1D were 25-hydroxyvitD deficient versus 61 % insufficient [31] .

Furthermore, (Janner et al.,2010) found 60.5 % of diabetic children were vitamin D deficient. Similarly, in North India, in a case-control study, 58 % of T1D versus 32 % of the control (Borkar et al .,2010). Piccini and his collegues in 2012 found that vitamin D deficiency was present in 43.9 % of patients and insufficiency in 35.5 % according to studies conducted on healthy children .[35,36,37].

Moreover,(Branco et al.,2012)found that there was insufficiency in 28 % of T1DM patients, deficiency in 32 %, severe deficiency in 9 % and normal in 31 %, 55 % deficiency of boys and 45 % of girls .[38]

The reasons for the different prevalence in vitamin D deficiency given from different countries could be related to the variability of vitamin D deficiency definition, as well as geographical environment and latitude, skin colou, nutritional, social habits and may be genetic influence. [40]Concerning glycemic control, good glycemic controlled children had insignificant difference than poor glycemic controlled children as regard age and duration of DM. This was in agreement with (Hartmann et al.,2001). Concerning 25-hydroxy vitD, good glycemic controlled children had significant higher levels than poor glycemic controlled children where $P < 0.001$ [41] .

We found significant strong negative correlation between 25-hydroxyvitD and HbA1c % ($P<0.001$). In contrast, Littorin et al. found that there was insignificant correlation between 25-hydroxy vit D levels and HbA1c % and this indicated that the diabetic state per say is a reason for low 25-hydroxyvitD levels and is not secondary to any hyperglycemic or insulin-resistant state. [29]

In our study, we also measured the intima-media thickness which is regarded as a marker of early atherosclerosis. We carried out measurements of aortic intima-media thickness (AIMT) which has been mostly supported by latest publications as a useful method for analyzing early atherosclerosis in young people compared to carotid artery .

Harrington et al.,2010 reported aortic intima-media thickness to be a more valuable indicator of early atherosclerosis in children diagnosed with diabetes mellitus type 1 as compared to carotid intima-media thickness. In that study, they found a significant correlation between aortic intima-media thickness and HbA1C and lipids .[40]

As regard aortic intima media thickness (aIMT) in our study, it was significantly (p-value <0.001) higher in diabetic group with mean ($0.059 \pm .0178$) in comparison to healthy controls with mean ($0.039 \pm .006$). This was in agreement with (Murat Ersoy et al.,2015) who found that diabetic children has higher aIMT compared to healthy controls , and this is an indicator of subclinical atherosclerosis.[42]

Also, we showed that good glycemic controlled diabetic children had significantly decreased aIMT where $p<0.001$. As well, we found significant negative correlation between aIMT and 25-hydroxyvitamin D level ($r = -0.894$, $p <0.001$).There was no significant correlation between aIMT and lipid profile, BMI, age and duration of diabetes.

These results were in agreement with(Harrington J et al .,2010) who found strong positive correlation between aIMT and HbA1c level in diabetic children, also found that aIMT was more accurate than cIMT in assessing subclinical atherosclerosis in children. [40]

Study limitations:

There are some limitations to the study as the small sample size and the fact that it was a single center study, which may reduce its generalizability.

Patients with hypertension and/or obesity were not included in our study and both are risk factors for subclinical atherosclerosis.

Conclusions:

Our study revealed Vitamin D deficiency in diabetic group in comparison to healthy controls. This work also reported a significant positive correlation between aIMT and HbA1C ($P < 0.001$). aIMT was increased significantly as HbA1C increased. We also noted a significant reversed correlation between vitamin D and the increase of aortic IMT ($P < 0.001$).

We concluded that conventional cardiovascular risk factors are linked to the increased IMT and Vitamin D is a significant determinant of an increase in IMT in type 1 diabetics. This process is likely an early stage of atherosclerosis. The significant association might point to a link in the pathogenesis of atherosclerosis .

However, searching for the presence of Vitamin D deficiency is recommended for assessing early atherosclerosis and cost benefit for type 1 diabetic children should be assessed.

Recommendations:

We recommend routine screening for Vitamin D deficiency in diabetic children and Vitamin D supplementation among children with type 1 Diabetes Mellitus.

Aortic intima media thickness is an early predictor for subclinical atherosclerosis and easy, non-invasive technique and we recommend routine screening for diabetic children for early detection of subclinical atherosclerosis.

