Correlation of glycosylated haemoglobin (HbA1c) levels with subclinical atherosclerosis in patients with type 2 diabetes mellitus

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ABSTRACT

Background: The most common cause of mortality in people with diabetes is cardiovascular disease. The relation between glycosylated hemoglobin (HbA1c), a marker of glycemic control, and the development of subclinical atherosclerosis is debated. An acceptable indicator of subclinical atherosclerosis is the use of ultrasound to measure carotid intima-media thickness (CIMT).

Objective: To conduct a cross-sectional study exploring the correlation between HbA1c and subclinical atherosclerosis as reflected by the carotid intima-media thickness in patients with type 2 diabetes that had no history of an atherosclerotic cardiovascular disease (ischemic heart disease or cerebrovascular accident).

Methods: A total of 71, type 2 diabetic patients participated in this study. Demographic, anthropometric and laboratory measures of the participants were collected. CIMT values were measured by using a high-resolution ultrasound. Increased CIMT values were accepted as >0.9 mm. Participants were categorized into two groups according to CIMT values: a normal CIMT value of ≤ 0.9 mm group, and a high CIMT value of > 0.9 mm group. HbA1c and other collected variables were compared between normal and increased CIMT groups. Furthermore, subgroup analysis was carried out for patients with poor glycemic control (HbA1c>9%).

Results: The mean CIMT was 1.048 ± 0.14 mm, and approximately 79% of the included population had increased CIMT (> 0.9 mm). 49% of participants were poorly controlled (HbA1c > 9%) and 92% of those with poor glycaemic control had increased CIMT.

Correlation analysis of data belonging to participants with poor glycaemic control (HbA1c > 9%) showed a significant correlation between HbA1c levels and CIMT, with a correlation coefficient of 0.409 (P = 0.015). In addition, a significant correlation was found in our initial analysis between CIMT and age, with a value of 0.359 (P = 0.002).

Conclusion: This study revealed that HbA1c levels in patients with poor glycemic control are positively correlated with increased CIMT measures, which is an indicator of subclinical atherosclerosis (SCA). Moreover, increased age is found to be a predictor factor for the development of SCA and, consequently, adverse macrovascular outcomes in patients with T2D.

Keywords: T2DM, CIMT and HbA1c

العلاقة بين مستويات الهيموغلوبين السكري مع تصلب الشرايين (دون السريري) في المرضى الذين يعانون من مرض السكري من النوع الثاني

المقدمة : تعتبر امراض القلب والأوعية الدموية السبب الأكثر شيوعا للوفيات عند المرضى الذين يعانون من مرض السكري. ان العلاقة بين الهيموغلوبين السكري (HbA1c)، وهو احدى علامات السيطرة على سكر الدم، وتطور تصلب الشرايين دون السريري تعتبر قيد النقاش. و كمؤشرا" مقبولا لتصلب الشرايين دون السريري هو استخدام الموجات فوق الصوتية لقياس سمك الطبقة البطانية–الوسطى للشريان السباتي (CIMT)

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الغرض من الدراسة: إجراء دراسة مقطعية مستعرضة لاستكشاف العلاقة بين نسبة الهيموغلوبين السكري (HbA1c) وتصلب الشرايين دون السريري كما يتضح من سمك الطبقة البطانية–الوسطى للشريان السباتي في المرضى الذين يعانون من داء السكري من النوع الثاني (T2DM) الذين ليس لديهم تاريخ مرضي يتعلق بأمراض القلب والأوعية الدموية.

طريقة عمل الدراسة: تم اشراك ما مجموعه ٧١ مريض من الذين يعانون من داء السكري من النوع الثاني (T2DM) في دراستنا. وقد جمعت القياسات الديموغرافية و القياسات البشرية اضافة للتدابير المختبرية للمشاركين. قيم سمك الطبقة البطانية–الوسطى للشريان السباتي (CIMT) قد قيست باستخدام الموجات فوق الصوتية عالية الدقة .القيم التي كانت اكبر من ٠.٩ ملم اعتبرت غير طبيعية. ثم ان المشاركين لدينا تم تصنيفهم إلى مجموعتين وفقا لقياس سمك الطبقة البطانية–الوسطى للشريان السباتي(CIMT) الى فريق ذو قيمة طبيعية اقل من او يساوي ٠.٩ ملم ، و اخر ذو قيمة غير طبيعية (اكبر من ٠.٩ ملم) ثم قارنا نسبة الهيموغلوبين السكري (HbA1c) وغيرها من المتغيرات التي تم جمعها بين القياسات الطبيعية والغير طبيعية لقياس سمك الطبقة البطانية– الوسطى للشريان السباتي (CIMT) وعلاوة على ذلك، تم إجراء تحليل لمجموعة فرعية من المرضى وهم الذين يعانون من نسب السكر في الدم الغير مسيطر عليها (وتوصف بالشديدة) والتي يكون فيها نسبة الهيموغلوبين السكري (HbA1c) اكثر من ٩%.

