Ethiopian Medical Journal 2022, 60(3)
Open access articles distributed in terms of Creative Commons Attribution Licence [CC by 4.0]
ISSN 0014-1755 eISSN 2415-2420
Hamri et al

Original Article

Association of microalbuminuria with metabolic indicators of atherosclerosis and inflammation in type 1 diabetic patients

Walid Hassene Hamri[1*], Mustapha Diaf[1], Noria Harir[1]

[1]Department of Biology, Faculty of Natural and Life Sciences, Djillali Liabes University, Sidi-Bel-Abbes, Algeria

*Corresponding author:walidhamri94@gmail.com

Abstract

Background: *Microalbuminuria is usually accompanied by undiagnosed dyslipidemia. We aimed to assess the correlation between microalbuminuria and early atherosclerotic changes in type 1 diabetics by comparing two groups of patients according to their UAER (Urinary Albumin Excretion Rate) status.*

Methods: *We conducted a retrospective study including 167 patients with confirmed type 1 diabetes segregated into the following groups (patients with normoalbuminuria vs. patients with microalbuminuria).*

Results: *Our study revealed a definite preponderance of males (52.10%). The mean age was 29.55±11.36 years, whereas the diabetes duration was 12.73±8.14 years. The prevalence of microalbuminuria was 39.5%. Significant correlation was observed between lipid profiles such as TG and LDL (r=0.227; r=0.166, respectively) and lipid ratios TC/HDL, LDL/HDL, and TG/HDL (r=0.322; r=0.351; r=0.386, respectively) with UAER. The findings showed that the last quartile of TC/HDL ratio (cOR=6.89[2.61-18.14]; p<10^{-3}) and LDL/HDL ratio (cOR=5.48 [2.10-14.30]; p=0.001) were higher in microalbuminuric patients. Similarly, we noticed higher values in the last two quartiles (3rd and 4th) of the TG/HDL ratio with p values of 0.05 and 10^{-3}, respectively. TG/HDL ratio was a strong indicator for atherosclerotic disease (sensitivity of 82.1%, specificity of 84.2%, and diagnostic accuracy of 0.775). In contrast to females who developed microalbuminuria, lipid ratios and lipid profiles were significantly greater in male patients.*

Conclusions: *Patients who develop microalbuminuria are characterized by dyslipidemia and a higher risk of atherosclerotic cardiovascular disease. Hence, early detection of microalbuminuria associated with dyslipidemia is crucial for the effective prevention of atherosclerotic cardiovascular diseases.*

Keywords: *Atherosclerotic cardiovascular disease; dyslipidemia; microalbuminuria; type 1 diabetes; UAER.*

Citation : *Hamri WH, Diaf M, Harir N, Association of microalbuminuria with metabolic indicators of atherosclerosis and inflammation in type 1 diabetic patients. Ethiop Med J 60(3) 227-235*

Submission date : *26 October 2021* ***Accepted:*** *31 May 2022* ***Published: 1 July 2022***

Introduction

Diabetic kidney disease (DKD) is the most severe type 1 diabetes (T1D) complication resulting from immune processes related to different proinflammatory signaling pathways, genetic predispositions, and some epigenetic mechanisms which were reported to be implicated in the inflammatory disease and the onset and progression of DKD (1). Past epidemiological studies demonstrated that 25% to 40% of subjects with T1D and 5% to 40% of individuals with type 2 diabetes (T2D) eventually develop DKD (2).

Microalbuminuria has been conventionally established as the primary predictive marker of the risk for progression to the advanced stages of DKD (3).

It has been defined by an increased urinary albumin excretion rate (UAER) approximately in the range of 30–300 micrograms per minute (4). In addition, 20% to 30% of subjects with T1D present with microalbuminuria after an average of 5-10 years of diabetes (2).

Current recommendations from the American Diabetes Association concerning screening for microalbuminuria in patients with T1D suggest annual testing after 10 years of age and after an average of 5 years with diabetes (5). Furthermore, these patients are at higher risk of cardiovascular diseases (CVDs) compared with diabetic patients without microalbuminuria which represents a significant burden to health care systems (6).

