Peripheral Atherosclerotic Profile in Type 1 Diabetic Patients: Lipid Ratios as a Predictive Marker of Asymptomatic Patients

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ABSTRACT

Objective: To investigate the relationship between Lipid ratios and asymptomatic peripheral artery disease (aPAD) in type 1 diabetic patients.

Materials and Methods: This cross-sectional study was performed among 223 diabetics. Patients were segregated with aPAD when their ankle-brachial index (ABI) was abnormal (ABI ≤ 0.90, or ABI > 1.20). Patients were segregated into the following groups (patients with normal ABI vs. patients with arterial stiffness). The association between lipid ratios and aPAD was analyzed using multivariate logistic regression analysis and the receiver operator characteristic curve.

Results: Our study reported a slight preponderance of females (108 males vs. 115 females), with a mean age of 30.70±9.69 years and a diabetes duration of 11.13±8.95 years. The prevalence of arterial stiffness was 38.11%. TC/HDL-C ratio was a significant predictor for atherosclerosis with a sensitivity of 77.3%, specificity of 62.5%, and diagnostic accuracy of 0.758%. The results revealed that the 4th quartile (odds ratio [OR]=12.52 [5.06-31.00], p=<0.001) of TC/HDL-C ratio was statistically higher in patients with arterial stiffness. Similarly, the last quartiles of LDL-C/HDL-C and TG/HDL-C ratio were higher in the arterial stiffness group (OR=3.70 [1.68-8.11], p=0.001; OR=4.74 [2.12-10.59], p=<0.001; respectively). In the arterial stiffness group, non-traditional lipid values were significantly higher in males compared to females.

Conclusion: Lipid ratios are correlated with aPAD in type 1 diabetic patients, and should thus be assessed in clinical decision-making and risk stratification on atherosclerotic cardiovascular disease.

Keywords: Ankle-brachial index; asymptomatic peripheral artery disease; atherosclerosis; lipid ratios. (Siriraj Med J 2022; 74: 874-882)

INTRODUCTION

Patients with type 1 diabetes (T1D) are highly predisposed to develop early atherosclerosis.[1] Asymptomatic peripheral artery disease (aPAD) is frequent in diabetics.[2] It is usually caused by atherosclerosis, in which an atherosclerotic plaque produces arterial stenosis or occlusion. As a consequence, blood flow to the affected limb is reduced. The majority of subjects are asymptomatic, although many suffer from occasional claudicating.[3] Diabetes-related peripheral neuropathy has a reported prevalence ranging from 15% to 86%,[4] with painful diabetic neuropathy described in around 26% of diabetic patients.[5] People with aPAD have a higher risk of diabetic foot amputation, myocardial ischaemia, and stroke, as well as

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mortality.[6] According to recent data, aPAD affects more than 200 million individuals globally.[7] Although current guidelines for screening of aPAD vary significantly,[8] the ankle-brachial index (ABI) as a routine examination to identify aPAD is highly recommended. Type 1 diabetic patients aged over forty have an aPAD prevalence of 20%, which rises to 29% over the age of fifty.[9]

Additionally, the clinical characteristics of aPAD in diabetic people differ from those reported in the general population, resulting in a worse prognosis.[10] Thus, an early detection is essential for diabetic patients, since aPAD is a significant risk factor for amputation, and is directly linked to cardiovascular diseases (CVDs).[11] Arterial stiffness, which may be regarded as a sign of subclinical atherosclerotic disease,[12] is an important parameter to study since it reflects CVD and mortality in diabetics and may serve as a valuable marker to prevent future vascular complications.[13]

Dyslipidemia is considered a risk factor for aPAD.[14] Conventional lipid measures, such as abnormal values of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), are prevalent risk factors for aPAD.[15] Specifically, numerous studies have highlighted that atherosclerosis develops and progresses under conditions of abnormal lipid values in diabetes. A high triglyceride (TG)/HDL-C ratio may be a favorable indicator of CVD.[17,18] Similarly, the total cholesterol (TC)/HDL-C ratio has also been linked to an increased risk of CVD.[19,20] The connection between the LDL-C/HDL-C ratio and aPAD has been well-established,[21] indicating that the LDL-C/HDL-C ratio was also a stronger marker for major CVD in a prospective observational study.[22]

As a result, identifying atherosclerotic risk factors in patients with T1D will ameliorate diabetes-based screening and preventive strategies in diabetics at higher risk for vascular complications. To that end, in this study, we sought to investigate the prevalence of arterial stiffness among diabetics in order to determine whether there is a link between aPAD and CVD, mainly subclinical atherosclerosis by evaluating lipid ratios in patients with T1D, as similar studies are currently scarce.

MATERIALS AND METHODS

Study design and sampling

The research was designed as a cross-sectional retrospective study that collected data from March 1, 2016, to February 2, 2020, on type 1 diabetic patients admitted to the Endocrinology Unit from an Academic Hospital in Sidi-Bel-Abbes, northwestern Algeria. The study was performed among 370 patients with T1D diagnosed in their pubertal phase (according to the WHO criteria). All the participants' files were revised for the following: medical history, other associated diseases, and complications such as diabetic retinopathy, neuropathy, and nephropathy.

The study included 223 patients with T1D who were above the age of 18, admitted to the hospital, and had no history of CVD. A total of 147 patients were excluded because they were younger than 18, lacked medical data, with missed informed consent (Fig 1).

