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Atherogenic Indices in Type 2 Diabetic Iraqi Patients and Its Association with Cardiovascular Disease Risk

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Abstract:

Background: Diabetes is a serious risk factor for atherosclerotic cardiovascular disease and an important cause of mortality. Dyslipidemia is commonly related to type 2 diabetes, and the atherogenic index of plasma is a strong marker to predict the risk of atherosclerosis and coronary heart disease.

Objective: To study the association of atherogenic indices lipids in type 2 diabetic Iraqi patients with cardiovascular disease.

Patients and Methods: This clinical study was conducted at Baghdad Teaching Hospital/ Medical City-Baghdad from October 2022 to February 2023. Sixty type 2 diabetic patients were recruited for this study: 30 patients with cardiovascular disease and 30 without cardiovascular disease. Their ages were between 40-55 years. Another 30 healthy individuals were selected as a control group.

Results: There were considerable rises in glycemic and lipid investigations in diabetic patients with cardiovascular disease compared to those without cardiovascular disease and the control group. The present results show higher levels of lipid ratios in diabetic patients with cardiovascular disease. The results also revealed high levels of non-high-density lipoprotein cholesterol for diabetic patients with cardiovascular disease (241.8±12.24 mg/dL) versus (150.1±7.12 and 68.9±5.1 mg/dL) for those without cardiovascular disease and the controls group respectively. The atherogenic index of plasma in diabetic patients with cardiovascular disease compared to diabetic and healthy control groups were (0.8±0.09) versus (0.7±0.03 and 0.2±0.08) respectively. There was a significant correlation between the atherogenic index of plasma and anthropometric factors, glycemic and lipid profile with their ratios in diabetic patients with and without cardiovascular disease.

Conclusions: The results of this study confirm that the lipid indices are risk indicators of glycemic control with higher prognostic value than traditional factors. So, non-high-density lipoprotein cholesterol and atherogenic index of plasma can be used as a significant predictor of glycemic control.

Keywords: Type 2 diabetes mellitus, Dyslipidemia, Cardiovascular disease, Lipid ratios, Atherogenic index of plasma.

Introduction:

Diabetes mellitus (DM) is considered a public health concern with a long-term metabolic condition due to genetic, environmental, and behavioral factors. Death rates from diabetes are rising for various reasons, including poor nutrition, obesity, smoking, and physical inactivity. Diabetes screening may be beneficial in some cases since early identification and treatment can lessen the burden of diabetes and its consequences (1).

Type 2 DM (T2DM) is a metabolic disease caused by the relative or absolute deficiency of insulin. It is associated with elevated blood glucose levels, which is linked with several other diseases, such as dyslipidemia, though the exact mechanisms for these. irregularities remain to be determined. As expected, hepatic insulin resistance (HIR) promotes excessive gluconeogenesis, which contributes to the development of pre-diabetes. Also, HIR promotes *de novo* lipid synthesis, leading to excessive deposition of fat in the liver (hepatic steatosis) and secretion of very low-density lipoproteins (VLDL) into the blood. Increased incorporation of the newly synthesized triglycerides (TG) into VLDL causes dyslipidemia, which promotes atherosclerosis and cardiovascular disease (CVD) (2). Cardiovascular disease is a main public health concern throughout the world. Diabetic patients have a 2-4-fold increased risk of progressing to coronary artery disease (CAD), proving that T2DM is a distinctive risk feature for heart disease (3). In the majority of cases, the primary cause of CVD is atherosclerosis, which is initiated when low-density lipoprotein (LDL) is oxidized, resulting in a flow of

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inflammatory cytokine production (4). The accumulation of oxidized LDL further damages the endothelial cells, leading to myocardial and cerebral ischemia (5).