Preliminary studies have shown that microalbuminuria is associated with markers of endothelial dysfunction and arterial stiffness (7). Hence, it can be used as a strong predictor of progressive trans-capillary leakage of lipoproteins that increases the risk of atherosclerotic cardiovascular diseases in selected populations, such as type 1 diabetic middle-aged and elderly patients with DKD (8). Additionally, there is compelling evidence that points to major mechanisms of diabetic atherosclerosis and vascular remodeling promoting each other and are part of a vicious combination leading to the advancement of the pathological process of microalbuminuria and CVD (9).

It has been found also that relation between microalbuminuria and some atherosclerotic cardiovascular risk factors, such as hypertension, glycosylated hemoglobin, and serum lipids were higher in type 1 diabetic patients compared with patients without T1D (10). Therefore, microalbuminuria can assume an important role as an index of atherosclerotic vascular disease.

In this regard, we aimed in this study to examine the prevalence of microalbuminuria among patients with T1D to establish whether there is any relationship between a decline in renal function and atherosclerotic cardiovascular disease risk, by assessing blood lipid ratios in type 1 diabetic Algerian patients where similar studies are still lacking.

Patients and Methods

Study design, area, and period:

This was a retrospective study reporting data from January 1, 2009, to December 30, 2019, on type 1 diabetics who visited the Diabetes Center in Sidi-Bel-Abbes, Northwestern Algeria.

Population:

Our study included 167 type 1 diabetics (87 males and 80 females) diagnosed in their pubertal period (according to the WHO guideline) that were over 13 years old during this study (11). All medical records of the participants were revised for the following: status of the diabetic disease, biochemical parameters, and other associated diseases such as low visual acuity, diabetic retinopathy, hypothyroidism, and diabetic foot.

Selection of study subjects:

All patients with previously diagnosed T1D, aged more than 13 years, and who visited the Diabetes Center at least two times a year with no history of any cardiovascular disease were enrolled in the analysis. Although, patients with T2D or T1D aged less than 13 years, missing medical records of the disease, and missing informed consent were excluded.

Data collection process:

For all patients, the anthropometric measurements including body height, weight, waist circumference, and body mass index (BMI) were taken from the patient's medical record. BMI was calculated as weight (kg)/ Height^2 (m), and the patients were classified into under weight, normal, overweight, and obese classes based on BMIs of <18.5, 18.5–24.9, 25–29.9, and ≥30 kg/m^2, respectively.

A sphygmomanometer was used to measure blood pressure in the supine position, followed by a standing measurement (after a few minutes). A systolic blood pressure (SBP) of 140 mmHg and diastolic blood pressure (DBP) of 90 mmHg or more were considered as elevated blood pressure (12). The latest biochemical test results including fasting blood glucose; glycated hemoglobin (HbA1c); high-sensitivity C-reactive protein (hs-CRP); urea; serum creatinine; lipid parameters - total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and triglycerides (TG); and thyroid-stimulating hormone (TSH) were collected from patients' medical records. Microalbuminuria was defined as a urinary albumin excretion rate (UAER) in at least two samples obtained within 3-6 months. Microalbuminuria observed for two or more consecutive years with UAER > 30 mg/24h was regarded as persistent (4). Furthermore, lipid ratios (TC/HDL, LDL/HDL, and TG/HDL) were measured as indicators of atherogenic risk.

Statistical analysis:

Data are shown as mean±SD with its respective 95% CI for continuous variables and as percentage (%) with its relative frequency for categorical variables. The differences between groups with and without microalbuminuria were analyzed by the Chi-square test for qualitative variables and the Student t-test for quantitative variables. A partial correlation test was applied to evaluate the correlation between lipid profile and lipid ratio with UAER levels. Receiver operator characteristic (ROC) curves were applied to identify the predictive values of lipid ratios for atherosclerosis. Statistically significant differences were maintained when the p-value was less than or equal to 0.05 ($p \leq 0.05$).