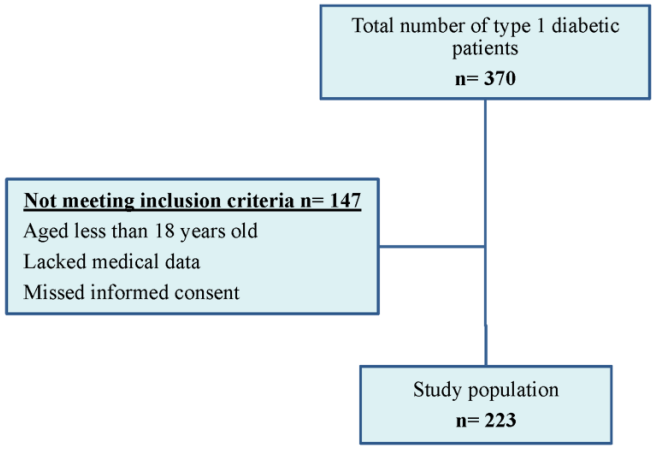

Fig 1. Flow chart of the study population

Data collection

All patients had a full anthropometric evaluation, which comprised height, weight, body mass index (BMI), and waist circumference measures. A sphygmomanometer was used to measure blood pressure in the supine position, followed by a second measurement (after a few minutes) in a standing position. Hypertension was defined as systolic blood pressure (SBP) of 140 mmHg or higher and diastolic blood pressure (DBP) of 90 mmHg or higher. Fasting blood glucose (FBG), glycated hemoglobin (HbA1c), urea, serum creatinine, urinary albumin excretion rate (UAER), and serum lipids (TC, HDL-C, LDL-C, and TG), as well as thyroid-stimulating hormone (TSH), were all collected from patients' medical records. Two noninvasive tests were used to assess the prevalence of aPAD (pulse examination, and ABI). Lower limbs were assessed for symptoms of aPAD, and peripheral pulses were measured at both dorsalis pedis and tibialis posterior arteries.[23] ABI was calculated using the lowest ankle SBP for each leg divided by the maximum brachial SBP to increase the positive test rate in a screening population.[24] ABI measurements were conducted using the Minidop ES 8 Mhz sonographic device.[25]

Normal (ABI = 0.91 to 1.20), decreased (ABI 0.90), and increased (ABI > 1.20) were the categories for ABI

results. This was considered to be comparable to arterial stiffness, using the following lipid ratios (TC/HDL-C, LDL-C/HDL-C, and TG/HDL-C) as markers of atherogenic risk. The presence of subclinical athérosclerosis was later evaluated in every patient.

Data management and analysis

Qualitative data were reported as percentages (%) and relative frequencies, and continuous variables were presented as mean ± standard deviation (SD) with associated 95 percent confidence intervals (95% CI). The Chi-square test was used for qualitative categorical factors and the Student *t*-test for quantitative data.

The association between ABI status and atherosclerosis, odds ratios (OR) and its 95% CI for lipid values were calculated utilizing the multivariate logistic regression analysis after adjusting across quartiles of lipid ratios. To establish the appropriate cut-off value and validity of lipid ratios, the receiver operator characteristic (ROC) curve was employed, and the area under the ROC curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were computed. When the *p*-value was less than or equal to 0.05 ($p \leq 0.05$), statistically significant differences were maintained. SPSS software was used to compute and analyze all data (SPSS 22, IBM Corporation; Chicago, IL. August 2013).

Ethical considerations

Written informed consent was maintained from all patients. This retrospective study was approved by the Ethics Committee of Academic Hospital with approval number AAU-5/2022.

RESULTS

The general features of the participants are summerized in Table 1. Two hundred and twenty three type 1 diabetic patients (108 males and 115 females) were admitted to the Diabetes Unit. Patients were arbitrarily segregated into the following groups based on their ABI whether <0.91 or >1.20 for arterial stiffness. Of the 223 diabetic patients, 138 (61.88%) patients had normal ABI while 85 (38.12%) patients had arterial stiffness. The mean age was 30.70±9.69 years, and the mean of diabetes duration was 11.13±8.95 years. The average age of diabetics with arterial stiffness was statistically higher than those with normal ABI (38.76±8.85 years *vs*. 25.73±6.24 years, $p<0.001$). The mean of duration diabetes was statistically increased in the arterial stiffness group compared to normal ABI group (16.05±9.67 years *vs*. 8.10±6.94 years, $p<0.001$) (Table 2).

Clinical features of the diabetics are presented in Table 2. In terms of anthropometric measurements, there was a higher statistical difference in body weight between the two groups (60.08 ± 11.82 kg and 63.60 ± 8.56 kg for the patients with and without normal ABI, respectively, $p=0.01$). Similarly, significant differences were noted in BMI ($p=0.02$), and waist circumference ($p<0.001$), while there was no significant difference in body height. Furthermore, statistically higher SBP and DBP values were reported in the arterial stiffness group compared to the normal ABI type 1 diabetic patients ($p<0.001$) (Table 2).

Remarkably, unlike FBG values, there was a statistical difference in HbA1c values (normal ABI: 10.06±2.51%, arterial stiffness: 10.79±2.25 %, $p=0.03$) between both groups on admission. Concerning lipid values, as shown in Table 2 when the *t*-test was applied to the TC, triglycerides, and HDL-C for the two groups, *p*-value was statistically significant ($p<0.001$, $p<0.001$, $p=0.01$; respectively). Moreover, all lipid ratios were statistically higher in diabetics with arterial stiffness ($p<0.001$).