Dyslipidemia is categorized by a considerable effect among diabetic patients who have higher TG levels, LDL-C levels, and lower high-density lipoprotein cholesterol (HDL-C). Also, they have a higher amount of smaller, denser LDL particles, which have been associated with CVD risk (6). The LDL-C levels in diabetic patients may not be raised, so the CV risk is not definitely recognized, National Cholesterol Education Program Adult Treatment Panel III (NCEPATP III) guidelines highlighted non-HDL-C as a beneficial predictor of CV risk. This is principally appropriate if the TG level is high (7).

Atherogenic index of plasma (AIP), is the logarithm of the molar ratio of TG to HDL-C. It has a significant sensitivity that reveals the interaction between atherogenic and protective lipoprotein. It has been postulated that AIP is an important indicator to assess the CVD risk (8). It is calculated using two influences: serum TG and serum HDL-C. The TGs and HDL-C in this fraction reveals the various exchanges during the lipoproteins metabolism and can be beneficial for calculating the atherogenicity (9). The aim of the current study is to investigate the role of atherogenic indices lipids in type 2 diabetic Iraqi patients with CVD.

Patients and Methods:

This clinical study was performed from October 2022 to February 2023 at Baghdad Teaching Hospital/ Medical City-Baghdad. Sixty type 2 diabetic patients participated in the current study; 30 were with CVD and 30 without CVD, between 40-55 years of age. They were examined and diagnosed by a specialist endocrinologist. Thirty healthy individuals were selected as the control group. They matched with the cases for age and gender. Control subjects were collected from the Teaching Laboratories-Medical City/ Baghdad, where all measurements were done with glycemic control inclusion criteria at fasting serum glucose (FSG) < 100 mg/dL and glycated hemoglobin (HbA1c) < 5.7%. Demographic, anthropometric, and clinical characteristics, including sex, age, weight, height, waist circumference (WC), waist-to-hip ratio (WHR), body mass index (BMI), systolic and diastolic blood pressure (SBP and DBP) for all participants were recorded. Consensus was given by all subjects prior to admission to the study.

Inclusion and Exclusion Criteria:

This study admitted individuals who were 40-55 years of age with clinical diagnoses of T2DM according to WHO criteria (10). Patients with T1DM, insulin users, a history of hepatic diseases, renal failure, autoimmune diseases, major chronic disorders, and pregnancy were excluded from this study. Figure 1 illustrates the flow diagram of the current study.

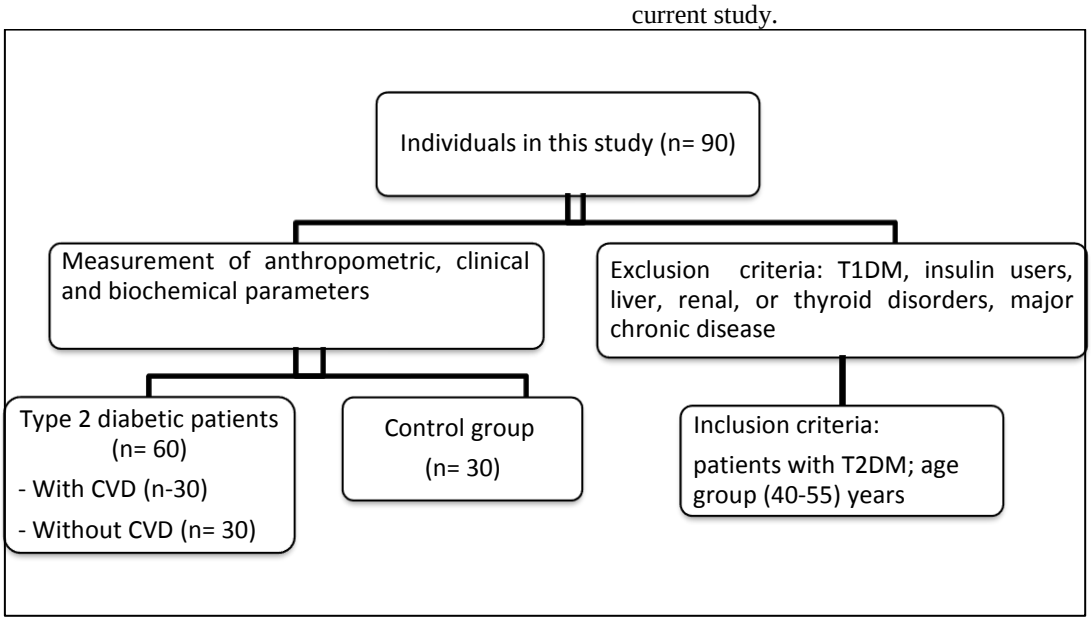

Figure 1: Flow diagram of the current study

Laboratory Measurements:

Blood samples were taken for laboratory investigations including FSG, TC, TG, and HDL-C, which were measured using a biochemical automated analyzer (Abbott C4000, USA). The Bio-Rad VARIANT hemoglobin A1C employs automated and precise ion-exchange high-performance liquid chromatography (HPLC) principles to separate HbA1c. Additionally, serum non-HDL-C was designed by subtracting HDL-C from TC (11). The AIP is deliberated using the formula, log (TG/HDL-C) ratio according to Dobiasova and Frohlichin method.

Statistical Analysis:

The data were analyzed by the Statistical Package for Social Sciences (SPSS) version 25. All the variables were expressed as means ± SD. Categorical data were presented by frequencies and percentages. The Student *t*-test and one-way analysis of variance (ANOVA) test were used to compare the studied variables. A *p*-value of less than 0.05 was considered significant.

Results:

There were no significant differences in gender and age between the patients and control. There were significant increases in other anthropometric and clinical characteristics in diabetic patients as compared to the healthy group (Table 1).

Table 1: Demographic, anthropometric, and clinical features of patients and controls

Parameters		Mean ± SD		*p*-value
		Patients (n= 60)	Control (n= 30)	
Gender No. (%)	Male	30(50%)	15(50%)	0.306
	Female	30 (50%)	15 (50%)	
Age (Years)		45.3 ± 5.67	42.4 ± 2.26	0.62
WC (cm)		104.2 ± 2.85	70.5 ± 1.22	0.0001
WHR		1.0 ± 0.02	0.7 ± 0.01	0.0001
BMI (kg/m^2)		32.5 ± 3.20	21.8 ± 1.56	0.0001
SBP (mmHg)		156.7 ± 5.23	116.0± 1.42	0.0001
DBP (mmHg)		95.9 ± 2.16	76.7 ± 1.22	0.0001
Duration of DM (Years)		8.5 ± 3.65	-	-

Data are revealed as mean±SD; p < 0.05 is significant.

Table 2 shows significantly higher mean values ($p < 0.05$) for FSG, HbA1c, TC, TG, LDL-C, and non-HDL-C and significantly lower mean values ($p= 0.001$) for serum HDL-C in T2DM patients with CVD compared to those without CVD and control. Table 2 also shows the lipid ratios between diabetic patients (with/ without CVD) and control, indicating higher levels of TC/HDL-C, LDL-C/HDL-C, and AIP in T2DM patients with CVD compared to those without CVD and healthy controls.

Table 2: Glycemic and lipid profile in patients and controls

Parameters	Mean ±SD			*p*- value
	T2DM with CVD (n= 30)	T2DM without CVD (n= 30)	Control(n= 30)	
FSG (mg/dL)	226.0±15.10^a	186.2±12.74^b	79.7±1.01^c	0.001
HbA1c (%)	12.6±3.35^a	9.3±1.86^{ab}	4.1±0.08^c	0.04
TC (mg/dL)	280.0±13.52^a	195.4±9.14^b	134.5±6.50^c	0.001
TG (mg/dL)	230.3±10.34^a	207.4±8.90^b	96.4±17.16^c	0.001
HDL-C (mg/dL)	38.2±1.28^a	45.3±2.02^b	65.6±1.4^c	0.001
LDL-C (mg/dL)	195.8±10.17^a	108.6±6.94^b	49.6±1.68^c	0.001
VLDL (mg/dL)	46.1±2.07^a	41.5±0.18^{ab}	19.3±3.42^c	0.001
Non-HDL-C (mg/dL)	241.8±12.24^a	150.1±7.12^b	68.9±5.1^c	0.01
TC/HDL-C ratio	7.3±10.56^a	4.3±2.52^{ab}	2.0±1.20^{bc}	0.03
LDL-C/HDL-C ratio	5.1±3.80^a	2.4±3.43^{ab}	0.8±0.20^c	0.01
AIP	0.8±0.09^a	0.7±0.03^b	0.2±0.08^c	0.01

