

## Relations between Vitamin D level and Carotid Artery Intima-Media Thickness in Adolescents with Type 1 Diabetes

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### Abstract

**Introduction:** Given that carotid artery intima-media thickness (cIMT) has been identified as a surrogate marker for increased cardiovascular risk, it is important to determine which factors, if any, contribute to the increment of cIMT value in T1DM adolescents. Some recent review studies concluded appreciated relation between vitamin D deficiency and development of atherosclerosis.

**Objectives:** to study the relation between vitamin D levels and cIMT in adolescents with T1DM.

**Methods:** The current cross sectional, case- control study included 80 subjects {40 adolescents with T1DM aged 12-18 years (14.56± 1.65 years) average glycosylated hemoglobin (HbA1C) of T1DM patients selected was >7%, and forty healthy age and sex matched adolescents as a control group}. All candidates were subjected to full clinical evaluation (including vital signs, complete systemic examination, assessment of pubertal development by Tanner staging and anthropometric measurements (weight, height, BMI and waist/hip ratio). All the candidates had the following laboratory investigation been done (fasting blood glucose (FBG), average HbA1C, C- peptide and 25 (OH) vitamin D). cIMT was done for all the subjects included in the study.

**Results:** cIMT levels were significantly higher in cases (0.051± 0.005 cm) than in healthy controls (0.045± 0.006 cm), P value < 0.001. Vitamin D level was significantly lower in cases (29.500±6.37 ng/dl), than in controls (40.25± 6.49 ng/dl), P value < 0.001. Significant negative linear correlation was found between cIMT and vitamin D (r value -0.265 and P value 0.018).

**Conclusion:** patients with type 1 diabetes have significantly increased mean (cIMT) and significantly reduced mean vitamin D level compared to the control subjects. Increased (cIMT) was inversely correlated with vitamin D level.

**Keywords:** T1DM, cIMT, vitamin D.

### بطانة الشريان السباتي في المراهقين المرضى بالسكري من النوع الأول

**مقدمة:** سمك بطانة الشريان السباتي هو أداة قيمة للتشخيص المبكر لتصلب الشرايين لذلك فمن المهم دراسة العوامل المؤثرة عليه. العديد من الدراسات الحديثة أثبتت دور لنقص فيتامين د في حدوث تصلب الشرايين.

**الأهداف:** الهدف من هذه الدراسة إكتشاف العلاقات بين سمك بطانة الشريان السباتي وفيتامين د في الدم وذلك في المراهقين المرضى بالسكري من النوع الأول.  
**المنهجية العلمية:** شملت الدراسة (دراسة عينة وعينة ضابطة) ثمانون مراهقاً، أربعون منهم مرضى بالنوع الأول من السكر وأربعون آخرون أصحاء كمجموعة ضابطة. تم أخذ التاريخ المرضي والعائلي وتم عمل فحص إكلينيكي كامل وأُشتمل هذا الفحص على العلامات الحيوية فحص إكلينيكي كامل لأجهزة الجسم تقييم درجة البلوغ باستخدام مقياس ترنر والقياسات الجسمية (الطول، الوزن، معدل كثافة الجسم، نسبة محيط الخصر إلى محيط الازداف). تم عمل التحاليل الأتية: مستوى فيتامين د، والجلوز الصائم، الهيموجلوبين السكري، البيبتيد ج. كما تم قياس سمك الشريان السباتي العام (الطبقة المتوسطة والداخلية) في الجهتين اليمنى واليسرى وحساب المتوسط الحسابي باستخدام جهاز الموجات فوق الصوتية.