To determine the optimal cut-off lipid ratios for detecting atherosclerosis, the ROC curve was used. The TC/HDL-C ratio was a reliable predictor of atherosclerosis. The best cut-off value was ≥ 4.0, with a sensitivity of 77.3%, specificity of 62.5%, a PPV of 71.2%, and a NPV of 53.6% with a diagnostic accuracy of 0.758 (Fig 2).

The multivariate regression between lipid ratio quartiles, as potent marker of atherosclerosis, revealed that the 4th quartile (OR=12.52[5.06-31.00]; $p<0.001$) of TC/HDL-C ratio was greater in the arterial stiffness group as indicated in Table 3. Likewise, in patients with arterial stiffness, the last quartile (4th) of the LDL-C/HDL-C, and the TG/HDL-C ratios were statistically higher (OR=3.70 [1.68-8.11], $p=0.001$; OR=4.74 [2.12-10.59], $p<0.001$; respectively).

As shown in Fig 3, all lipid ratios were significantly greater in men than females with arterial stiffness. Males with arterial stiffness had greater TC, LDL-C, and TG values as compared to females

DISCUSSION

Our study examined the clinical and biological characteristics in long-term patients with T1D with a broad range of ABI to discover the variables linked with the existence of aPAD in these patients and to assess whether the link of these findings with more established atherosclerosis could be validated. The gender distribution of diabetics revealed a slight preponderance of females (51.60%) over males (48.40%) with a sex-ratio of 0.93. In patients with arterial stiffness, the percentage of men was statistically higher than that of women (70.60 % *vs*.

TABLE 1. General characteristics of the type 1 diabetic patients.

Variables	All Patients n=223 Number (%)	Normal ABI n=138 Number (%)	Arterial Stiffness n=85 Number (%)	*P* value*
Gender, n (%)				<0.001*
Male	108 (48.40)	48 (34.80)	60 (70.60)	
Female	115 (51.60)	90 (65.20)	25 (29.40)	
Age groups, years				<0.001*
[18-29]	120 (53.80)	108 (78.20)	12 (14.10)	
[30-39]	65 (29.20)	23 (16.70)	42 (49.40)	
[40-49]	26 (11.70)	7 (5.10)	19 (22.40)	
[50-59]	11 (4.90)	0 (0.00)	11 (12.90)	
≥ 60	1 (0.40)	0 (0.00)	1 (1.20)	
Smoking history, n (%)				<0.001*
Male	39 (17.50)	12 (8.70)	27 (31.80)	
Female	--	--	--	
Prevalence of weight categories, n (%)				0.07
Underweight, BMI <18.5 Kg/m²	47 (21.10)	28 (20.30)	19 (22.40)	
Normal weight, BMI=18.5-25.0 Kg/m²	137 (61.40)	99 (71.70)	38 (44.70)	
Overweight, BMI=25.0-29.9 Kg/m²	29 (13.00)	9 (6.50)	20 (23.50)	
Obesity, BMI ≥30 Kg/m²	10 (4.50)	2 (1.50)	8 (9.40)	
Other associated diseases, n (%)				
Low visual acuity	65 (29.10)	29 (21.00)	36 (42.40)	0.001*
Diabetic retinopathy	41 (18.40)	17 (12.30)	24 (28.20)	0.02*
Diabetic nephropathy	19 (8.50)	2 (1.50)	17 (20.00)	<0.001*
Hypertension	28 (12.60)	5 (3.60)	23 (27.10)	<0.001*
Hypothyroidism	18 (8.10)	13 (9.40)	5 (5.90)	0.34
Anemia	66 (29.60)	42 (30.40)	24 (28.20)	0.72
Dyslipidemia	6 (2.70)	1 (0.70)	5 (5.90)	0.02*

(*) percentages were compared with Chi-square test, $p \leq 0.05$ was considered as significant.
Abbreviations: ABI; Ankle-Brachial Index, BMI; body mass index.

29.40 %, $p<0.001$). A cross-sectional study by Nattero-Chàvez et al[26] revealed that 92 patients with T1D had an abnormal ABI; of those, 59 (64.0%) were men, whereas, another study displayed that 73 patients with T1D had an arterial stiffness; of those, 48 (66.0%) were men.[26,27] Our research revealed a significant effect of age and diabetes duration on differences between ABI. The results are consistent with the literature where the most notable risk factors for arterial stiffness were age, and longer diabetes duration.[26-28] In this study, a significant difference between BMI in both groups was noted. These results are in accordance with reports from the literature showing that higher BMI values and obesity were significant risk factors for arterial stiffness.[26,27,29] Interestingly, retinopathy was reported to be linked with an increased prevalence of arterial stiffness, which was consistent with a prior retrospective study of diabetics.[30] In our research group, hypertension was diagnosed in 28 cases, and it was present in 23 (27.10 %) patients with arterial stiffness. Our results are consistent with prior research demonstrating that the

TABLE 2. Comparison of clinical features according to the absence or presence of arterial stiffness.