After adjusting for quartiles of lipid ratios, multivariate logistic regression analysis was utilized to measure crude odds ratios (cOR) and 95% CI for lipid ratios to examine the correlation between microalbuminuria and atherosclerotic disease. All data were computed and analyzed using SPSS software (SPSS 22, IBM Corporation; Chicago, IL. August 2013).

Ethics:

The Ethics Committee of Diabetic Center approved this research and since its retrospective research, ethical approval was acquired from the center in which the research was conducted.

Result

Socio-demographic profile:

The summarized characteristics of the enrolled participants are shown in Table 1. A total of 167 type 1 diabetic patient (52.10% males and 47.90% females) were included in this study. Arbitrarily, patients were segregated into two groups according to the level of urinary albumin excretion rate (UAER) whether below or above 30 mg/24h (patients with normoalbuminuria "UAER<30 mg/24h" vs. patients with microalbuminuria "UAER>30 mg/24h").

Of the 167 diabetic patients, 101 (60.48%) patients were normoalbuminuric while 66 (39.52%) patients were microalbuminuric (Table 1).

Table 1: Summarized characteristics of study participants.

Variables	All Patients n=167 Number (%)	Normoalbuminuria n=101 Number (%)	Microalbuminuria n=66 Number (%)	P-value
Gender (%)				
Male	87 (52.10)	43 (42.60)	44 (66.70)	
Female	80 (47.90)	58 (57.40)	22 (33.30)	0.002
Age groups (years)				
[13-19]	34 (20.40)	28 (27.70)	6 (9.10)	
[20-29]	60 (35.90)	41 (40.60)	19 (28.80)	
[30-39]	40 (24.00)	19 (18.80)	21 (31.80)	$<10^{-3}$
[40-49]	22 (13.20)	11 (10.90)	11 (16.70)	
[50-59]	9 (5.40)	2 (2.0)	7 (10.60)	
≥ 60	2 (1.20)	0 (0.00)	2 (3.0)	
Smoking history (%)				
Male	21 (12.60)	5 (5.00)	16 (24.20)	$<10^{-3}$
Prevalence of weight categories (%)				
Underweight, BMI <18.5 (Kg/m²)	41 (24.60)	22 (21.8)	19 (28.70)	
Normal weight, BMI=18.5-25.0'(Kg/m²)	100 (59.90)	63 (62.40)	37 (56.10)	0.69
Overweight, BMI=25.0–29.9(Kg/m²)	22 (13.20)	15 (14.90)	7 (10.60)	
Obesity, BMI ≥30 (Kg/m²)	4 (2.40)	1 (1.00)	3 (4.50)	
Other associated diseases (%)	58 (34.70)	27 (26.70)	31 (47.00)	0.007
Low visual acuity	38 (22.80)	16 (15.90)	22 (33.30)	0.004
Diabetic retinopathy	29 (17.40)	0 (0.00)	29 (43.90)	$<10^{-3}$
Diabetic nephropathy	26 (15.60)	1 (1.00)	25 (37.90)	$<10^{-3}$
Hypertension	28 (10.20)	5 (5.00)	12 (18.20)	0.37
Hypothyroidism	5 (3.00)	0 (0.00)	5 (7.60)	0.005
Dyslipidemia	29 (17.40)	6 (6.00)	23 (34.90)	$<10^{-3}$
Diabetic foot				

Percentages (%) were compared with Chi-square test, p≤0.05 was considered as statistically significant. BMI: body mass index.

The mean age of the patients was 29.55±11.36 years, whereas the mean diabetes duration was 12.73±8.14 years. The mean age of patients with microalbuminuria was greater than in those with normoalbuminuria (p<0.001). Likewise, the mean duration of T1D was statistically greater among those who had microalbuminuria ((p<0.001) (Table 2).