**النتائج:** عند مقارنة المراهقين المرضى بالنوع الأول من السكر مع الأصحاء من المجموعة الضابطة وجدت فروق مهمة احصائياً في كلا من: متوسط سمك الطبقة الوسطى والداخلية للشريان السباتي العام أعلى في الحالات (0.051 ± 0.005) سم عنها في المجموعة الضابطة (0.045 ± 0.006) سم قيمة p < 0.001. وايضاً وجد فرق مهم احصائياً بين الحالات والمجموعة الضابطة في مستوى فيتامين د في الحالات (29.5 ± 6.37) ng/dl أقل من المجموعة الضابطة (40.25 ± 6.49) ng/dl قيمة p < 0.001. كما كانت هناك علاقة عكسية مهمة احصائياً بين سمك الطبقة الوسطى والداخلية للشريان السباتي مع فيتامين د قيمة r تساوى -0.265 وقيمة p تساوى 0.018.

**الاستنتاج:** لقد أظهرت نتائج هذه الدراسة أن وجود علاقة عكسية بين قيمة سمك بطانة الشريان السباتي وبين مستوى فيتامين د في الدم في المراهقين المرضى بالسكر من النوع الأول.

**الكلمات الدالة:** السكر من النوع الأول، فيتامين د، سمك بطانة الشريان السباتي.

### Introduction:

Morbidity and mortality in type 1 diabetic patients derive mainly from advanced microvascular, neuropathic, and macrovascular complications (Mohammadi et al., 2009). The development of such complications is related to the duration of diabetes and the degree of glycemic control.

Given that cIMT has been identified as a surrogate marker for increased cardiovascular risk, it is important to determine which factors, if any, contribute to the cIMT increment in T1DM adolescents (Sibal et al., 2011 & Lee et al., 2011). cIMT value has been correlated to cardiac risk factors and established as a cardiac screening tool in studies on high risk adults (Gupta et al., 2013).

The risk factors predicting cIMT value increment are not well established in paediatric diabetic patients (Jarvisalo et al., 2002 & Rathsman et al., 2012). Few follow up studies indicate that progression of cIMT is influenced by factors like HbA1C, BMI, disease duration and serum LDL (Pozza et al., 2011).

Some recent review studies concluded appreciated relation between vitamin D deficiency and development of atherosclerosis like Chua et al., 2011 who concluded that vitamin D deficiency could be an independent risk factor for the development of peripheral arterial disease (PAD). In addition, vitamin D deficiency is significantly associated with increased risk of cardiovascular adverse events. McGreevy and Williams, 2011, in their review study found that Emerging evidence indicates that vitamin D deficiency, cardiovascular disease, and endothelial dysfunction are linked by biological associations. However, no clear evidence indicates that vitamin D supplementation has a role to play in the prevention of cardiovascular disease.

Hypovitaminosis D is now being identified as a prevalent health problem in both adults and children (Holick and Garabedian 2006). The mean level of vitamin D was found to be lower in patients with T1DM at the time of diagnosis compared with controls. In a study from Australia, 43% of adolescents with T1D were found to be vitamin D deficient (Greer et al 2007). The mean level of vitamin D was found to be lower in patients with T1DM compared with controls in a study done in Assiut, Egypt (Enas et al., 2011).

Hypovitaminosis D has been reported to be associated not only with lowered insulin secretion and sensitivity but also with adverse effects on total cholesterol, low density lipoprotein (LDL) cholesterol and high density lipoprotein (HDL) cholesterol concentrations in studies of healthy men and women from several racial and ethnic groups (Pérez-Lopez 2009), 25-hydroxyvitamin D levels recently have been shown to correlate positively with HDL levels and insulin sensitivity and inversely with HbA1C in obese children (Alemzadeh et al., 2008). A highly significant positive and independent correlation has been reported between serum 25(OH) D and apolipoprotein (Apo) A-I and with high density lipoprotein (HDL) cholesterol levels, being the relations independent of calcium (Pérez-Lopez 2009).

### Aim Of The Study:

The aim of this study was to study the relation between cIMT and 25 OH vitamin D in adolescents having T1DM.