Variables	All patients n=223		Normal ABI n=138		Arterial stiffness n=85		*P* value*
	Mean±SD	95% CI	Mean±SD	95% CI	Mean±SD	95%CI	
Mean age (years)	30.70 ± 9.69	29.42-31.98	25.73 ± 6.24	24.68-26.78	38.76 ± 8.85	36.86-40.67	<0.001*
Diabetes duration (years)	11.13 ± 8.95	9.95-12.31	8.10 ± 6.94	6.93-9.27	16.05 ± 9.67	13.96-18.14	<0.001*
Age at 1st diagnosis (years)	19.65 ± 7.98	18.60-20.71	17.67 ± 7.35	16.44-18.91	22.87 ± 7.96	21.15-24.59	<0.001*
Body height (m)	1.66 ± 0.07	1.65-1.67	1.66 ± 0.07	1.65-1.68	1.66 ± 0.08	1.64-1.67	0.46
Body weight (Kg)	61.42 ± 10.81	60.00-62.85	60.08 ± 11.82	58.09-62.07	63.60 ± 8.56	61.76-65.45	0.01*
BMI (Kg/m²)	22.12 ± 3.66	21.64-22.60	21.54 ± 4.07	20.85-22.22	23.06 ± 2.64	22.49-23.63	0.002*
Waist circumference (cm)	85.00 ± 9.41	82.98-87.02	80.26 ± 9.18	77.25-83.28	88.75 ± 7.84	86.47-91.03	<0.001*
SBP (mmHg)	113.1 ± 12.6	111.4-114.8	110.1 ± 10.6	108.3-111.9	117.9 ± 14.1	114.8-120.9	<0.001*
DBP (mmHg)	66.4 ± 8.32	65.3-67.5	65.6 ± 7.56	64.3-66.9	71.8 ± 8.31	69.8-74.9	<0.001*
FBG (g/l)	3.00 ± 1.21	2.84-3.15	2.89 ± 1.25	2.68-3.10	3.17 ± 1.11	2.93-3.41	0.09
HbA1c (%)	10.33 ± 2.44	10.00-10.67	10.06 ± 2.51	9.62-10.49	10.79 ± 2.25	10.29-11.30	0.03
Hemoglobin (g/l)	12.28 ± 1.67	12.04-12.52	10.95 ± 1.29	10.60-12.24	12.79 ± 1.92	12.38-13.21	<0.001*
Total cholesterol (g/l)	1.46 ± 0.33	1.42-1.50	1.38 ± 0.27	1.33-1.43	1.59 ± 0.37	1.51-1.67	<0.001*
HDL-C (g/l)	0.46 ± 0.11	0.44-0.47	0.48 ± 0.08	0.46-0.49	0.42 ± 0.13	0.39-0.45	<0.001*
LDL-C (g/l)	0.87 ± 0.24	0.84-0.91	0.86 ± 0.21	0.83-0.90	0.89 ± 0.27	0.83-0.95	0.38
Triglycerides (g/l)	0.94 ± 0.61	0.86-1.02	0.86 ± 0.54	0.77-0.96	1.07 ± 0.68	0.93-1.22	0.01*
TC/HDL-C	3.37 ± 1.18	3.21-3.53	2.93 ± 0.68	2.81-3.04	4.09 ± 1.45	3.77-4.40	<0.001*
LDL-C/HDL-C	2.01 ± 0.72	1.92-2.11	1.84 ± 0.54	1.75-1.93	2.29 ± 0.87	2.10-2.48	<0.001*
TG/HDL-C	2.26 ± 1.89	2.01-2.51	1.82 ± 1.01	1.65-1.99	2.98 ± 2.64	2.41-3.55	<0.001*
Creatinine (mg/l)	12.22 ± 12.35	9.87-14.58	8.18 ± 2.65	7.54-8.83	18.83 ± 8.02	13.14-24.51	<0.001*
Urea (g/l)	0.37 ± 0.30	0.31-0.43	0.26 ± 0.14	0.22-0.29	0.56 ± 0.39	0.43-0.68	<0.001*
UAER (mg/24h)	152.15 ± 60.27	87.31-226.59	28.51 ± 6.83	9.52-33.98	216.04-112.83	128.43-339.62	<0.001*
TSH (µIU/mL)	7.13 ± 4.54	2.67-12.46	3.57 ± 2.86	3.10-5.94	12.20 ± 6.57	5.06-22.48	<0.001*

(*) means were compared with independent sample Student's *t*-test, a $p<0.05$ was considered as significant.

Abbreviations: SD; standard deviation, CI; confidence interval, ABI; Ankle-Brachial Index, BMI; body mass index, FBG; Fasting blood glucose, HbA1c; glycosylated hemoglobin, SBP; systolic blood pressure, DBP; diastolic blood pressure, TC; total cholesterol, HDL-C; high-density lipoprotein cholesterol, LDL-C; low-density lipoprotein cholesterol, TG; triglycerides, UAER; urinary albumin excretion rate, TSH; thyroid-stimulating hormone.