The correlation coefficient of AIP with other study parameters in T2DM with and without CVD is demonstrated in Table 3. The table shows significant positive correlations ($p < 0.05$) between AIP and age, WC, WHR, BMI, SBP, DBP, FSG, HbA1c, TC, TG, LDL-C, VLDL, non-HDL-C, and lipid ratios, while a significant negative correlation ($p < 0.05$) was found between AIP and serum HDL-C in T2DM with and without CVD.

Table 3: Correlation coefficient of AIP with study parameters in diabetic patients

AIP/ Parameters	T2DM with CVD	T2DM without CVD
	r	r
Age (Years)	0.85***	0.82***
WC (cm)	0.63**	0.62**
WHR	0.62**	0.58**
BMI (Kg/m^2)	0.58**	0.51*
SBP (mmHg)	0.52*	0.49*
DBP (mmHg)	0.51*	0.56**
FSG (mg/dL)	0.68**	0.63**
HbA1c (%)	0.72***	0.59**
TC (mg/dL)	0.66**	0.68**
TG (mg/dL)	0.58**	0.62**
HDL-C (mg/dL)	-0.65**	-0.78***
LDL-C (mg/dL)	0.74***	0.72***
VLDL (mg/dL)	0.50*	0.49*
Non HDL-C (mg/dL)	0.53*	0.58**
TC/HDL-C ratio	0.59**	0.53*
LDL-C/HDL-C ratio	0.51*	0.55**

$^*p$ <0.05: Significant, $^{**}p$ <0.001: Highly significant.

Discussion:

Diabetes can cause macro- and microvascular disease. Furthermore, CVD causes 75% of the deaths among diabetic patients. Although DM by itself is considered an independent health risk, there are coexisting conditions, such as high BP, obesity, and dyslipidemia, which are major risk factors for atherosclerosis (12). Complications of T2DM including CV and cerebrovascular are related with age. As age increases, the metabolic rate decreases, which ultimately raises blood sugar levels, BMI, dyslipidemia, and BP levels, which consequently leads to an increased risk of CVD (13), which is in agreement with the present results.

The correlation of obesity with T2DM has been long documented and clearly explains that T2DM is a main risk factor for CVD. Obesity is frequently associated with dyslipidemia, hypertension, and many metabolic and CV risk factors (14). Thus, obesity in this study is a prevalent factor of altered metabolism and CVD that can be managed by pharmacotherapies but also altered by lifestyle modifications. Moreover, a previous study has shown that most of the CVD risk results from a high BMI or a high WC, largely caused by altered risk factors, such as atherogenic dyslipidemia, DM, and hypertension (15). In the current study, diabetic patients with CVD had a significantly higher WC, WHR, and BMI compared to those without CVD. Hypertension was the most common comorbidity in both patients' groups. It was found that hypertension increased the incident cases of CVD and atrial fibrillation in patients with DM (16). These consequences are due to hyperglycemia, which is the main distinctive feature of DM. Blood glucose level is toughly controlled by two main processes: insulin secretion and insulin action on main tissues, i.e., skeletal muscle, liver, and adipose tissue. T2DM is frequently related with obesity and IR is characterized by hyperinsulinemia (17). Hepatic insulin signaling suppresses gluconeogenesis but promotes *de novo* lipid synthesis. Paradoxically, HIR enhances both gluconeogenesis and *de novo* lipid synthesis. Elucidation of the etiology of this paradox, which participates in the pathogenesis of non-alcoholic fatty liver disease (NAFLD), CVD, metabolic syndrome (MetS), and hepatocellular carcinoma, has not been fully achieved. Such involvement of gluconeogenesis in lipid synthesis rationalizes the fact that several types of antidiabetic drugs ameliorate NAFLD. Thus, dietary, lifestyle and pharmacological targeting of HIR and hepatic gluconeogenesis may be the most viable approach for the prevention and management of the HIR-associated link of diseases (18).

