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The association of glycated hemoglobin and lipid profile with peripheral artery disease in metabolic syndrome patients from Northwestern Algeria.

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Abstract

Glycated hemoglobin (HbA1c) was incorporated as an indicator of dysglycemia, as opposed to fasting glycaemia, for the purpose of classifying patients based on their vascular incidents. This choice was made due to HbA1c's robust correlation with vascular factors like pulse wave velocity, intima media thickness, and the albumin/creatinine ratio (ACR). However, the relationship between HbA1c and lipid profile in developing artery disease remain uncertain. We set out to investigate the association of HbA1c and lipid profile with peripheral artery diseases (PAD) in patients with metabolic syndrome (MetS) in north-western Algeria. Our cross sectional study was carried out during six months. The BMI was calculated as weight(kg)/height^2(m^2). Ankle-brachial index (ABI)<0.9 and angiography was used to diagnosed PAD and MetS was defined according NCEP-ATPIII criteria. Statistical test, involving correlations and linear regression, were employed to establish the link between HbA1c, fasting glycemia, lipid profile, and the occurrence of PAD in individuals with MetS. In a sample of 300 MetS patients, 53% were male. Positive associations were observed between HbA1c, fasting blood glucose (FBG) (r=0.753, p<0.001), and triglycerides (TG) (r=0.288, p<0.001), with a negative correlation seen with high-density lipoprotein (HDL) (r= -0.356, p<0.001). HbA1c exhibited no significant correlation with total cholesterol (TC) and low-density lipoprotein (LDL). Lipid ratios (LDL/HDL, TC/HDL, TG/HDL) were positively linked to HbA1c (r=0.232, r=0.332 and r=0.43, respectively). Linear regression affirmed these findings. HbA1c displayed positive ties with FBG and TG, while negatively correlated with HDL, showing independence from LDL and TC. Notably, all three lipid ratios showed significant associations with HbA1c

Keywords: Glycated hemoglobin, lipid profile, lipid ratio, metabolic syndrome, peripheral artery disease.

Introduction

The metabolic syndrome (MetS) is a pathological condition that affects a large proportion of the worldwide population, characterized by the coexistence of different metabolic factors simultaneously, such as arterial hypertension, diabetes and atherogenic dyslipidemia [1].

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Dyslipidemia is defined as an imbalance in serum lipid levels, whether of primary or secondary origin.It is a chronic metabolic disorder characterized by hypertriglyceridemia, total hypercholesterolemia, high LDL and low HDL levels [2]. This coexistence leads to various complications, such as kidney diseases, hepatic steatosis, obstructive sleep apnea, cancer, polycystic ovary syndrome, chronic inflammation, sympathetic activation and hyperuricemia, and above all atherothrombotic cardiovascular disease (CVD) [3, 4].

Atherothrombosis, in turn, results from thrombus formation induced by atherosclerotic plaque ulceration and platelet activation.Atherosclerosis is due to the accumulation of modified lipids (oxidized LDL) in the walls of large and medium-caliber arteries [5]. This causes a number of different complications, such as peripheral arterial disease (PAD) that affects the arteries that pump blood to the legs and feet. In addition to narrowing and blockages, artery walls lose their elasticity, preventing them from dilating to increase blood flow. Inadequate circulation can cause intermittent claudication and muscle weakness, skin lesions (tissue ulceration and necrosis) and even amputations, all of which affect quality of life [6].

Glycated hemoglobin (HbA1c) is regularly tested in diabetics to monitor blood glycemia. It is recognized as the gold standard for glycemic control. A level of below 7% is considered the target for optimal glycemic control [7, 8]. Glycated hemoglobinhas emerged as a biomarker of cardiovascular and metabolic risk. Previous studies have demonstrated a strong association between HbA1c and MetS components[9] suggesting that an elevated HbA1c may predict dysmetabolism [10].

The International Diabetes Federation (IDF) has included HbA1c as a marker of dysglycemia rather than fasting blood glucose (FBG) to categorize patients according to their vascular attacks, based on their cardiovascular and metabolic risk linked to atherosclerosis [11], as the HbA1c is strongly associated with vascular parameters such as pulse wave velocity,intima media thicknessand Albumin-to-Creatinine ratio (ACR) [12-14]. Several studies have reported a significant relationship between lipid profile and HbA1c [15], while others reported no considerable relationship [16]. Theaim of this study is to investigate the association of glycated hemoglobin and lipid profile with PAD in MetS patients from Northwestern Algeria.