النتائج: تم تضمين ما مجموعه ٧١ مشاركا في هذه الدراسة. وكان متوسط سمك الطبقة البطانية الوسطى للشريان السباتي لديهم حوالي ١.٠٤٨ ± ٠.١٤ملم، وحوالي ٧٩٪ من هؤلاء المرضى كانوا يعانون من زيادة في سمك هذه الطبقة (اكبر من ٠.٩ ملم). ٤٩٪ من المرضى كانت نسب الهيموغلوبين السكري مرتفعة ارتفاعا شديدا (اكثر من ٩%) و ان ٩٢٪ من هذه المجموعة كانت زيادة سمك الطبقة البطانية الوسطى للشريان السباتي اكبر من ٠.٩ ملم. وقد أظهر تحليل الارتباط (correlation coefficient) للبيانات المنتمية للمشاركين الذين يعانون من عدم السيطرة الشديدة على نسبة السكر في الدم وجود علاقة ارتباط مؤثرة بين مستويات الهيموغلوبين السكري(HbA1c) مع سمك الطبقة البطانية–الوسطى للشريان السباتي (CIMT)، بمعامل ارتباط ٠.٤٠٩ وقيمة احتمالية ($P = 0.015$). وبالإضافة إلى ذلك، تم العثور على ارتباط كبير في النتائج الأولية بين العمر وسمك الطبقة البطانية–الوسطى للشريان السباتي بمعامل ارتباط ذو قيمة ٠.٣٥٩ وقيمة احتمالية ($P = 0.002$).

الاستنتاج: لقد كشفت هذه الدراسة أن مستويات نسبة الهيموغلوبين السكري (HbA1c) في المرضى الذين يعانون من عدم السيطرة الشديدة على نسب السكر في الدم تتناسب طرديا مع زيادة سمك الطبقة البطانية– الوسطى للشريان السباتي(CIMT) ، وهو مؤشر على تصلب الشرايين دون السريري. وعلاوة على ذلك، تم العثور على زيادة العمر ليكون عاملا مؤشرا لتصلب الشرايين دون السريري، وبالتالي يؤدي الى نتائج سلبية لتصلب الشرايين الكبيرة في المرضى الذين يعانون من داء السكري النوع الثاني(T2D) .