Despite its inadequacy among patients with hemoglobinopathies, HbA1c is the gold standard for defining glycemic control among diabetic patients. It is used to give an idea of glycemic control (19). In the same content, diabetic patients in this study had raised the value of HbA1c. Several determinants of metabolic illnesses, i.e., DM, CVD, dyslipidemia, elevated serum uric acid, and hypertension are proposed to be related to BMI and blood lipids. Lipoprotein lipase (LPL) gene mutations may play an important role in dyslipidemia in T2DM patients. Insulin disturbs apolipoprotein production and causes a decrease in the activity of LPL enzyme resulting in increased levels of LDL-C, TC, TG, and reduced levels of HDL-C (20).

The abnormalities of lipid metabolism in the current study are hypercholesterolemia and hypertriglyceridemia (HTG). Different values of serum lipid profile in various studies might be due to diverse lifestyles among obese, compared to the non-obese diabetic and healthy control (21). Moreover, HTG is a frequently met lipid irregularity associated with other lipid and metabolic disorders. Elevated IR and TG are inversely relevant to reduced HDL-C. The HTG might be due to secondary reasons such as a high-fat diet, medicines, extreme alcohol intake, and diseases such as DM and hypothyroidism (22).

The current study revealed significantly higher levels of TC, TG, VLDL, LDL-C, and a significantly lower level of HDL-C in type 2 diabetic patients as compared to healthy controls. The incorporation of independent metabolic indicators such as serum levels of TG and HDL-C that were considered for visceral adiposity calculation resulted in the preserved ability for treatment follow-up in terms of CV risk changes and even enhanced ability to predict metabolic outcomes at treatment follow-up stages and routine monitoring in clinical practice (23).

Non-HDL-C measures the quantity of cholesterol carried by the atherogenic B comprising lipoproteins such as VLDL, intermediate-density lipoprotein, LDL, lipoproteins (a), and chylomicron. The treatment target is predictable at 30 mg/dL greater than that for LDL-C. It had been agreed that patients with 190 mg/dL of serum non-HDL-C level or higher had a more than 2-fold increased risk of death from CVD as regard to those with a level of 130 mg/dL or less. It has been considered that 190 mg/dL is the significant threshold of death from CVD, while 130 mg/dL is a treatment target (24). Non-HDL-C, which was assessed in the current study, provides a measure of all apo B-containing lipoproteins, all of which have the prospective to transport cholesterol into the arterial wall and lead to atherosclerotic lesions. This measure reveals that atherogenic risk is not assessed by LDL-C measurement only, predominantly in the situation of higher TG, which is in agreement with earlier results (25,26).

In both of the diabetic groups, lipid ratios such as TC/HDL-C and LDL-C/HDL-C result from lipid components and are revealed by numerous analysis trials as well as predictive of CVD than any lipid marker alone (27). The current data suggested that ratios can be employed as further markers for