Clinical profile:

The clinic characteristics and laboratory indexes are described in Table 2. Regarding the anthropometric measurements on admission, significant differences were highlighted in body height (p=0.003) in the microalbuminuria group. Furthermore, concerning blood pressure, significant differences were observed in diabetics who developed microalbuminuria (SBP, p<0.001; DBP, p<0.001) (Table 2).

Remarkably, fasting plasma glucose and HbA1c levels were statistically increased in patients with microalbuminuria (p<0.001 for both cases). A significant difference was observed in terms of hs-CRP (p=0.02).

Regarding lipid levels, HDL-c and triglyceride values statistically differed between the two groups (p<0.001). Moreover, it was revealed that lipid ratios (TC/HDL-c, LDL/HDL-c, and TG/HDL-c) were statistically higher in patients with microalbuminuria (p<0.01).

Regarding thyroid function, serum TSH levels were higher in patients with microalbuminuria than those with normoalbuminuria (p= 0.06).

Table 2: Comparison of clinical characteristics between Normoalbuminuric and Microalbuminuric type 1 diabetic patients.

Variables	All Patients n=167		Normoalbuminuria n=101		Microalbuminuria n=66		P-value
	Mean±SD	95% CI	Mean±SD	95% CI	Mean±SD	95% CI	
Mean age (years)	29.55 ± 11.36	27.81-31.29	26.22 ± 9.66	24.31-28.13	34.64 ± 11.92	31.72-37.58	$<10^{-3}$
Diabetes duration (years)	12.73 ± 8.14	11.49-13.97	10.62 ± 6.81	9.28-11.97	15.96 ± 8.96	13.75-18.16	$<10^{-3}$
Age at 1st diagnosis (years)	16.84 ± 9.51	15.39-18.30	15.61 ± 9.40	13.76-17.47	18.73 ± 9.45	16.40-21.05	0.03
Body height (m)	1.67 ± 0.07	1.65-1.68	1.65 ± 0.07	1.64-1.67	1.69 ± 0.07	1.67-1.71	0.003
Body weight (kg)	59.18 ± 11.19	57.47-60.89	58.40 ± 10.84	56.26-60.54	60.36 ± 11.69	57.48-63.23	0.27
BMI (kg/m²)	21.16 ± 3.52	20.62-21.70	21.24 ± 3.44	20.56-21.92	21.03 ± 3.67	20.13-21.94	0.71
Waist circumference (cm)	80.90 ± 9.33	78.25-83.55	79.04 ± 9.36	75.41-82.67	83.27 ± 8.94	79.31-87.24	0.11
SBP (mmHg)	114.2 ± 13.8	112.0-116.3	109.1 ± 9.2	107.3-110.9	122.0 ± 15.9	118.1-125.9	$<10^{-3}$
DBP (mmHg)	66.3 ± 9.16	64.9-67.7	63.7 ± 8.1	62.1-65.3	70.5 ± 9.2	68.2-72.8	$<10^{-3}$
Fasting plasma glucose (g/l)	2.76 ± 1.28	2.56-2.96	2.50 ± 1.20	2.26-2.73	3.16 ± 1.28	2.85-3.48	0.001
HbA1c (%)	9.47 ± 2.17	9.13-9.81	8.51 ± 1.57	8.19-8.84	10.87 ± 2.19	10.33-11.42	$<10^{-3}$
Hs-CRP (mg/dl)	51.57 ± 68.70	17.40-85.73	7.20 ± 8.53	0.68-15.09	79.80 ± 75.66	28.96-130.63	0.02
Total cholesterol (g/l)	1.60 ± 0.36	1.55-1.66	1.58 ± 0.29	1.52-1.64	1.64 ± 0.45	1.53-1.75	0.26
HDL-c (g/l)	0.44 ± 0.10	0.42-0.46	0.47 ± 0.09	0.45-0.49	0.39 ± 0.10	0.37-0.42	$<10^{-3}$
LDL-c (g/l)	0.88 ± 0.26	0.84-0.92	0.85 ± 0.20	0.81-0.89	0.93 ± 0.33	0.85-1.01	0.06
Triglycerides (g/l)	0.93 ± 0.59	0.83-1.02	0.78 ± 0.39	0.70-0.85	1.15 ± 0.76	0.97-1.34	$<10^{-3}$
TC/HDL-c	3.81 ± 1.19	3.62-3.99	3.45 ± 0.85	3.28-3.62	4.35 ± 1.42	4.00-4.70	$<10^{-3}$
LDL/HDL-c	2.12 ± 0.82	2.00-2.25	1.89 ± 0.64	1.77-2.02	2.47 ± 0.94	2.24-2.71	$<10^{-3}$
TG/HDL-c	2.33 ± 2.02	2.03-2.64	1.79 ± 1.47	1.50-2.08	3.17 ± 2.43	2.57-3.76	$<10^{-3}$
Creatinine (g/l)	13.78 ± 19.04	10.74-16.82	7.28 ± 1.17	6.94-7.62	26.04 ± 28.64	18.15-33.94	$<10^{-3}$
Urea (g/l)	0.42 ± 0.41	0.35-0.48	0.23 ± 0.07	0.21-0.24	0.77 ± 0.54	0.62-0.92	$<10^{-3}$
Microalbuminuria (mg/24h)	133.30 ± 356.87	78.78-187.83	8.01-6.83	6.66-9.35	325.04-513.28	198.86-451.22	$<10^{-3}$
TSH (µIU/ml)	6.84 ± 15.37	2.83-10.85	4.97 ± 5.73	3.29-6.65	14.15 ± 32.19	6.30-34.60	0.06