Materials and Methods

Data collection

This cross-sectional study was conducted over six-months (from January to June 2023), in the diabetology-endocrinology department of the University Hospital of the *Wilaya* of Sidi-Bel-Abbes, located in the northwestern Algeria. Adult diabetics suffering from MetS with or without PAD were included in this study in order to investigate the association of HbA1c and lipid profile with PAD in MetS.

Patients' medical records were analyzed for biochemical parameters such as C-Reactive protein (CRP), FBG, HbA1c, Total Cholesterol (TC), Triglycerides (TG), High-Density Lipoprotein (HDL) and Low-Density Lipoprotein (LDL) as well as for medicalhistory. A face-to-face interview was carried out to obtain additional information about the patient (age of the patient, age of pathologies such as diabetes, hypertension and dyslipidemia). Anthropometric parameters (body weight, height and waist circumference) were measured in the standing position. The BMI wascalculated as BMI (kg/m^2) = weight(kg)/height^2 (m^2). Blood pressure wasmeasured using a sphygmomanometer. Hypertension was defined as a systolic blood pressure of 140 mmHg and diastolic blood pressure of about 90 mmHg or more. MetS was defined according to NCEP ATP III criteria[3]. PAD was diagnosed by an ankle-brachial index (ABI) <0.9 and confirmed by angiography.

Study population

We enrolled adult diabetic individuals seeking consultation at the diabetology-endocrinology department of the University Hospital of Sidi Bel Abbes, located in north-western Algeria, during the period from January to June 2023. This recruitment included those with Metabolic Syndrome (MetS) in association with Peripheral Arterial Disease (PAD) (n = 91), as well as those without this association (n = 209).

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Inclusion Criteria

- Adult men and women with diabetes and Metabolic Syndrome;
- Participants willing to participate in the interview;
- Individuals not afflicted by cancer, severe cardiovascular disease (CVD), chronic kidney disease, acute infections, autoimmune diseases, infectious diseases, HIV, or HCV.

Exclusion Criteria

- Participants who declined to take part in the interview;
- Individuals without Metabolic Syndrome, those with cancer, severe CVD, chronic kidney diseases, acute infections, autoimmune diseases, infectious diseases, HIV, and HCV;
- Pregnant women.

Statistical analysis

Data analysis were processed and performed usingthe Statistical Package for Social Sciences® software (SPSS, version20.0) and the Microsoft Excel 2013 program. Results are presented as means ± standard deviations. Student's independent *t*-test was used to compare mean values between the two groups of PAD (with PAD and without PAD). Patients are then classified into two groups according to HbA1c levels (<7 %, ≥ 7%) based on the American Diabetes Association classification[17]. The Pearson correlation coefficient and linear regression test were applied to determine the association between HbA1c, FBG and lipid profile.

Results

Three hundred patients with MetS were included in the present study, 53% were males and 91 (30.35%) participants developed PAD. All participants were diabetics (100%), 39.33% were hypertensive, and 35.33% had dyslipidemia. Patients with PAD were significantly (p< 0.001) older than those without PAD, with a meanage of 65.28 (±10.87) and 51.43 (±16.54) years, respectively. Comparing the two groups of PAD (without PAD and with PAD), Highly significant differences (p< 0.001) were demonstrated through Student's *t*-test regarding, CRP, HDL, TC, TG levels and lipid ratios (LDL/HDL, TC/HDL and TG/HDL). Significant differences were highlighted for waist circumference (p= 0.013), LDL (p= 0.003), HbA1c (p = 0.002) and FBG (p =0.002) levels. CRP, TC, TG, LDL, HbA1c, FBG levels and lipid ratios were higher in the PAD group. In contrast, HDL levels were low (Table1).

Table 1. Basic characteristics of metabolic syndrome patients with and without peripheral artery diseases.