IR. The TG/HDL-C ratio > 3.5 and TC/HDL-C ratio > 4.5 were used as cut-off points to recognize patients with IR. Atherogenic dyslipidemia, categorized as HTG and raised LDL-C/HDL-C ratio, is related to greater CVD risk (28). Raised lipids and lipoproteins levels can modify the vascular endothelial function and impair some of its pro-fibrinolytic functions and anti-thrombotic regulatory mechanisms result in the initiation of atherosclerosis (29). A previous study validated that the lipid ratios (lipid indices) of TC/HDL-C, TG/HDL-C, in addition to LDL-C/HDL-C were reliably related to various MetS modules, and based on IR. The lipids indices counting evidence on a minimum of two factors could have a greater incorporated clarification than one lipid assessment, i.e., HDL-C or TG (30). Nevertheless, in the Cai et al. study, it was found that TC/HDL-C and TG/HDL-C ratios were considerably interrelated with IR. So, it is imperative to note that, though the TG/HDL-C ratio has been suggested as an alternate for IR, the association between TG and TG/HDL-C with insulin may fluctuate by ethnicity as in particular people for calculating IR might not be suitable. They also suggested that AIP was significantly associated with CVD (31). In contrast, an earlier study indicated that patients with good glycemic control have lesser TC/HDL-C ratio, LDL-C/HDL-C ratio, and AIP compared to those with uncontrolled diabetes, but the difference was not significant (32).

The AIP in this study has been shown to be a useful method for identifying CVD in T2DM patients. Ethnicity, diet, lifestyle, gender, demographic factors, and metabolic and hormonal changes can affect AIP value. Also, drugs that influence lipid metabolism such as lipid-lowering drugs, β-blockers, or diuretics might be considered. Hence, the logarithmic conversion of TG/HDL-C to estimate AIP might be deliberated as clinical prospect influence (33). Wu et al. showed a case–control study, which indicated that AIP is an influence risk factor for CVD (34). Another study from China on cases who experienced coronary angiography found that AIP as a novel indicator seemed to be a progressive predictor of CVD severity (35). Won et al. study comprised cases who had coronary computed tomography angiography and found that AIP was a predictive value of progress features (36). Numerous assumptions may clarify this phenomenon. In stroke cases, trials have revealed that diverse sizes of lipid particles have diverse influences on stroke, particularly small dense LDL (sdLDL), which was the most strictly linked to atherogenic stroke and was an independent risk influence (37). The sdLDL could simply pass through the vascular endothelium and combine with the glycoprotein to form lipid deposition on the arterial walls. Moreover, apoB100 of sdLDL is difficult to combine with LDL receptors, and it significantly lessens the clearance level (38). Also, sdLDL is simply oxidized, and ultimately causes the accumulation of some molecules such as chemokines, and triggers the monocytes. Then, macrophage phagocytes oxidize LDL-C to yield foam cells, releasing higher levels of cholesterol, which form the core of atherosclerotic plaque. That progression might worsen acute stroke and subsequently lead to stroke (39). It has been noticed that the AIP value was contrariwise proportionate to the diameter of oxidized LDL particles and ultimately revealed sdLDL particle size (40).

Treatment of both T2DM and CVD differ significantly worldwide and though much of the CVD risk in T2DM may be related to the long-term complications of T2DM. Certain antidiabetic drugs affect this risk, i.e., sulfonylureas which are the second most frequently used antidiabetic drug after metformin, have been found to be related to CV events and mortality. Recent antidiabetic medications have been seen to lessen the risk of CVD among T2DM patients; nevertheless, these medications are usually proposed to be used as the second or third line, and may be many years before patients are able to benefit from them (41).

Conclusions:

Dyslipidemia is interrelated with poor glycemic control among the diabetic population particularly those with CVD. The outcomes of the current study authorized that the lipid indices are risk indicators of glycemic control with higher prognostic value than traditional factors. So, non-HDL-C and AIP can be used as significant predictors of glycemic control. As their susceptibility to atherosclerosis and other CVD is correlated to their atherogenic plasma, AIP may be a good indicator for the detection of CV events.

Authors Declaration: Authors' declaration:

Conflicts of Interest: None

We hereby confirm that all the Figures and Tables in the manuscript are ours. Besides, the Figures and images, which are not ours, have been given permission for re-publication and attached to the manuscript.

Ethical Clearance: The Institutional Scientific Committee at the University of Baghdad approved this study according to the Declaration of Helsinki for human studies (Consent number: 4737 on 13/9/2022).