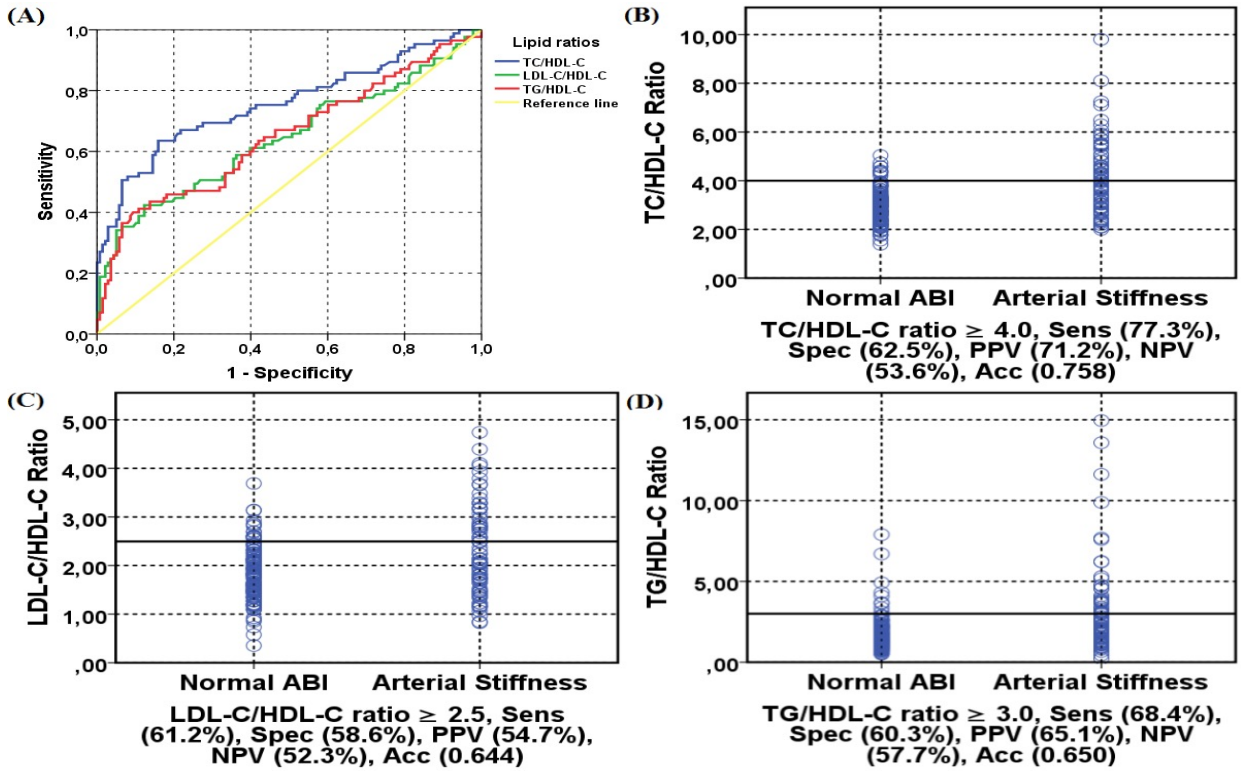

Fig 2. ROC curve to define the best cut-off lipid ratios to detect atherosclerosis.
Abbreviations: ABI; Ankle-Brachial Index, Sens; sensitivity, Spec; specificity, PPV; positive predictive value, NPV; negative predictive value, Acc; accuracy, TC; total cholesterol, LDL-C; low-density lipoprotein cholesterol, HDL-C; high-density lipoprotein cholesterol, TG; triglycerides, ROC; receiver operating characteristics.

TABLE 3. Multivariate analysis of the relationship between lipid ratios quartiles and ABI status in type 1 diabetic patients.

Variables	Normal ABI n= 183 Number (%)	Arterial stiffness n= 85 Number (%)	Odds ratio (95% CI OR)	*P* value*
TC/HDL-C ratio				
1st quartile (1.39-2.55)	41 (29.7)	12 (14.1)	**Reference**	---
2nd quartile (2.56-3.10)	45 (32.6)	12 (14.1)	0.91 [0.36-2.25]	0.84
3rd quartile (3.11-3.91)	40 (29.0)	17 (20.0)	1.45 [0.61-3.42]	0.39
4th quartile (3.92-9.80)	12 (8.7)	44 (51.8)	12.52 [5.06-31.00]	<0.001*
LDL-C/HDL-C ratio				
1st quartile (0.35-1.48)	37 (26.8)	18 (21.2)	**Reference**	---
2nd quartile (1.49-1.92)	41 (29.7)	15 (17.6)	0.75 [0.33-1.70]	0.49
3rd quartile (1.93-2.43)	40 (29.0)	16 (18.8)	0.82 [0.36-1.84]	0.63
4th quartile (2.44-4.74)	20 (14.5)	36 (42.4)	3.70 [1.68-8.11]	0.001*
TG/HDL-C ratio				
1st quartile (0.22-1.26)	39 (28.3)	16 (18.8)	**Reference**	---
2nd quartile (1.27-1.79)	41 (29.7)	15 (17.6)	0.89 [0.38-2.04]	0.78
3rd quartile (1.80-2.46)	39 (28.3)	17 (20.0)	1.06 [0.47-2.39]	0.88
4th quartile (2.47-14.95)	19 (13.8)	37 (43.5)	4.74 [2.12-10.59]	<0.001*

(*) multivariate logistic regression significant at $p \leq 0.05$.
Abbreviations: CI; confidence interval, OR; Odd ratio, Q; quartiles, ABI; Ankle-Brachial Index, TC; total cholesterol, LDL-C; low-density lipoprotein cholesterol, HDL-C; high-density lipoprotein cholesterol, TG; triglycerides.