Parameters	Total (n=300)	Without PAD (n=209)	With PAD (n=91)	*p*
Male gender; n (%)	159 (53.00)	96 (60.37)	63 (39.62)	< 0.001*
Age (years)	55.63±16.33	51.43±16.54	65.28±10.87	< 0.001#
Diabetes;n (%)	300 (100)	209 (69.66)	91 (30.35)	-
Hypertension;n (%)	118 (39.33)	71 (60.16)	47 (39.83)	0.004*
Dyslipidemia; n (%)	106 (35.33)	15 (14.15)	91 (85.84)	< 0.001*
BMI (kg/m^2)	26.63±05.89	26.35±05.38	27.50±07.20	0.201#
Waist circumference (cm)	99.51±14.85	97.79±14.22	104.31±15.69	0.013#
Systolic pressure (cmHg)	12.37±2.11	12.30±2.25	12.53±1.75	0.391#
Diastolic pressure (cmHg)	7.18±1.06	7.21±1.05	7.11±1.11	0.476#
HbA1c (%)	9.99±3.25	9.60±3.38	10.90±2.74	0.002#
Fasting blood glucose (g/L)	2.75±1.17	2.59±1.24	3.10±0.94	0.002#
CRP (g/L)	53.81±69.39	37.35±57.50	78.43±79.25	< 0.001*
LDLc (g/L)	1.12±0.53	1.01±0.42	1.26±0.61	0.003#
TC (g/L)	1.88±0.59	1.70±0.47	2.17±0.66	< 0.001#
TG (g/L)	1.64±0.70	1.35±0.45	2.92±0.88	< 0.001#
HDLc(g/L)	0.36±0.08	0.39±0.09	0.32±0.05	< 0.001#
LDL/HDL	3.25±1.80	2.70±1.63	3.98±2.04	< 0.001*
TC/LDL	5.49±2.34	4.43±1.63	6.90±2.42	< 0.001*
TG/LDL	6.08±4.31	3.47±1.37	9.71±4.39	< 0.001*

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Quantitative variables are given in mean (±Standard Deviation); Qualitative variables are given in number (frequency); (#) *p* value for student *t* test; (*) *p* value for Chi-square test; $p \leq 0.05$ was considered as statistically significant. PAD: Peripheral Artery Disease, BMI: Body Mass Index, HbA1c: Glycated hemoglobin, CRP: C-Reactive Protein, LDL: Low Density Lipoprotein, TC: Total Cholesterol, TG: Triglycerides, HDL: High Density Lipoprotein.

Comparison of traditional lipid parameters (HDL, LDL, TG and TC) and FBG between patients with and without PAD according to HbA1c levels shows higher levels of FBG, TC, TG and LDL in PAD patients for both classes of HbA1c. However, HDL levels were lower (Fig.1).

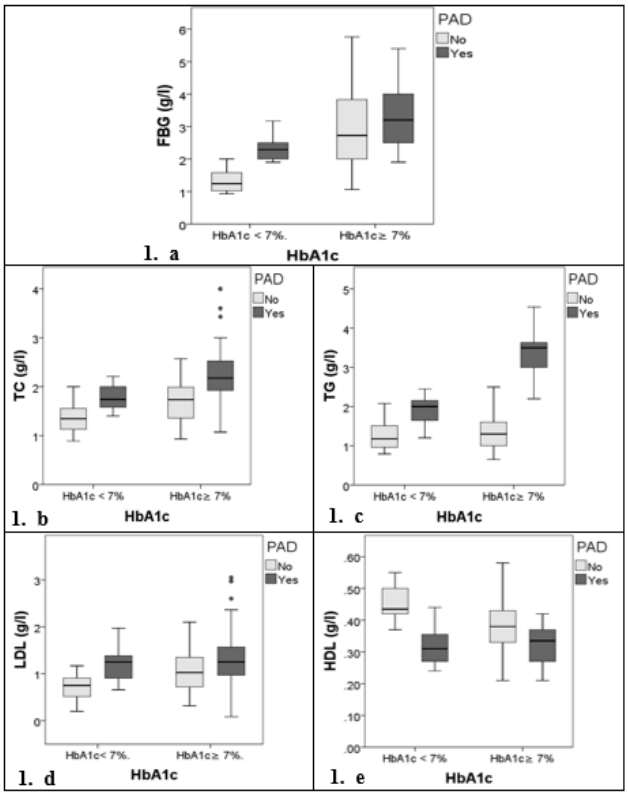

Figure 1.Comparison of fasting blood glucose levels and lipid profile between patients with and without PAD according to HbA1c levels.