REFERENCES

[1] Holick, M.F., D. Vitamin, 2004. : importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis.Am J Clin Nutr.,79(3): 362-371.
[2] Danaei, G., M.M. Finucane, et al., 2011. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet., 378(9785): 31-40.
[3] Sicree, R., J. Shaw, P. Zimmet, 2006. Prevalence and projections.In Diabetes Atlas. 3rd ed. Brussels, Belgium: International Diabetes Federation., pp: 16-104.
[4] Soltesz, G., C. Patterson and G. Dahlquist, 2010. Global trends in childhood type 1 diabetes. IDF Diabetes Atlas,4 th ed.
[5] Laing, S.P., A.J. Swerdlow, S.D. Slater, et al., 2003. Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. Diabetologia, 46: 760-5.
[6] Krishna, G., Seshadri, Bubblu Tamilselvan, et al., 2011. Role of Vitamin D in Diabetes. J Endocrinol Metab., 1(2): 47-56.
[7] Liu, E., J.B. Meigs, A.G. Pittas, N.M. McKeown, et al., 2009. Plasma 25-hydroxyvitamin d is associated with markers of the insulin resistant phenotype in nondiabetic adults. J Nutr., 139(2): 329-334.
[8] Martini, L.A., R.J. Wood, D. Vitamin and blood, 2008. Pressure connection:update on epidemiologic, clinical, and mechanistic evidence. Nutr Rev., 66: 291e7.
[9] Torun, E., H. Genç, E. Gönüllü et al., 2013. The clinical and biochemical presentation of vitamin D deficiency and insufficiency in children and adolescents. J Paediatric Endocrine Met., 26: 469-475.
[10] American Diabetes Association (ADA): 2014. Standards of Medical Care in diabetes-Diabetic care 37(1): S14-62.
[11] Bischoff-Ferrari, H.A., E. Giovannucci, W.C. Willett, et al., 2006. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr., 84: 18-28.
[12] Parfrey, P.S., S.M. Griffiths, B.J. Barrett, M.D. Paul, M. Genge, J. Withers, N. Farid, P.J. McManamon,1989. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. N Engl J Med., 320: 143-153.
[13] Thacher, T.D., B.L. Clarke, 2011. Vitamin D insufficiency. Mayo Clin Proc., 86: 50-60.
[14] Agustin, B., A. Bianca and O. Leonid, 2011. INTECH; Medicine, Endocrinology and Metabolism, Role of Vitamin D in the Pathogenesis and Therapy of Type 1 Diabetes Mellitus, type 1 diabetes complications, pathogenesis and alternative treatments, 19: 403.
[15] Sabrina Maufa, Marissa Penna-Martineza, Thorsten Jentzschb, et al., 2015. Immunomodulatory effects of 25-hydroxyvitamin D3 on monocytic cell differentiation and influence of vitamin D3 polymorphisms in type 1 diabetes. The Journal of Steroid Biochemistry and Molecular Biology, 147: 17-23.
[16] Maria Nordwall, Mariann Abrahamsson, Meryl Dhir, et al., 2015. Impact of HbA1c, Followed From Onset of Type 1 Diabetes, on the Development of Severe Retinopathy and Nephropathy: The VISS Study (Vascular Diabetic Complications in Southeast Sweden). Diabetes Care , ADA 38(2): 308-315.
[17] Boden, W.E. and D.P. Taggart, 2009. Diabetes with coronary disease: a moving target evolving therapies. N Engl J Med., 360: 2570.
[18] Orasanu, G. and J. Plutzky, 2009. "The Continuum of Diabetic Vascular Disease: From Macro- to Micro-," Journal of the American College of Cardiology, 53(5): 35-42.