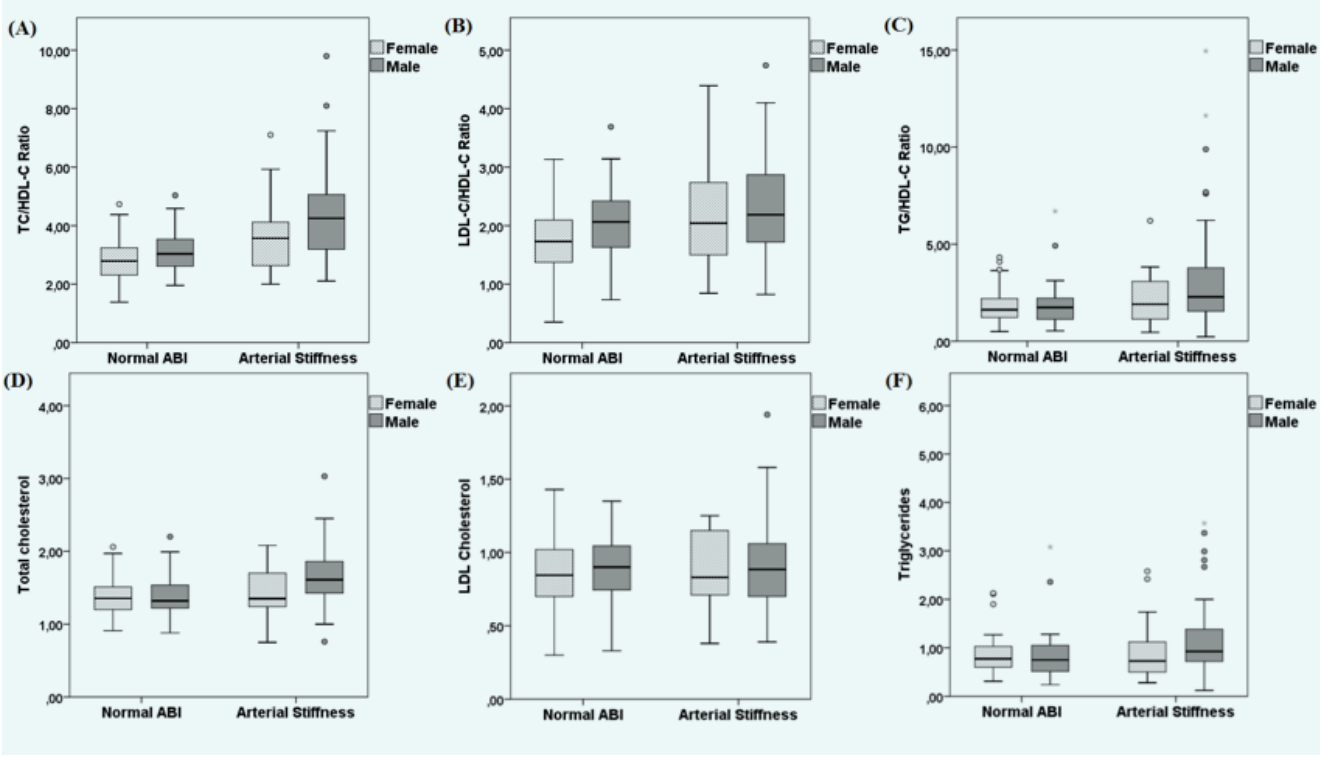

Fig 3. Comparison of lipid ratios levels between patients with and without arterial stiffness according to their gender
Abbreviations: ABI; Ankle-Brachial Index, TC; total cholesterol, LDL-C; low-density lipoprotein cholesterol, HDL-C; high-density lipoprotein cholesterol, TG; triglycerides.

incidence of resistant hypertension rises with advanced aPAD and that hypertension is the greatest risk factor for arterial stiffness.[26-28,29]

Additionally, consistent with the literature review,[31] we discovered that the risk of arterial stiffness is impending in these subjects with each incremental increase in HbA1c. Similarly, Adler et al[32] reported that every 0.9% increase in HbA1c was correlated with a 29% increased risk of incident aPAD in diabetics.[32] Our findings demonstrated a significant increase in hemoglobin values among the arterial stiffness group. Comparable results regarding higher hemoglobin concentrations were independently associated with abnormal ABI in the general population, indicating that a rise in this level may be linked with higher risk of atherosclerosis.[33] We also found that diabetics with increased ABI had an atherogenic lipoprotein profile, defined by greater plasma levels of TC and TG concentrations, and reduced HDL-cholesterol levels, these findings are in consistent with the literature.[26,29,30,32] In addition, we also highlighted a higher values of UAER (≥ 30 mg/24h) in diabetics with arterial stiffness, which may have increased the reliability of the results. Zander et al[29] confirmed that in patients with microalbuminuria and macroalbuminuria, aPAD was observed significantly more often.[30] An significant finding of our investigation was the association between elevated ABI and serum TSH levels in patients with T1D. Our results echo those of Zhao et al[34] who concluded that higher serum TSH values may be a predictor of arterial stiffness.[34]