The three lipid ratios show elevated values in PAD patients in both classes of HbA1c (Fig. 2).

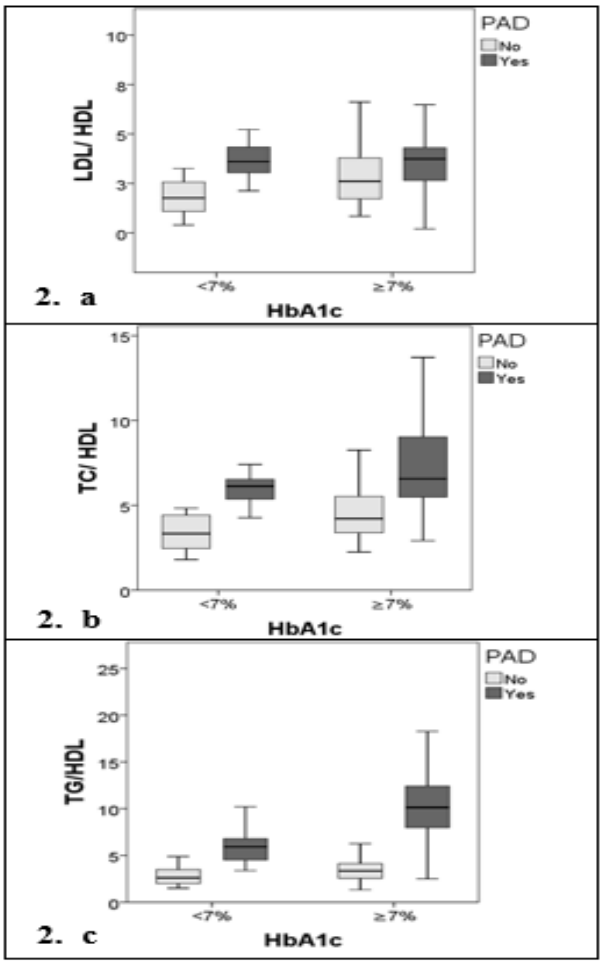

Figure 2. Comparison of lipid ratios between patients with and without PAD according to HbA1c levels.

Pearson correlation of HbA1c with FBG and traditional lipid parameters (HDL, LDL, TC and TG) shows a strong and significant positive relationship between HbA1c and FBG (r = 0.753, $p<0.001$) and a weak significant positive correlation between Hba1c and TG (r= 0.288, $p<0.001$). However, a negative correlation was found with HDL (r= -0.356, $p<0.001$). There was no significant correlation with TC and LDL. Likewise, lipid ratios; LDL/HDL, TC/HDL, TG/HDL were positively correlated with HbA1c (r= 0.232, r= 0.332 and r=0.43, respectively) (Table 2).

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Table 2. Correlation and linear regression analysis (between HbA1c, fasting blood glucose, and lipid parameters)

Parameters	Correlation Coefficient	*P*-value[#]	Regression Unstandardized coefficients b	*P*-value*
FBG (g/L)	0.753	**<0.001**[#]	1.951	**<0.001***
HDL (g/L)	-0.356	**<0.001**[#]	-12.622	**<0.001***
LDL (g/L)	0.068	0.405	10.117	0.405
TC (g/L)	0.132	0.066	0.660	0.065
TG (g/L)	0.288	**<0.001**[#]	0.860	**<0.001***
LDL/HDL	0.232	**0.004**[#]	0.366	**0.004***
TC/HDL	0.332	**<0.001**[#]	0.406	**<0.001***
TG/HDL	0.430	**<0.001**[#]	0.295	**<0.001***

(#) *p* value for **Pearson correlation**; (*) *p* value for **linear regression test;** $p \leq 0.05$ was considered as statistically significant. FBG: Fasting blood glucose, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, TC: Total Cholesterol, TG: Triglycerides, HbA1c: Glycated hemoglobin.

The linear regression revealed that HbA1c levels were positively associated with FBG, TG and lipid ratios ($p<0.05$), negatively associated with HDL ($p<0.001$) and independent of other parameters (LDL and TC) (Table 2).