[19] Weber, C. and H. Noels, 2011. Atherosclerosis: current pathogenesis and therapeutic options. Nat Med., 17: 1410.
[20] Aloi, M., L. Tromba, G. Di Nardo, et al., 2012. Premature subclinical atherosclerosis in pediatric inflammatory bowel disease. J Pediatr., 161(4): 589-94.e581.
[21] American Diabetes Association, 2013. Diagnosis and classification of Diabetes Mellitus. Diabetes Care., 36: 72.
[22] Thon, A., E. Heinze, K.D. Feilen, et al., 1992. Development of height and weight in children with diabetes mellitus: report on two prospective multicentre studies, one cross-sectional, one longitudinal. Eur J Pediatr., 151: 258-262.
[23] Paulino, M.F., S.H. de Lemos-Marini, G. Guerra-Júnior, et al., 2006. Growth and body composition in children with type 1 diabetes mellitus. Arq Bras Endocrinol Metabol., 50: 490-498.
[24] Mao, L., W. Lu, F. Ji, et al., 2011. Development and linear growth in diabetic children receiving insulin pigment. J Pediatr Endocrinol Metab., 24: 433-436.
[25] Ciechanowski, P.S., I.B. Hirsch, W.J. Katon, 2002. Interpersonal predictors of HbA(1c) in patients with type 1 diabetes. Diabetes Care., 25: 731-736.
[26] Petrova, N.L., A.V. Foster, M.E. Edmonds, 2005. Calcaneal bone mineral density in patients with Charcot neuropathic osteoarthropathy: differences between Type 1 and Type 2 diabetes. Diabet Med., 22: 756-761.
[27] Giarratana, N., G. Penna, S. Amuchastegui, et al., 2004. Vitamin D analog down-regulates proinflammatory chemokine production by pancreatic islets inhibiting T cell recruitment and type 1 diabetes development. J Immunol., 173: 2280-7.
[28] Soliman, G.T., B.A. Ali, A.A. Mohamed, et al., 2015. Assessment of Vitamin D Status in Egyptian Children with Type-1 Diabetes Mellitus. J Diabetes Metab., 6: 573. doi:10.4172/2155-6156.1000573
[29] Littorin, B., P. Blom, A. Schölin, et al., 2006. Lower levels of plasma 25-hydroxyvitamin D among young adults at diagnosis of autoimmune type 1 diabetes compared with control subjects: results from the nationwide Diabetes Incidence Study in Sweden (DISS). Diabetologica., 49: 2847-52.
[30] Bin-Abbas, B.S., M.A. Jabari, S.D. Issa, et al., 2011. Vitamin D levels in Saudi children with type 1 diabetes. Saudi Med J., 32: 589-592.
[31] Bener, A., A. Alsaied, M Al-Ali., et al., 2009. High prevalence of vitamin D deficiency in type 1 diabetes mellitus and healthy children. Acta Diabetol., 46: 183-189.
[32] Littorin, B., P. Blom, A. Schölin, et al., 2006. Lower levels of plasma 25-hydroxyvitamin D among young adults at diagnosis of autoimmune type 1 diabetes compared with control subjects: results from the nationwide Diabetes Incidence Study in Sweden (DISS). Diabetologica., 49: 2847-52.
[33] Szanya, V., J. Ermann, C. Taylor, et al., 2002. The subpopulation of CD4+CD25+ splenocytes that delays adoptive transfer of diabetes expresses L-selectin and high levels of CCR7. J Immunol., 169: 2461-2465.
[34] Zemunik, T., V. Skrabic, V. Boraska, et al., 2005. FokI polymorphism, vitamin D receptor, and interleukin-1 receptor haplotypes are associated with type 1 diabetes in the Dalmatian population. J Mol Diagn., 7: 600-604.
[35] Piccini, A., F. Barni, M. Gausti, et al., 2012. Vitamin D levels in youth with type 1 diabetes:effects of vitamin D supplementation on glycemic control. Pediatric Diabetes., 13: 48.
[36] Janner, M., P. Ballinari, P.E. Mullis, et al., 2010. High prevalence of vitamin D deficiency in children and adolescents with type 1 diabetes. Swiss Med Wkly, 140: w13091.
[37] Borkar, V.V., Devidayal, S. Verma, et al., 2010. Low levels of vitamin D in North Indian children with newly diagnosed type 1 diabetes. Pediatr Diabetes., 11: 345-350.
[38] Branco, S., C. Rego, C. Costa, D. Vitamin, 2012. deficiency in children and adolescents with type 1 diabetes. Pediatric Diabetes., 13: 91-2.
[39] Svoren, B.M., D. Butler, B.S. Levine, et al., 2003. Reducing acute adverse outcomes in youths with type 1 diabetes: a randomized, controlled trial. Pediatrics., 112: 914-922.
[40] Harrington, J., A.S. Peña, R. Gent, et al., 2010. Aortic intima media thickness is an early marker of atherosclerosis in children with type 1 diabetes mellitus.J Pediatr., 156(2): 237-41.
[41] Hartemann-Heurtier, A., S. Sultan, C. Sachon, et al., 2001. How type 1 diabetic patients with good or poor glycemic control cope with diabetes-related stress. Diabetes Metab., 27: 553-559.
[42] MURAT ERSOY, HATICE NILGUN, SELCUK DURU, et al. 2015. AORTIC INTIMA-MEDIA THICKNESS AND MEAN PLATELET VOLUME IN CHILDREN WITH TYPE 1 DIABETES MELLITUS. IRAN J PEDIATR. 25(2): E368.
[43] Enric Serra, Planas, Eva Aguilera M, Luisa Granada, Barta Soldevila, Isabel Salinas, et al., 2015. High Prevalence Of Vit D Deficiency And Lack Of Association With Subclinical Atherosclerosis In Asymptomatic Patients With Type I Diabetes Mellitus From A Mediterranean Area.Acta Diabeticol., 52: 773-779.