### Patients And Methods:

Eighty subjects were included (40 adolescents with T1DM, and 40 healthy adolescents as a control group). This cross sectional, case-controlled study was conducted from July 2012 till December 2012, and was conducted in diabetes clinic Ain Shams University hospital. The selected patients had the following

inclusion and exclusion criteria:

1. Inclusion Criteria:
  - a. Adolescents with type 1 diabetes, aged from 12 to 18 years. All the selected patients had no episode of diabetic ketoacidosis one month prior to enrolment in the study.
  - b. Duration of illness more than 5 years.
  - c. Patients with average HbA1C more than 7% (average of last 3 readings).
2. Exclusion Criteria:
  - a. Adolescents with disorders predisposing them to vitamin D deficiency e.g Vitamin D dependent rickets, hypophosphatemic rickets and chronic renal Failure.
  - b. Adolescents with disorders associated with bone disease e.g Osteogenesis Imperfecta, or impairment of calcium metabolism e.g hypoparathyroidism or pseudohypoparathyroidism.
  - c. Adolescents with previous vitamin D supplementation during the last year before enrollment in the study.
3. Ethical aspect of the study:
  - a. Written informed consent was obtained from the parents after explanation. Informed verbal assent was taken also from all the patients after a simplified explanation of the aim and benefits of the study for them. All the patients data were confidential, neither the data nor the collected samples were used in other researches.
  - b. Approval was taken to conduct this research from the ethical committee of the Institute of Postgraduate Childhood Studies Ain Shams University, the ethical committee of the faculty of medicine Ain Shams University and the ethical committee of the National Research Center (NRC) of Egypt.
4. Examination And Measurements: All Adolescents were subjected to the following:
  - a. Full History.
    - ✧ Complete clinical examination including pubertal assessment.
    - ✧ Anthropometric measurements (body weight using regularly calibrated and serviced weight scale, standing height using stadiometer, hip and waist circumference using inelastic insertion tape.
  - b. Laboratory Investigation:
    - ✧ Vitamin D (25OH vitamin D) level using ELISA technique.
    - ✧ Fasting blood glucose (FBG) using colorimetric method.
    - ✧ Hemoglobin A1C (HbA1c) using quantitative colorimetric determination of glycol-hemoglobin in whole blood sample.
    - ✧ C-peptide using ELISA technique.
    - ✧ Imaging study: cIMT was done for all the subjects included in the study.

### Statistical Analysis:

The statistical analysis of the data was obtained in the present study was carried out using SPSS version 16. Nominal data were presented as frequency and percentage and were compared using Chi Square Tests. Numerical data were expressed as mean and standard deviation. Means were compared using t-tests. Correlation between various variables was done using Pearson's and Spearman's correlations were used for detection of the relation between 2 variables (Quantitative and Qualitative respectively). P-values less than 0.05\*

were considered significant (S), P-values less than 0.01\*\* were considered highly significant (HS). r was considered weak if <0.25, mild if >0.25- <0.5, moderate if >0.5- <0.75 and strong if >0.75.

**Results:**

The subjects were classified into two groups, Group 1 (T1DM patients) and Group 2 (control subjects). Forty adolescents with type 1 diabetes mellitus were enrolled in this study and forty non-diabetic healthy siblings and family members of the selected patients. The diabetic cases were 22 males and 18 females. The control subjects were 23 males and 17 females.

The studied diabetics have a mean duration of diabetes of (7.88± 2.69) years (ranged from (5- 14) years, all the studied subjects were on multiple daily injection insulin regimen with variable glycemic control as assessed by the mean HbA1c 9.04±1.04 ranged from (7.5- 11.5%). The mean total daily dose was (59.45±18.2) units which equal nearly (1.1±.26) unit per kg per day. The mean weight was (54.93± 9.19), the mean height was (157.75 ±8.06) cm and the mean BMI was (21.82± 2.27) kg/m<sup>2</sup>. The studied diabetics have a mean Waist/Hip ratio of (0.78±0.020) significantly higher than control Waist /Hip ratio of (0.75± 0.035). No significant differences were noted neither in systolic nor diastolic blood pressure between cases and control subjects.