INTRODUCTION

Diabetes mellitus is considered to be a major health problem worldwide, [1] with 387 million people having diabetes worldwide, which is expected to rise to 592 million by 2035. In fact, diabetes is not only a condition with an increasing prevalence, but it is also a serious health problem. The International Diabetes Federation (IDF) published that diabetes led to approximately five million deaths in 2015.[2] Moreover, the World Health Organization (WHO) considers that diabetes will be the seventh leading cause of death by 2030.[3] Unfortunately, the diagnosis of type 2 diabetes mellitus (T2DM) is often not made for many years because hyperglycaemia, at early stages, is usually not severe enough to provoke symptoms of the disorder. Thus, patients with T2DM are at a high risk for developing complications early after the diagnosis.[4] Strongly supported evidence shows that there is an increased risk of macrovascular complications (coronary artery disease, stroke and peripheral artery disease) in diabetes; the overall risk of cardiovascular disease (CVD) increases two- to fourfold.[5] Also, despite a considerable improvement in diabetes management, deleterious cardiovascular outcomes still occur in a large proportion of patients with diabetes.[6] Therefore, every attempt should be carried out to avoid these complications by early detection of diabetes in high-risk groups, as well as by finding which risk factors can predict the development of such complications as early as possible and before they become obvious clinically. In type 1 diabetes mellitus, it has been proven that tight glycemic control has a protective effect against both macro- and microvascular complications, as shown by the results of the Diabetes Complications and Control Trial–Epidemiology of Diabetes Intervention (DCCT) trial. [7] However, in T2DM, it has been well established that glycosylated haemoglobin (HbA1c) levels, a marker of glycemic control, are closely related to the risk of microvascular complications and this finding led to the use of HbA1c in the diagnosis of diabetes by the International Expert Committee in 2009. [8] Nonetheless, the issue of the correlation between glycosylated haemoglobin (HbA1C), a marker of glycemic control, and macrovascular outcomes has received considerable critical attention. [6] Major studies around this topic, such as ACCORD trial, [9] ADVANCE trial, [10] and VADT, [11] have failed to show that lowering HbA1c levels can reduce the incidence of macrovascular adverse effects. However, the ACCORD trial was stopped prematurely due to high mortality rate;[12] therefore, their results cannot be considered. The VADT was a small study with a predominantly male sample (only three females were recruited), meaning it was not representative of the general population; in addition, male gender is considered as an independent risk factor for CVDs.[4] Furthermore, the UK Prospective Diabetes Study (UKPDS) showed a statistically insignificant reduction in the CV endpoints after an intervention period of ten years.[13] Surprisingly, the 10-year follow-up of UKPDS (UKPDS 80) showed that there was a statistically significant reduction in the incidence of myocardial infarction ten years after the intervention period had ended.[14] However, an argument against this emerging benefit is that the growing number of events in both groups over this long period may have contributed to the change in analysis. As results from major studies about the benefit of reducing HbA1c on cardiovascular outcomes are variable, it raises the question about whether the HbA1C level is related to the development of macro vascular complication. In fact, atherosclerosis is the underlying disease process that leads to coronary artery disease, stroke, and peripheral artery disease. Atherosclerosis is a condition in which the fatty plaques where deposited inside the arteries. [15] A well accepted non-invasive indicator of the development of the early stages of atherosclerosis (subclinical atherosclerosis (SCA)) is the measurement of carotid intima-media thickness (CIMT), which is calculated by using high-resolution B-mode ultrasonography.[16] Therefore, and for a better understanding of the association between glycemic control and macrovascular complications, several epidemiological studies have investigated the correlation between HbA1c levels, as a marker of glycemic control, and CIMT measurements, as a predictor of SCA, which is the underlying process in the pathophysiology of macrovascular complications. Some of these studies have investigated this association in Asian populations (17-22), while others have done so in western populations (23-25). However, results from these studies showed conflicting findings, with some determining a positive correlation between HbA1c and CIMT, and others being unable to confirm this association.

The aim of the study: the aim of this study is to clarify the correlation between HbA1c levels and CIMT measurements in patients with T2DM and to determine other risk factors for cardiovascular disease, including lipids, blood pressure, smoking, obesity, male gender, and increasing age.

PATIENTS AND METHODS

Study Design and Population:

The study protocol had been approved by the scientific committee of the department of internal medicine and the ethical committee of College of Medicine, University of Basrah. All methods were carried out in accordance with guidelines and regulations followed at the College of Medicine and its Teaching Hospital (AL-Sadder Teaching Hospital). A cross-sectional observational study was conducted to answer the research question on the correlation between HbA1c levels and CIMT measurements.[26] From March 2016 to September 2016, a total of 111 patients were collected from AL-Sadder Teaching Hospital in Basrah city. All of them were outpatients. Patients included in this study were known cases of T2DM, and had no atherosclerotic cardiovascular disease (ASCVD), namely, ischemic heart disease or cerebral vascular accident. Forty patients were excluded because they had one or more of the exclusion criteria listed below. The study exclusion criteria were categorized as factors that may have influenced the accuracy of the HbA1c readings (27-28) and factors that may have affected the development of SCA. The former criteria are if a patient had one or more of the following conditions:

1. ***Iron deficiency anaemia, vitamin B12 deficiency, or hemoglobinopathies.***
2. ***A recent blood transfusion.***
3. ***Chronic kidney disease or chronic liver disease***
4. ***Hyperbilirubinemia.***
5. ***Acute blood loss.***
6. ***Alcoholism.***

The use of statin belonged to the second category, as this may prevent or delay the development of SCA if taken at an appropriate dose. [29] Also the patients with history of ASCVD were excluded.

Ethics and Consent

Informed consent was obtained from all patients, and their identities remained anonymous during the entire study process.