Means were compared with independent sample Student's t-test, $p<0.05$ was considered as significant. SD: standard deviation, CI: confidence interval, HbA1c: glycosylated hemoglobin, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, hs-CRP: high-sensitivity C-reactive protein, TC: total cholesterol, HDL-c: high-density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol, TG: triglycerides, TSH: thyroid-stimulating hormone.

Partial correlation was applied to establish the correlation of lipid profiles and lipid ratio to UAER values in patients with T1D by controlling for age, gender, disease duration, and HbA1c levels. There was a significant positive correlation between TG (r=0.227), LDL (r=0.166), TC/HDL ratio (r=0.322), LDL/HDL ratio (r=0.351), and TG/HDL ratio (r=0.386) with the UAER levels. These results elucidate that an increase in lipid values is correlated with an increase in the UAER levels. Conversely, there was a negative correlation between HDL and UAER levels ($r=-0.400$; $p<0.001$), which means that there was an inverse correlation between HDL and UAER (Table 3).

Table 3: Partial correlation between lipid profile and lipid ratio with UAER level after adjustment for age, gender, disease duration, and HbA1c

Variables	UAER (mg/24h)		
	N	r (correlation coefficient)	P-value
Single lipid measures	167		
TC, g/L		0.077	0.321
TG, g/L		0.227	0.003
HDL, g/L		-0.400	$<10^{-3}$
LDL, g/L		0.166	0.032
Lipid ratios			
TC/HDL		0.322	$<10^{-3}$
LDL/HDL		0.351	$<10^{-3}$
TG/HDL		0.386	$<10^{-3}$

The partial correlation was significant at $p\leq0.05$. UAER: urinary albumin excretion rate, TC: total cholesterol, LDL: low-density lipoprotein cholesterol, HDL: high-density lipoprotein cholesterol, TG: triglycerides.

The multivariate regression was utilized to identify the relative risk of atherosclerosis according to lipid ratio quartiles. The results showed that the fourth quartile of the TC/HDL ratio was statistically greater in the microalbuminuria group ($p<0.001$).

Similarly, the last quartile (4^{th}) of the LDL/HDL ratio was significantly higher in the microalbuminuria group ($p=0.001$). Likewise, the ($3^{rd}$and 4^{th}) quartiles of the TG/HDL ratio were significantly higher in patients with microalbuminuria ($p=0.05$, $p<10^{-3}$; respectively) (Table 4).