Table (1) Comparison between control and case regarding laboratory and radiological data.

	Control N= 40	Study N= 40	T Value	P
	Mean ± SD	Mean ± SD		
C-Peptide (ng/ml)	1.58±0.64	0.065±0.04	14.93	<0.001 **
25 OH Vitamin D (ng/dl)	40.25±6.49	29.5±6.37	7.46	<0.001 **
Radiological Data	Control	Study		
Cimt (Cm)	0.045±0.006	0.051±0.005	4.274	<0.001**

\*\* Highly Significant

Significant differences between T1DM adolescents and controls were noted regarding the following, vitamin D mean level in cases is (29.5± 6.37) ng/ml significantly lower than in controls (40.25± 6.49) ng/ml (p <0.001, T=7.46). Regarding mean cIMT level a significant difference was noted between the studied T1DM patients' cIMT mean level which equals (0.051± 0.005) cm and the mean cIMT level of the control group which equals (0.045± 0.006) cm.

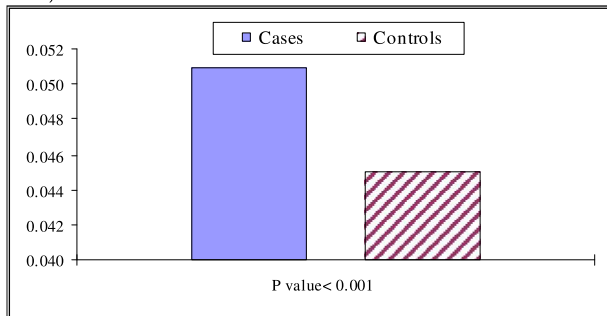


Figure (1) comparison between mean cIMT levels in cases and controls

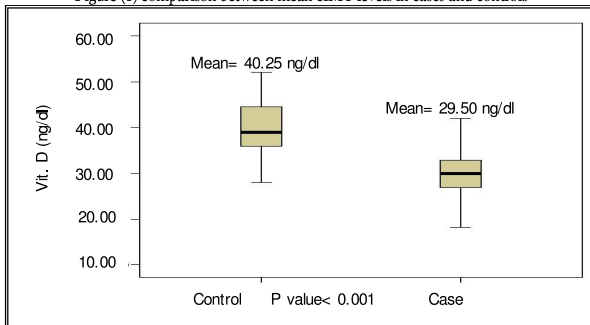


Figure (2) comparison between mean 25 OH vitamin D levels in cases and controls

No statistically significant correlation could be found between cIMT and any of the clinical variables studied. cIMT shows a statistically significant negative correlation with C-peptide level and 25 OH Vitamin D, while the relation with mean HbA1C and blood glucose level both were positive.

A significant negative correlation was noticed between cIMT and 25 OH vitamin D, r value (-0.265) and P value (0.018).

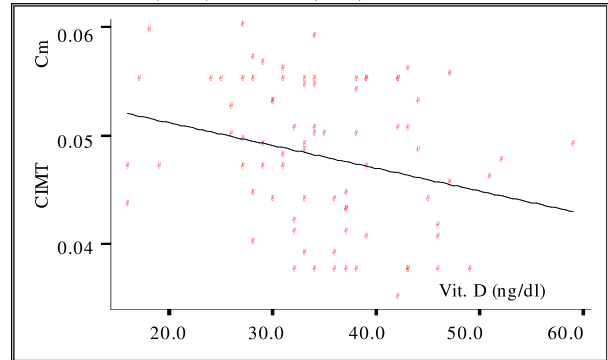


Figure (3) The correlation between cIMT and 25 OH vitamin D (r value-0.265 and P value 0.018).