Clinical Evaluation and Anthropometric Measurements

All patient demographics were recorded regarding age, gender, history of hypertension (on antihypertensive treatment or not) and smoking history. Participants were classified according to smoking history as current smokers who have smoked 100 cigarettes in their life and, currently, smoke any number of cigarettes, or non-smokers, including both former smokers and never smokers.[30] Self-reported information was taken regarding hypertension and smoking history. Height and weight of all included participants were measured, and body mass index (BMI) was calculated by the formula of weight/height^2 (kilograms per square meter) and recorded for all included patients. In order to stratify them according to BMI, the patients were divided into those with BMI < 25 kg/m^2, and other whose BMI ≥ 25 kg/m^2 (overweight/obese)[31] to see the prevalence of increased CIMT in each category.

Blood Collection and Biochemical Parameters

Random blood samples were drawn for total cholesterol (TC), triglycerides (TG), and HbA1c assays. According to HbA1c level, the patients were divided into those with HbA1C level ≤ 9% and those with HbA1c > 9%. We used 9% value of HbA1c as a cut-off point as glycemic control is considered to be poor if HbA1c value is more than 9%.[4] Lipid profile and HbA1c were measured using an automated biochemical instrument (Cobas Integra 400, Roche, Germany). The HbA1c determination is based on the turbidimetric inhibition immunoassay (TINIA)

Measurement of Carotid Intima-Media Thickness

A certified investigator examined common carotid arteries (CCAs) bilaterally by a B-mode ultrasound, using a high-resolution instrument (SonoSite Inc., Bothell, WA 98021 USA). Ultrasound measurements were performed according to Mannheim CIMT Consensus.[32] CIMT was measured on both CCAs, at a point located approximately 20 millimetres from the bulb. Three measurements were obtained from different sites of this segment, and the mean value of six measurements (of both sides) was used for analysis. A value up to 0.9 mm was accepted as a normal value of CIMT according to the European Society of Cardiology/ European Society of Hypertension guidelines, [33] published in 2013. According to CIMT values, participants were divided into two groups: a normal CIMT value of ≤ 0.9 mm group, and a CIMT value of > 0.9 mm group, before collected variables were compared between the two.

Statistical Analysis

The statistical analysis of collected data used descriptive analysis in addition to an analytic approach to determine the relationship between the study output index (CIMT and the demographic, and predictor variables included in the study). Descriptive analysis includes determining the frequency (in tables) and pictorial presentation (bar charts, histograms, and pie charts). Continuous data is expressed as a mean with standard deviation, while categorical data is expressed as a frequency. Analytical tests used the chi-square and correlation coefficient using the Statistical Package for Social Science version 20 (SPSS-20) at a significance level of 0.05.

RESULTS

A total of 71 patients were recruited in the study. The response rate was (100%). The mean age was (52.7 ± 6.42) years. The gender distribution showed that 44 patients (61.97%) were females and the remaining (38.03%) were males (Figure-1).

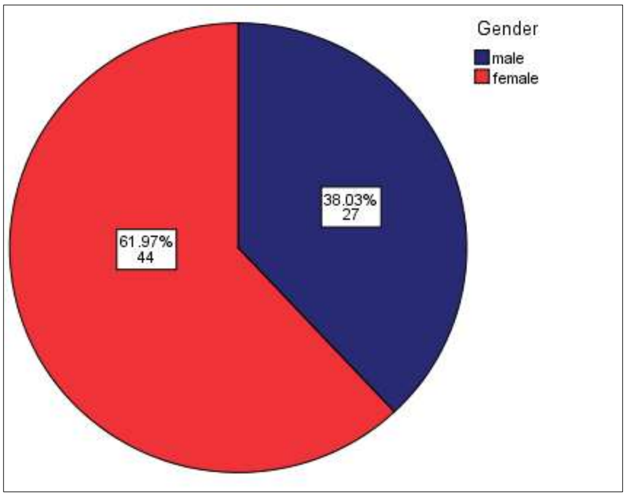

Fig 1. The gender distribution among T2DM patients (n=71)

The mean BMI was 29.55 ± 4.72 Kg/m^2. About one-half of the patients (36 patients, 50.7%) were hypertensive, while only three patients (4.22%) were smokers. The minimum, maximum, mean and standard deviations of the measured indices of the participants are shown in (Table-1).

Table 1. Minimum, maximum, mean and standard deviation of the patients' variables.