Authors' Contribution:

Hind Shakir Ahmed: Conceptualization, Data curtain, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, writing—original draft preparation, Writing—review and editing.

Melak Saleh Mohammed: Conceptualization, Data curtain, Formal analysis, Methodology, Resources, Validation, writing—review and editing.

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مؤشرات تصلب الشرايين لدى المرضى العراقيين المصابين بالسكري من النوع الثاني وعلاقتها بمخاطر أمراض القلب والأوعية الدموية

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الخلاصة:

خلفية البحث: مرض السكري هو عامل خطر لأمراض القلب والأوعية الدموية وتصلب الشرايين وسبب مهم للوفاة. يرتبط خلل الدهون في الدم بشكل شائع بمرض السكري من النوع الثاني ويعتبر مؤشر تصلب الشرايين في البلازما علامة قوية للتنبؤ بخطر الإصابة بتصلب الشرايين وأمراض القلب التاجية.

الهدف من البحث: دراسة ارتباط المؤشرات الدهنية لتصلب الشرايين لدى المرضى العراقيين المصابين بالسكري من النوع الثاني ولديهم أمراض قلبية وعائية.

المرضى وطرق العمل: أجريت هذه الدراسة السريرية في مستشفى بغداد التعليمي/ مدينة الطب - بغداد في الفترة من تشرين الأول 2022 ولغاية شباط 2023. تم مشاركة 60 مريضًا مصاباً بالسكري من النوع الثاني في هذه الدراسة. ثلاثون مريضا منهم كانوا يعانون من أمراض القلب والأوعية الدموية و 30 غير مصابين بأمراض القلب والأوعية الدموية. تراوحت أعمارهم بين 40-55 سنة. تم اختيار 30 فردًا سليما كمجموعة سيطرة.

النتائج: كان هناك ارتفاع كبير في فحوصات نسبة السكر والدهون في الدم لدى مرضى السكري المصابين بأمراض القلب والأوعية الدموية مقارنة مع أولئك الذين لا يعانون من أمراض القلب والأوعية الدموية ومجموعة السيطرة. أظهرت النتائج الحالية مستويات مرتفعة من نسب الدهون لدى مرضى السكري المصابين بأمراض القلب والأوعية الدموية. كشفت النتائج أيضًا عن مستويات عالية من البروتين الدهني غير عالي الكثافة لدى مرضى السكري المصابين بأمراض القلب والأوعية الدموية (241.8 ± 12.24 ملغم/ ديسيلتر) مقابل (150.1 ± 7.12 و 68.9 ± 5.1 ملغم/ ديسيلتر) لأولئك الذين لا يعانون من أمراض القلب والأوعية الدموية ومجموعة السيطرة على التوالي. كان مؤشر تصلب الشرايين للبلازما لدى مرضى السكري المصابين بأمراض القلب والأوعية الدموية مقارنة بمجاميع مرضى السكري والأصحاء (0.8 ± 0.09) مقابل (0.7 ± 0.03 و 0.2 ± 0.08) على التوالي. كان هناك ارتباط معنوي موجب بين مؤشر تصلب الشرايين للبلازما والعوامل الجسمية، صورة السكر والدهون في الدم مع نسبها لدى مرضى السكري مع وبدون أمراض القلب والأوعية الدموية.

الاستنتاجات: تؤكد نتائج هذه الدراسة أن مؤشرات الدهون هي مؤشرات خطر لضبط نسبة السكر في الدم بقيمة تنبؤية أعلى من العوامل التقليدية. أيضًا، ممكن اعتبار البروتين الدهني غير عالي الكثافة ومؤشر تصلب الشرايين في البلازما من العوامل الهامة للسيطرة على نسبة السكر في الدم.

الكلمات المفتاحية: داء السكري من النوع الثاني، خلل الدهون في الدم، أمراض القلب والأوعية الدموية، نسب الدهون ، مؤشر تصلب الشرايين في البلازما.