Table (2) Correlations between cIMT and other laboratory variables.

	cIMT	
	r	p
C-Peptide	-0.394	<0.001**
FBG (fasting blood glucose)	0.385	<0.001**
mHbA1C% (mean HbA1C)	0.311	0.040 *

\* Significant, \*\* highly significant

Two significant negative correlations were found between vitamin D and both BMI and W\H ratio, where P values equals 0.018 and 0.005 respectively, while no statistically significant relation could be proved between vitamin D and any of other clinical variables studied. Vitamin D shows statistically significant positive correlation with C-peptide and shows also statistically significant negative correlations, with FBG and mHbA1C.

Table (3) Correlations between vitamin D with clinical and laboratory variables.

	Vit D	
	r	p
BMI	-0.263	0.018 *
W\H Ratio	-0.311	0.005 **
Systolic Blood Pressure	-0.045	0.689
Diastolic Blood Pressure	-0.014	0.905
C-Peptide	0.572	<0.001 **
FBG	-0.594	<0.001 **
mHbA1c% (mean HbA1c)	-0.624	<0.001 **

\* Significant, \*\* highly significant

**Discussion:**

Carotid arteriopathy has been reported in paediatric patients with diabetes (Mitsnifes et al., 2004). Abnormalities of the carotid artery have been accepted as markers of the early, asymptomatic phase of the atherosclerotic process in adults. The early stages of atherosclerosis are associated with changes in arterial structure. Subtle structural changes such as thickening of arterial intima-media complex thickness (IMT) occur early in the atherosclerotic disease process (Bhatt et al., 2013).

The mean value of cIMT in T1DM patients was (0.051± 0.005) cm higher than healthy subjects with mean values of (0.045± 0.006) cm, this difference is statistically significant (P value< 0.001, T value 4.274), this goes with the results of the study done by El Samahy et al., 2013, also the current study results are in association with the results of the studies done by Margeisdottir et al., 2010& Danielson, 2013& Järvisalo et al., 2003& Faienza et al., 2013).

Atwa and Shora, 2011 found that Diabetic children had a significantly higher cIMT than the control group in a study done in Ismailia, Egypt. Sherif et al., 2011 study results showed that T1DM Patients had increased cIMT compared to controls with mean age of (14.4± 3.4) years. Saleh et al., 2013 study results showed that Diabetic children have higher cIMT (P= 0.0001) compared to controls, in a study done in El Minia Egypt.

On the other hand, few authors found no difference in cIMT values of T1DM against controls studied (Parikh et al., 2000 & Gunczler et al., 2002). Singh et al., 2003 study found no difference in cIMT between T1DM adolescents and controls in a study in USA.

The mean value of vitamin D in T1DM was (29.5± 6.37) ng/dl lower than healthy children with mean values of (40.25± 6.49) ng/dl, this difference is statistically significant (P value <0.001, T value 7.46). This difference is in agreement with Mutlu et al., 2011, in a Turkish study done on 120 subjects. This also goes with a recent study done in Saudi Arabia by Bin-Abbas et al., 2011 who recommended screening of T1DM patients for vitamin D deficiency and supplementation of children with low vitamin D levels. Jannera et al., 2010 documented similar results, in a study done for 129 Swiss children and adolescents with type 1 diabetes. The authors advised for screening for vitamin D deficiency and supplementation in children with low vitamin D levels. Regarding Egyptian studies Mohammed et al., 2012 found that 25(OH) vitamin D was significantly lower in T1DM patients than controls (24± 12.1) vs (31± 16.2) ng/mL, in a study done in Zagazig University, Egypt for 70 T1DM patients and 30 healthy controls. El Samahy et al., 2012 found that Vitamin D was found to be insufficient in 70% of T1DM patients and in 53% of their health siblings.

The current study revealed significant negative linear correlation between cIMT and vitamin D (r value- 0.265 and P value 0.018). These results are in association with the results of the study done by Young et al., 2011 in a prospective study included 374 non-Hispanic white individuals with type 1 diabetes mean age (40 ±9) years. They concluded that Vitamin D deficiency independently predicts development of coronary artery plaque burden as a marker for atherosclerosis; in individuals with type 1 diabetes (they didn't measure cIMT).