Table 4: Multivariate analysis of the relationship between lipid ratio quartiles and albuminuria status in type 1 diabetic patients.

Variables	Normoalbuminuria, n=101 Number (%)	Microalbuminuria, n=66 Number (%)	cOR (95% CI)	P-value
TC/HDL ratio				
1st quartile (2.09-3.00)	28 (27.7)	13 (19.7)	Reference	---
2nd quartile (3.01-3.63)	34 (33.7)	10 (15.2)	0.63 [0.24-1.66]	0.35
3rd quartile (3.64-4.34)	29 (28.7)	11 (16.7)	0.81 [0.31-2.12]	0.67
4th quartile (4.35-8.10)	10 (9.9)	32 (48.5)	6.89 [2.61-18.14]	$<10^{-3}$
LDL/HDL ratio				---
1st quartile (0.73-1.74)	28 (27.7)	11 (16.7)	Reference	0.23
2nd quartile (1.85-2.13)	38 (37.6)	8 (12.1)	0.53 [0.19-1.50]	0.09
3rd quartile (2.14-2.74)	22 (21.8)	19 (28.8)	2.19 [0.86-5.56]	0.001
4th quartile (2.75-5.14)	13 (12.9)	28 (42.4)	5.48 [2.10-14.30]	
TG/HDL ratio				
1st quartile (0.45-1.27)	34 (33.7)	7 (10.6)	Reference	---
2nd quartile (1.28-1.85)	31 (30.7)	12 (18.2)	1.88 [0.65-5.38]	0.23
3rd quartile (1.86-2.63)	28 (25.7)	15 (22.7)	2.80 [0.99-7.86]	0.05
4th quartile (2.64-14.95)	10 (9.9)	32 (48.5)	15.54 [5.27-45.75]	$<10^{-3}$

Multivariate logistic regression significant at $p\leq0.05$. CI: confidence interval, cOR: Crude odd ratio, TC: total cholesterol, LDL: low-density lipoprotein cholesterol, HDL: high-density lipoprotein cholesterol, TG: triglycerides.

ROC curve for lipid ratios showed strong discriminatory power for detecting atherosclerotic disease. The TG/HDL ratio was a strongly indicator for atherosclerosis. The optimum cut-off value was ≥3.0, with a sensitivity of 82.1%, specificity of 84.2%, positive predictive value of 78.3%, and negative predictive value of 67.6% with a diagnostic accuracy of 0.775. (Figure 1B, D).