Discussion

Recently, HbA1c has emerged as a biomarker of cardiovascular and metabolic risk. Previous studies have demonstrated a strong association between HbA1c and MetS components, suggesting that an elevated HbA1c may predict dysmetabolism [10].

IDF has included HbA1c as a marker of dysglycemia rather than FBG for the classification of patients according to their vascular attacks, based on their cardiovascular and metabolic risk linked to atherosclerosis[11], as the HbA1c is strongly associated with vascular parameters such as pulse wave velocity, intima media thickness and ACR [12-14].Preliminary findings of the present study showed that 30.35% of MetS patients with a mean age of 55.63 ± (16.33) years developed PAD. In the present study, all patients were diabetics (100%), 39.33% were hypertensive, of which 39.34% with PAD and 35.33% had dyslipidemia, of which 85.84 % with PAD.

In the United States, in 2020, 21 million people (18%) aged 65 and over have PAD. Given the ageing of the population, this number is projected to rise to 23.8 million by 2030 [18]. In two other recent studies, the prevalence of PAD in people aged 65 and over was 13.5% and 27.7% [19]. In an Indian study, the prevalence was 36% in diabetics. A higher prevalence (62.3%) was estimated in diabetic patients by Gninkoun et al [20]. In Algeria, Rachid et al reported that 16% of patients with coronary artery diseases had PAD [21]. The incidence of PAD in MetSpatients was 1.7% (23/1382) versus 0.87% (30/3435) in non-MetS subjects (30/3435) [22]. Moreover, Petra et al reported that MetS affects 58% of PAD patients [23].

The present PAD patients were significantly older than those without PAD. Several previous studies have reported that the prevalence of PAD in patients with diabetes increases with age [24, 25]. The PAD group showed higher levels of TG, TC, LDL, HbA1c, FBG and waist circumference than the second group. In agreement with the present study, Mohammed et al reported that age, gender, BMI, systolic and diastolic blood pressure, HbA1c, serum LDL, TG and current or past smoking are potential risk factors presenting significant associations with the incidence of PAD[26].In addition,Hafida's statistical analysis demonstrated a significant relationship between obliterative arterial disease of the lower limbs and age, smoking, TC and LDL [27].Recent results from the Bypass Angioplasty Revascularisation Investigation in type 2 diabetes (BARI 2D) study revealed that a 1% increase in HbA1c was associated with a 21% increased risk of PAD in type 2 diabetics [28].Moussio et al, noted an increase in HbA1c levels in type 2 diabetics with PAD [29, 30].Our findings highlighted higher levels of FBG, TC, TG and LDL in the presence of PAD

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associated with elevated HbA1c levels. However, HDL levels were lower.

We found a strong and significant positive association between HbA1c and FBG (r = 0.753, p<0.001) and a weak and significant positive correlation between Hba1c and TG (r = 0.288, p<0.001). However, a negative correlation was found with HDL (r= -0.356, p<0.001). There was no significant correlation with TC and LDL, our results concurred with those reported by several previous studies, HbA1c levels rise as lipid profile parameters increase (TC, TG, LDL, and VLDL) and HDL levels decrease [31 - 33].Alzahrani et al,found no relationship betweenHbA1c and lipid profile (TC, LDL and HDLc), with the exception of TG; they suggest that TG may predict CVD and is a risk factor in type 2 diabetes[34]. In contrast,a minority of studies have revealed a positive relationship between HbA1c and HDL [8, 35]**.** The currentfindings revealed that HbA1c levels were positively associated with FBG and TG (p<0.001), negatively associated with HDL (p<0.001) and independent of other parameters (LDL and TC). Another study reported that HbA1c could be a predictive factor for TG, TC and LDL in contrast FBG and age did not correlate with HbA1c [32]. In this study, lipid ratios (LDL/HDL, TC/HDL, TG/HDL) had significant associations with HbA1c levels. These outcomes are consistent with those reported by Artha et althe lipid ratio parameter TC-TG-LDL/HDL ratio were significantly higher in the group with poor glycemic control (p<0.05) [36].*Hussain et al* (2017) found that HbA1c was positively and significantly related to LDL/HDL ratio [32].