The variable	Minimum	Maximum	Mean	Std. Deviation
Age (in years)	40	70	52.70	6.422
Serum cholesterol (in mg/dl)	98	281	211.21	40.176
Serum triglycerides (in mg/dl)	60	485	206.76	86.472
BMI (in kg/m2)	20	48	29.55	4.723
HbA1c (%)	6	13	9.24	1.553
CIMT (in mm)	0.7	1.5	1.048	0.148

Abbreviations: std. deviation: standard deviation; BMI: Body Mass Index; CIMT: Carotid Intima-Media Thickness.

The graphical presentation of both CIMT measures (Figure-2) and HbA1c values (Figure-3) were almost normal.

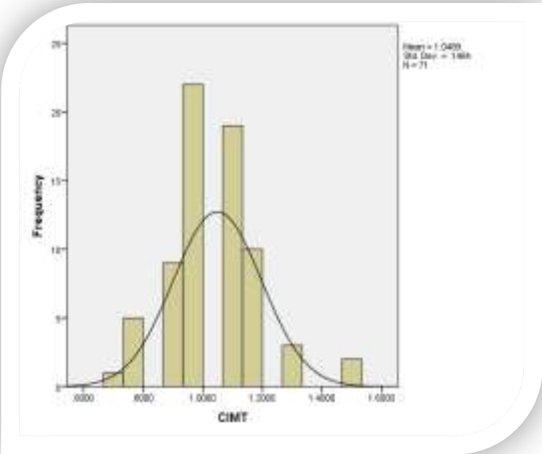

Fig 2. Histogram distribution of CIMT measures.

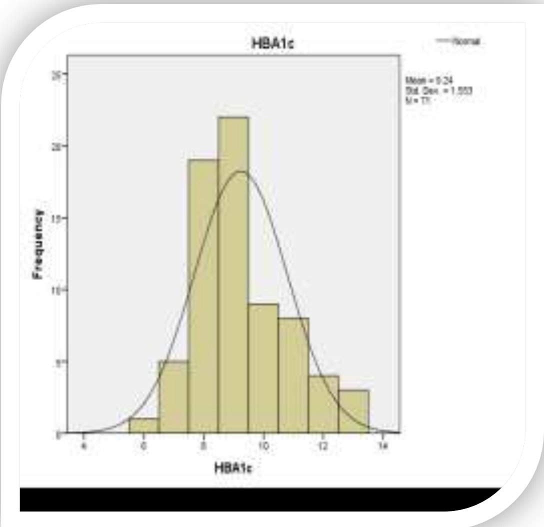

Fig 3. Histogram distribution of HbA1c values

The percentage of increased CIMT (> 0.9 mm) in the studied samples was about 78.8% (56 subjects out of a total 71 participants), as demonstrated in (Figure-4).

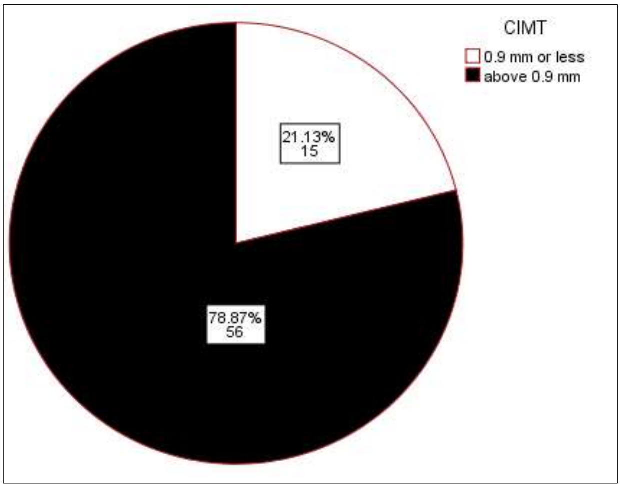

Fig 4. The percentage of increased CIMT amongst T2DM patients

There was no significant difference in CIMT measures between the two genders (Table-2).

Table 2. Gender distribution and CIMT measures

Gender	Cimt (mm)		Total
	≤ 0.9 mm	*> 0.9 mm*	
Male	7	20	27
Female	8	36	44
Total	15	56	71

Chisq = 0.60, P = 0.438

When patients were divided according to BMI (i.e. those with BMI < 25 kg/m^2 and those with BMI of ≥ 25 kg/m^2), a significant difference in CIMT was found between the two groups. Fifty three patients out of sixty four overweight / obese patients display increased CIMT (Chisq = 6.05, P = 0.014).