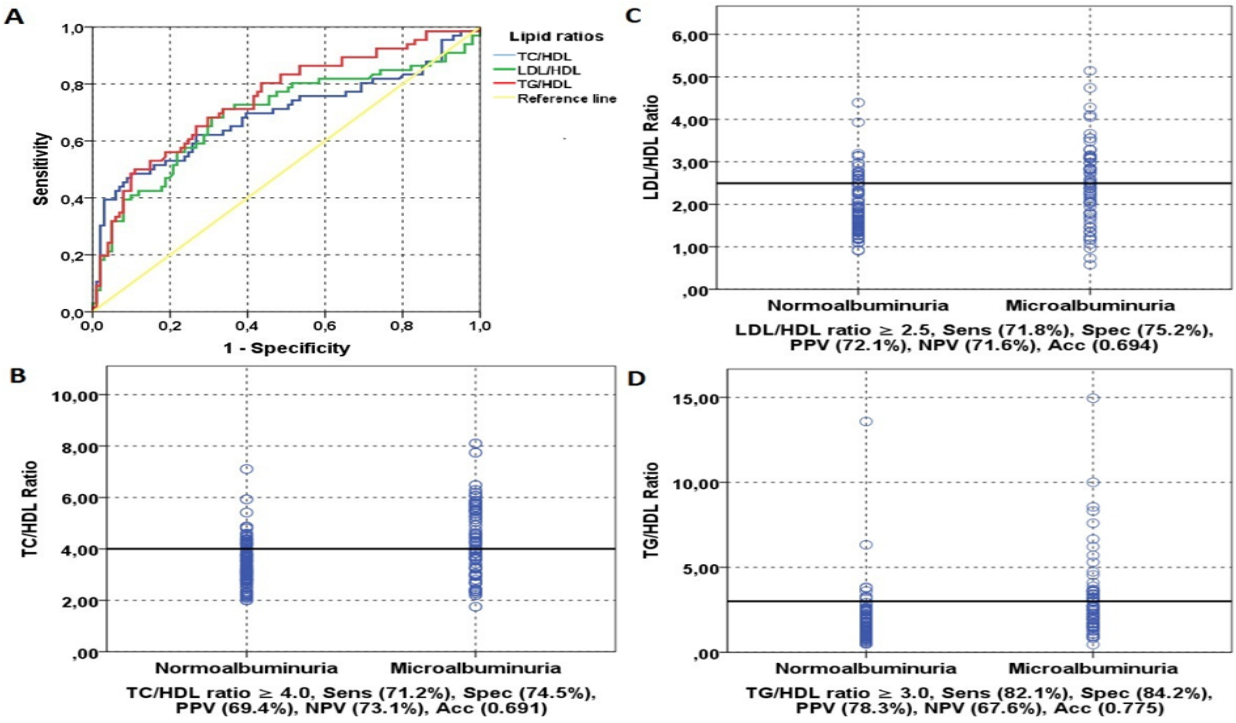

Figure 1: Receiver operating characteristic curve to define the best cut-off lipid ratios to detect atherosclerosis. Sens: sensitivity, Spec: specificity, PPV: negative predictive value, NPV: positive predictive value, Acc: accuracy, TC: total cholesterol, LDL: low-density lipoprotein cholesterol, HDL: high-density lipoprotein cholesterol, TG: triglycerides.

As displayed in Figure 2, in contrast to females who developed microalbuminuria, when comparing all lipid parameters (lipid ratios and conventional lipid parameters) between the two genders, higher values were found in male patients with microalbuminuria.