These results supported also by many studies found a relation between vitamin D and cIMT in adults with T1DM and in other diseases. We couldn't find any studies addressing the relation between cIMT and vitamin D in children or adolescents with T1DM (like the present study), but Young et al., 2011 correlate CAC as a marker for early atherosclerosis with vitamin D), although many studies focused on this relation in adults, T2DM or in other disease other than DM.

Findings of this study regarding the correlation between cIMT and vitamin D are supported by the study of Carrelli et al., 2011 who found that Low 25-hydroxy vitamin D levels were associated with increased intima-media thickness in U.S.A. adults. Shroff et al., 2008 found that there was a correlation between 1, 25 (OH) vitamin D levels, and with cIMT (P= 0.0001), this study was done for 61 patients children on dialysis in London. Also supported with the results of Cross et al., 2011 study that found that vitamin D level was negatively correlated with cIMT in HIV- positive adults. And the study of Choi et al., 2011 who observed an independent association between vitamin D insufficiency and higher cIMT thickness in a cross-sectional analysis of 139 HIV-infected persons, also this results goes with that of the study done

by Bajaj et al., 2012.

Some recent review studies concluded appreciated relation between vitamin D deficiency and development of atherosclerosis like the following studies. Chua et al., 2011 conducted a review study they reviewed the published literature on peripheral arterial disease (PAD) and vitamin D using Medline, Pub Med, and Embase. And they concluded that vitamin D deficiency could be an independent risk factor for the development of PAD and that this risk factor is easily correctable. In addition, vitamin D deficiency is significantly associated with increased risk of cardiovascular adverse events. McGreevy and Williams, 2011, in their review study found that Emerging evidence indicates that vitamin D deficiency, cardiovascular disease, and endothelial dysfunction are linked by biological associations. However, no clear evidence indicates that vitamin D supplementation has a role to play in the prevention of cardiovascular disease.

These results of the current study regarding the correlation between Carotid intima-media thickness (cIMT) and vitamin D are against the results of the study done by Sachs et al., 2013 to test associations of circulating vitamin D metabolite concentrations with subclinical atherosclerosis (using Coronary artery calcification (CAC), cIMT) among 1,193 participants with type 1 diabetes in the DCCT/ EDIC study but they did not find evidence linking impaired vitamin D metabolism with increased subclinical atherosclerosis in type 1 diabetes. In the study done in London by Kiani et al., 2013 for 200 patients enrolled in the Lupus Atherosclerosis Prevention Study, they conclude that 25 (OH) vitamin D was not associated with any measure of subclinical atherosclerosis. Also Mok et al., 2011 found that in patients with vascular risk factors, subclinical atherosclerosis is not associated with hypovitaminosis D, but they found that Vitamin D deficiency is associated with dyslipidaemia as shown in the results of the current study.

This variation may be accounted for by variation in measurements techniques and confounding factors like race, genetics, and environmental factors. Differences in methodology and study population may offer an explanation for the discrepancy.

#### **Conclusion:**

The results of the present study shows that patients with type 1 diabetes have significantly increased mean common carotid intima-media thickness (cIMT) compared to the age and sex matched control subjects. Increased cIMT was inversely correlated with vitamin D level.

Children and adolescents with type1 diabetes are more prone to atherosclerosis than the healthy control as shown by the result of the cIMT. This may be related to the fact that They have lower vitamin D level.

#### **Recommendations:**

1. Regular Measurement of cIMT and 25 OH vitamin D in patients known with T1DM especially after 3 to 5 years after diagnosis.
2. Further longitudinal studies are needed to detect the correlation between cIMT and 25 OH vitamin D with other cardiovascular risk factors in T1DM children and adolescents.
3. Further studies on the effect of vitamin D supplementation, proper glycemic control, apolipoproteins monitoring and correction if needed on the improvement of cIMT values are needed in T1DM adolescents.

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