Table 3. BMI and CIMT distributions amongst T2DM patients

BMI (KG/M^2)	CIMT (mm)		Total
	≤ 0.9	> 0.9	
< 25	4	3	7
≥ 25	11	53	64
Total	15	56	71

Chisq = 6.05, P = 0.014

When the patients were divided according to hypertension history into two groups, no significant difference in CIMT measures was found between the two groups (Table-4).

Table 4. History of hypertension and CIMT distributions amongst T2DM patients

History of hypertension	CIMT		Total
	≤ 0.9	*> 0.9*	
HT	8	27	35
No HT	7	29	36
Total	15	56	71

Chisq = 0.124, P = 0.72

The patients were divided according to HbA1c level into two groups; the first group includes patients with HbA1C ≤ 9%, while the second one includes patients with HbA1C > 9%. The former group included 50.70% of patients, while 49.30% belonged to the latter, as illustrated by the pie chart in Figure 5.

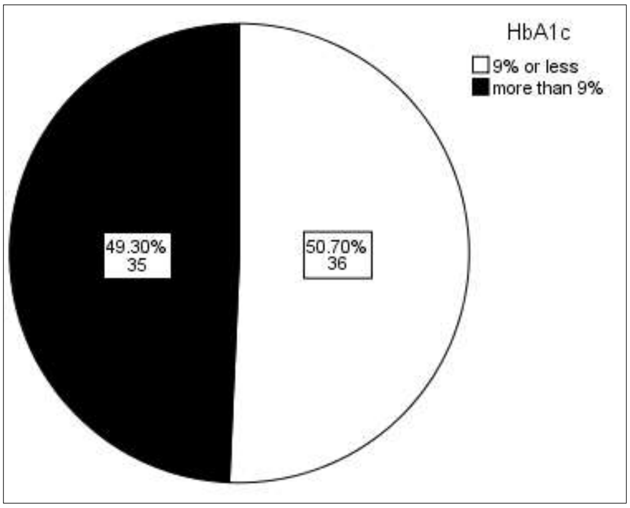

Fig 5. The frequency and percentage of patients according to glycemic control

A significant difference in CIMT between these two groups was found. Thirty two patients out of thirty five with poorly controlled diabetes (HbA1c > 9%) had increased CIMT (Chisq = 6.53, P = 0.010), as shown in (Table-5).

Table 5. HbA1c levels and CIMT measures distribution amongst T2DM patients.

HbAbc (%)	CIMT		Total
	≤ 0.9	*> 0.9*	
> 9	3	32	35
≤ 9	12	24	36
Total	15	56	71

Chisq = 6.53, P = 0.010

Correlation coefficient analysis between CIMT was nonsignificant. HbA1c correlation was 0.113 (P = 0.348), total cholesterol correlation was 0.15 (P = 0.904), TG correlation was 0.096 (P = 0.425), BMI correlation was 0.083 (P = 0.390). Interestingly, the only significant correlation found in this study was between CIMT and age, which was 0.359 (P = 0.002).

Table 6. CIMT correlation coefficients with study variables in T2DM patients

Correlation of carotid intima media thickness	With	Correlation coefficients (pearson's r)	Significance
CIMT	HBA1c	0.113	0.348
CIMT	TC	0.015	0.904
CIMT	TG	0.096	0.425
CIMT	BMI	0.083	0.390
CIMT	Age	0.359	**0.002**

Abbreviations: TC: Total Cholesterol; TG: Triglyceride; HT: Hypertension.

Further analysis was carried out for subjects with poor glycemic control (HbA1c > 9%). The result of analysis of data belonging to this group showed a significant correlation between HbA1c levels and CIMT, with correlation coefficients of 0.409 and P value of 0.015, while other variables had no significant correlation.

Table 7. CIMT correlation coefficients with the study variables amongst poorly controlled T2DM patients

Correlation of carotid media intimal thickness	With	Correlation coefficients (pearson's r)	Significance
CIMT	HBA1c	0.409	**0.015**
CIMT	T.Ch	0.112	0.521
CIMT	TG	0.226	0.192
CIMT	BMI	0.298	0.082
CIMT	Age	0.270	0.117