Considering the substantial link between ABI and increasing values of TC/HDL-C, LDL-C/HDL-C, and TG/HDL-C in this research, we may presume that increased ABI values in individuals with T1D may be indicative of increased CVD risk. Gender disparity is one of the most notable aspects of CVD. Multiple studies demonstrated the influence of gender differences on the prevalence of atherosclerosis risk factors.[35,36] In our study, male participants with higher ABI values had dyslipidaemia, and increased values of lipid ratios that indicate atherosclerosis and stroke. Several studies have analyzed the relationship between TC/HDL-C ratio and arterial stiffness; this ratio has a good discriminating potential for predicting various CVD pathologies such as coronary diseases.[19] Furthermore, a clinical study identified the TC/HDL-C ratio to be the main lipid, or inflammatory indicator for incident aPAD with relative risk of 3.8 [95% CI 1.6–8.5] for patients with the highest TC/HDL-C ratio quartile compared to those with the lowest quartile.[20] On the contrary, minimal evidence suggests an association between LDL-C and incident aPAD. Hence, an inconsistent correlation between LDL-C and aPAD has been established in the studies that have

assessed the values of this lipoprotein.[21] A cross-sectional study included 1911 aPAD patients (467 male *vs* 1444 female) with a mean age of 80 years, indicating that each 1 mg/dL increase in LDL-C was correlated with a 1.8% increased risk of aPAD.[37] Conversely, according to the Women's Health Study, there was no association between LDL-C and incidence aPAD.[38] Based on our findings, the association of the TG/HDL-C ratio with elevated ABI levels and aPAD was stronger in diabetics with arterial stiffness. Thus, TG/HDL-C ratio might be a positive predictor of CVD even in the earliest stages of abnormal lipid metabolism.[17] Moreover, previous study reported that an increased TG/HDL-C ratio independently predicted a decrease in HDL-C and has been strongly linked to a higher risk of atherosclerosis and arterial stiffness.[18]

Like other studies, our research has some limitations. First, this was a cross-sectional retrospective study and, therefore, we cannot identify the severity of aPAD. Second, the lack of non-invasive tests other than ABI has limited our ability to assess arterial stiffness and aPAD prevalence in patients with normal ABI results. Our study also offers several strengths, including the employment of the ROC curve to investigate which lipid ratio is highly associated with arterial stiffness. This research also presented epidemiological evidence from a particular population-based study employing nationally representative data from a single ethnicity. According to our knowledge, this is currently the first study to establish the association between arterial stiffness and dyslipidemia in patients with T1D utilizing an atherogenic lipid profile in Algerian population.

To conclude, in our population of adult patients with T1D, arterial stiffness determined by ABI was related to higher lipid ratio values and subclinical atherosclerosis in a large proportion of patients independent of other conventional CVD risk factors. Therefore, non-invasive methods such as the ABI and the implementation of lipid ratios are highly recommended and may detect a subgroup of cases with undiagnosed aPAD who might benefit from early therapy of CVD risk factors.

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REFERENCES

1. de Ferranti SD, de Boer IH, Fonseca V, Fox CS, Golden SH, Lavie CJ, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Circulation 2014;130:1110-30.
2. Hinchliffe RJ, Brownrigg JR, Apelqvist J, Boyko EJ, Fitridge R, Mills JL, et al. IWGDF guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes. Diabetes Metab Res Rev 2016;32:37-44.
3. Crawford F, Welch K, Andras A, Chappell FM. Ankle brachial index for the diagnosis of lower limb peripheral arterial disease. Cochrane Database Syst Rev 2016;9:CD010680.
4. Sobhani S, Asayesh H, Sharifi F, Djalalinia S, Baradaran HR, Arzaghi SM, et al. Prevalence of diabetic peripheral neuropathy in Iran: a systematic review and metaanalysis. J Diabetes Metab Disord 2014;13:97.
5. Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. Diabetes Care 2006;29:1518-22.
6. Thiruvoipati T, Kielhorn CE, Armstrong EJ. Peripheral artery disease in patients with diabetes: Epidemiology, mechanisms, and outcomes. World J Diabetes 2015;6:961-9.
7. Dua A, Lee CJ. Epidemiology of Peripheral Arterial Disease and Critical Limb Ischemia. Tech Vasc Interv Radiol 2016;19:91-5.
8. Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries Endorsed by: the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J 2018;39:763-816.
9. International Diabetes Federation. IDF Diabetes Atlas, 9th ed. Brussels, 2019.p.88-9.
10. Elgzyri T, Larsson J, Thorne J, Eriksson KF, Apelqvist J. Outcome of ischemic foot ulcer in diabetic patients who had no invasive vascular intervention. Eur J Vasc Endovasc Surg 2013;46:110-17.
11. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease. Circulation 2006;113:e463-654.
12. Urbina EM, Wadwa RP, Davis C, Snively BM, Dolan LM, Daniels SR, et al. Prevalence of increased arterial stiffness in children with type 1 diabetes mellitus differs by measurement site and sex: the SEARCH for Diabetes in Youth Study. J Pediatr 2010;156:731-7.