The presentstudy is firstly limited by the cross-sectional design. Secondly, the majority of our participants were treated with antihypertensive drugs, oral antidiabetics, insulin and statins, which could reduce lipid and blood sugar estimations. third, this single-center study conducted on a small sample size precludes generalizability of the findings to a large diverse population.

Conclusion

High levels of TC, TG, LDL, HbA1c and FBG were associated with PAD in MetS patients; HbA1c was positively correlated with FBG and TG, negatively correlated with HDL and independent of LDL and TC. However, all three lipid ratios are significantly associated with HbA1c, suggesting that regular monitoring of the glycaemic and lipid profile may contribute to preventing or slowing the progression of PAD in MetS patients. Further interventional studies should be conducted to confirm this association.

Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- Authors sign on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee at University of Djillali LIABES.

Authors' Contribution Statement

S. S., M. A. and M. A. contacted the patients and set up the interviews to collect data, entered the data, developed and analyzed the statistical tests. I. B. and M. D. Contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

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ارتباط الهيموجلوبين السكري ونسبة الدهون مع أمراض اللأوعية الدموية الطرفية في المرضى الذين يعانون من الاضطراب الأيضي من شمال غرب الجزائر.

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الخلاصة

تم إدماج الهيموجلوبين السكري (Hb1Ac) كمؤشر لخلل السكر في الدم بدلا من غلوكوز الدم الصائم (FGB)، لتصنيف المرضى بناء على حوادث الأوعية الدموية ،حيث يرتبطHb1Acارتباطا وثيقا بعوامل الأوعية الدموية مثل سرعة موجة النبض وسمك الوسائط الداخلية، نسبة الألبومين / الكرياتينين (ACR) ومع ذلك فإن العلاقة بينHb1Acونسبة الدهون في تطور أمراض الشرايين لاتزال غير مؤكدة. هدفنا الرئيسي من هذه الدراسة هو التحقيق في ارتباطHb1Acونسبة الدهون مع أمراض الأوعية الدموية الطرفية (PAD) في المرضى الذين يعانون من الاضطراب الأيضي (MetS) في شمال غرب الجزائر. أجريت دراستنا المقطعية لمدة ستة أشهر. تم حساب مؤشر كتلة الجسم كالتالي: (BMI (kg/m²)=weight(kg)/height²(m²، تم استخدام مؤشر الكاحل والعضد (ABI) أقل من 0.9 وتصوير الأوعية لتشخيص PAD وحددنا MetS وفقا لمعاييرNECP-ATPIII. تم استعمال اختبار تحليل الارتباط (correlation test) والانحدار الخطي (linear regression) لدراسة الصلة بينHb1Ac، نسبة السكر في الدم، نسب الدهون وحدوث أمراض الشرايين الطرفية لدى الأفراد المصابين بالاضطراب الأيضي. من بين 300 مصاب الاضطراب الأيضي، 53 % تمثل الذكور. لوحظ وجود ارتباطات إيجابية بينHb1Ac،FGB (r=0.753, p<0.001) والتري غلسيريد (TG) (r=0.288, p<0.001) وارتباط سلبي مع البروتين الدهني عالي الكثافة (HDL) (r=-0.356, p<0.001) . لم يظهرHb1Ac أي ارتباط مع الكوليسترول الكلي (TC)و البروتين الدهني منخفض الكثافة (LDL). أظهرت نسب الدهون (TC/HDL , LDL/HDL, TG/HDL)ارتباطات ايجابية مع).Hb1Acr=0.332 r=0.232, r=0.43(أكد اختبار الانحدار الخطي هذه النتائج. أظهر Hb1Ac ارتباطات ايجابية مع FGB و TG في حين أنه يرتبط سلبا بالبروتين الدهني عالي الكثافة(HDL) . و مستقل عن البروتين الدهني منخفض الكثافة(LDL) والكوليسترول الكلي (TC) و الجدير بالذكر أن نسب الدهون الثلاثة) TC/HDL , LDL/HDL (TG/HDL أظهرت ارتباطات ايجابية مع Hb1Ac.

الكلمات المفتاحية: لهيموجلوبين السكري، الدهون، نسب الدهون، الاضطراب الأيضي، مرض الأوعية الدموية الطرفية.