Abbreviations: TC: Total Cholesterol; TG: Triglyceride; HT: Hypertension

DISCUSSION

Diabetes mellitus is associated with serious complications. Both micro- and macrovascular complications of diabetes are associated with atherosclerosis. An acceptable indicator of subclinical atherosclerosis is the use of ultrasound to measure CIMT. [16] In this study, the correlation between glycemic control, reflected by HbA1c, and the development of subclinical atherosclerosis, measured by the CIMT of CCAs, were investigated in patients with T2DM who have no history of ASCVD. This study showed that approximately 79% of patients with T2DM had increased CIMT values (> 0.9 mm), 49% of participants were poorly controlled (HbA1c > 9%), and 90% of our population were overweight/obese. 92% of those with poor glycemic control had increased CIMT (Chisq = 6.53, P = 0.010) and approximately 83% (53 subjects out of 64) of overweight/obese participants had increased CIMT (Chisq = 6.05, P = 0.014). Thus, there was a significant association between poor glycemic control and increased CIMT, as well as a significant association between high BMI (≥ 25 kg/m^2) and increased CIMT. The correlation analysis of data initially was nonsignificant between HbA1c and CIMT (P = 0.348). The only significant correlation found in the initial analysis was between CIMT and age, with a value of 0.359 (P = 0.002). Nonetheless, the subgroup analysis of data belonging to participants with poor glycemic control (HbA1c > 9%) showed a significant correlation between HbA1c levels and CIMT, with a correlation coefficient of 0.409 (P = 0.015). Indeed, several cross-sectional studies have also investigated this correlation and many published studies on western or Asian populations support our findings. The Kora 4 study was a large population-based study on a western population and recruited participants with and without diabetes.[24] The authors concluded that the relation between HbA1c and CIMT faded after adjustment for other cardiovascular risk variables. However, the mean HbA1c of those with known diabetes in the KORA 4 study was 6.9% ± 0.9, which is lower than the mean of our population. This supports the positive correlation of our study that appeared only in the subgroup analysis of data belonging to the poor glycaemic control (HbA1c > 9%) group. Similarly, no correlation was found between these two variables in a study conducted on an elderly population by Du HW et al. in which the mean HbA1c level was also lower than that of our population (6.9 ± 1).[22] Moreover, they recruited old age people for whom the impact of diabetes on the development of cardiovascular events was significantly smaller than a younger age group, as found by a post Hoc analysis of participants included in two studies: (the Cardiovascular Health Study and the Atherosclerosis Risk in Communities study).[34] Du HW et. al concluded that the presence of hypertension had a bigger impact than hyperglycaemia on the development of CIMT. Also, Olt et al. conducted their study on an Asian population with a mean HbA1c value of 8.6 ± 2, and found that there was no significant association between HbA1c levels and CIMT values.[35] However, no effort was given to performing subgroup analysis according to glycemic control level as we did. In contrast, many studies have confirmed a significant positive correlation between high HbA1c levels and increased CIMT values. [18-20, 36] We can explain the results of the positive correlation between glycated haemoglobin and CIMT in participants with poor glycemic control can be explained via two concepts. Firstly, as HbA1c is a glycated protein and regarded as a precursor for advanced glycation end products (AGEs) (37-38), it is considered an important factor in the pathogenesis of atherosclerosis in patients with diabetes.[39] Secondly, HbA1c is closely related to fasting plasma glucose (FPG) levels, which are caused by insulin resistance more than insulin deficiency, [40] with the former having been proven as an associated factor with atherosclerosis. [41] Consequently, increased HbA1c may contribute to the development of CIMT through insulin resistance. However, the correlation coefficient of 0.4 found in this study is considered to be an intermediate correlation, i.e. not a strong correlation.[42] This can be explained by the fact that postprandial glucose (PPG) levels, which are not reflected by HbA1c, as well as glucose instability with peaks and troughs, are independent risk factors for atherosclerosis and macrovascular complications.[4]

CONCLUSION AND IMPLICATIONS

This cross-sectional study revealed that HbA1c levels in patients with poor glycemic control are positively correlated with increased CIMT measures, which is an indicator of SCA. Moreover, increased age is found to be a predictor factor for the development of SCA and, consequently, adverse macrovascular outcomes in patients with T2DM. This study provided an implication for managing patients with diabetes, particularly those who are elderly, to prevent unfavourable cardiovascular outcomes. In Iraq, as a developing country, the rate of adequate glycemic control for patients with diabetes is still disappointingly low. Depending on our results, clinicians should aim to maintain HbA1c levels within normal range as a priority to avoid the development of cardiovascular events.

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Additional Information

Competing Interests

The authors declare that they have no competing interests (financial AND non-financial interests)