13. Cecelja M, Chowienczyk P. Role of arterial stiffness in cardiovascular disease. JRSM Cardiovasc Dis 2012;1:1-10.
14. Joosten MM, Pai JK, Bertoia ML, Rimm EB, Spiegelman D, Mittleman MA, et al. Associations between conventional cardiovascular risk factors and risk of peripheral artery disease in men. JAMA 2012;308:1660-7.
15. Aponte J. The prevalence of asymptomatic and symptomatic peripheral arterial disease and peripheral arterial disease risk factors in the US population. Holist Nurs Pract 2011;25:147-61.
16. Wongtiraporn W, Luenee P, Opartkiattikul N, Wongtiraporn W, Laiwejpithaya S, Sangkarat S, et al. Tissue Factor Expression of Endothelial Cell in Response to Atherosclerotic Risk Factors. Siriraj Med J 2011;63:1-3.
17. Su Y, Zhang R, Xu R, Wang H, Geng H, Pan M, et al. Triglyceride to high-density lipoprotein cholesterol ratio as a risk factor of repeat revascularization among patients with acute coronary syndrome after first-time percutaneous coronary intervention. J Thorac Dis 2019;11:5087-95.
18. Jia L, Long S, Fu M, Yan B, Tian Y, Xu Y, et al. Relationship between total cholesterol/high-density lipoprotein cholesterol ratio, triglyceride/high-density lipoprotein cholesterol ratio, and high-density lipoprotein subclasses. Metabolism 2006;55: 1141-8.
19. Millán J, Pintó X, Muñoz A, Zúñiga M, Rubiés-Prat J, Pallardo LF, et al. Lipoprotein ratios: physiological significance and clinical usefulness in cardiovascular prevention. Vasc Health Risk Manag 2009;5:757-65.
20. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of c-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. JAMA 2001;285: 2481-5.
21. Aday AW, Everett BM. Dyslipidemia profiles in patients with peripheral artery disease. Curr Cardiol Rep 2019;21:42.
22. Zhong Z, Hou J, Zhang Q, Zhong W, Li B, Li C, et al. Assessment of the LDL-C/HDL-C ratio as a predictor of one year clinical outcomes in patients with acute coronary syndromes after percutaneous coronary intervention and drug-eluting stent implantation. Lipids Health Dis 2019;18:40.
23. American Diabetes Association. 10. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes-2018. Diabetes Care 2018;41:S105-S18.
24. Taylor-Piliae RE, Fair JM, Varady AN, Hlatky MA, Norton LC, Iribarren C, et al. Ankle brachial index screening in asymptomatic older adults. Am Heart J 2011;161:979-85.
25. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation 2012;126:2890-9.
26. Nattero-Chávez L, Redondo López S, Alonso Díaz S, Garnica Ureña M, Fernández-Durán E, Escobar-Morreale HF, et al. The peripheral atherosclerotic profile in patients with type 1 diabetes warrants a thorough vascular assessment of asymptomatic patients. Diabetes Metab Res Rev 2019;35:e3088.
27. Nattero-Chávez L, Redondo López S, Alonso Díaz S, Garnica Ureña M, Fernández-Durán E, Escobar-Morreale HF, et al. Association of Cardiovascular Autonomic Dysfunction With Peripheral Arterial Stiffness in Patients With Type 1 Diabetes. J Clin Endocrinol Metab 2019;104:2675-84.
28. Jude EB, Eleftheriadou I, Tentolouris N. Peripheral arterial disease in diabetes--a review. Diabet Med 2010;27:4-14.
29. Konin C, Essam N'loo AS, Adoubi A, Coulibaly I, N'guetta R, Boka B, et al. Artériopathie des membres inférieurs du diabétique noir africain: aspects ultrasoniques et facteurs déterminants [Peripheral arterial disease of the lower limbs in African diabetic patients: ultrasonography and determining factors]. J Mal Vasc 2014;39:373-81.
30. Zander E, Heinke P, Reindel J, Kohnert KD, Kairies U, Braun J, et al. Peripheral arterial disease in diabetes mellitus type 1 and type 2: are there different risk factors? Vasa 2002;31:249-4.
31. Morley RL, Sharma A, Horsch AD, Hinchliffe RJ. Peripheral artery disease. BMJ 2018;360:j5842.
32. Adler AI, Stevens RJ, Neil A, Stratton IM, Boulton AJ, Holman RR. UKPDS 59: hyperglycemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. Diabetes Care 2002;25:894-9.
33. Chenglong Z, Jing L, Xia K, Yang T. Association of hemoglobin with ankle-brachial index in general population. Clinics (Sao Paulo) 2016;71:375-80.
34. Zhao W, Zeng H, Zhang X, Liu F, Pan J, Zhao J, et al. A high thyroid stimulating hormone level is associated with diabetic peripheral neuropathy in type 2 diabetes patients. Diabetes Res Clin Pract 2016;115:122-9.
35. Leening MJ, Ferket BS, Steyerberg EW, Kavousi M, Deckers JW, Nieboer D, et al. Sex differences in lifetime risk and first manifestation of cardiovascular disease: prospective population based cohort study. BMJ 2014;349:g5992.
36. Madonna R, Balistreri CR, De Rosa S, Muscoli S, Selvaggio S, Selvaggio G, et al. Impact of Sex Differences and Diabetes on Coronary Atherosclerosis and Ischemic Heart Disease. J Clin Med 2019;8:98.
37. Ness J, Aronow WS, Ahn C. Risk factors for symptomatic peripheral arterial disease in older persons in an academic hospital-based geriatrics practice. J Am Geriatr Soc 2000;48: 312-4.
38. Aday AW, Lawler PR, Cook NR, Ridker PM, Mora S, Pradhan AD. Lipoprotein Particle Profiles, Standard Lipids, and Peripheral Artery Disease Incidence. Circulation 2018;138:2330-41.