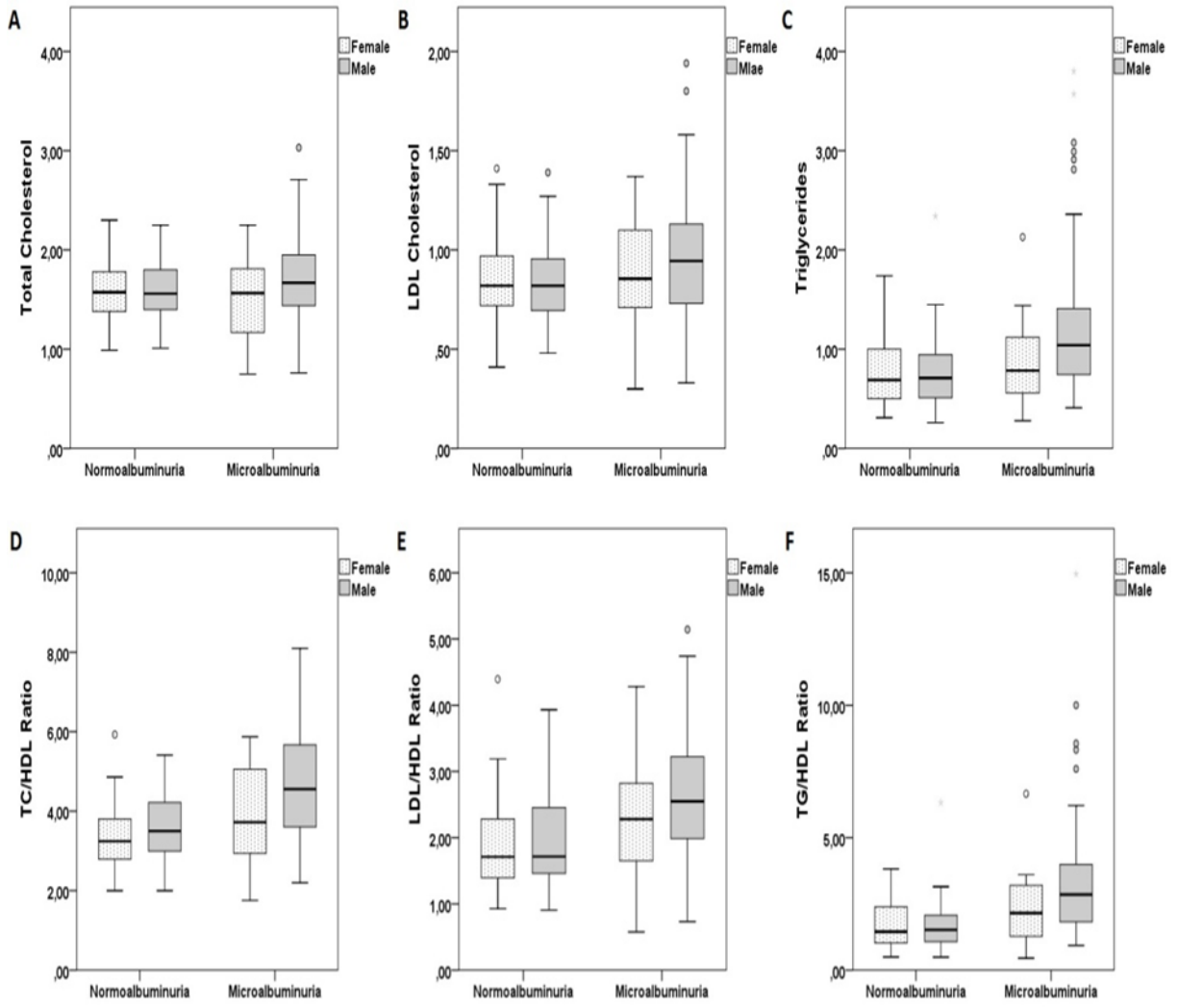

Figure 2: Comparison of lipid ratio levels between patients with and without microalbuminuria according to patients' gender. TC: total cholesterol, HDL-c: high-density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol, TG: triglycerides.

Discussion

The current study assessed the potential role of biological and clinical features in diabetics with and without elevated urinary albumin excretion rate (UAER) to establish the factors related to the existence of microalbuminuria in this population and to determine whether the association of this clinical finding with atherosclerosis risk could be confirmed by assessing blood lipid ratios in type 1 diabetic patients.We revealed that the distribution of diabetics by gender was inequitable, emphasizing a clear male preponderance over females (52.10% - 47.90%) with a male to female ratio of 1.09. Compared to microalbuminuric patients with UAER>30 mg/24h, the proportion of men was significantly higher than that of women among type 1 diabetic patients. A longitudinal study conducted by Jenkins and colleagues (13) after a mean follow-up time of 14.5 years showed that 824 patients with T1D had an AER < 40 mg/24h; of those, 448 (54.4%) had AER < 40 mg/24h were men, whereas, in the microalbuminuria (40–299 mg/24h) group and the macroalbuminuria (≥300 mg/24h) group, 30 (59.8%) and 30 (71.4%) were men. The results also are consistent with previous studies in the literature (14-16).

Our study displayed significant impacts of age and duration of diabetes on the variance between UAER. The findings concord with other studies' conclusions where the most prominent risk factors for microalbuminuria were age at onset of diabetes and longer diabetes duration (14,15,17).

Another noteworthy finding of the present inquiry was that smoking was associated with increased albuminuria. Numerous studies have shown that cigarette consumption promotes the onset and progression at all stages of DKD in diabetes (T1D and T2D) (17,18). Furthermore, exposure to cigarette smoke could influence vascular phenotypes of early atherosclerosis in patients with T1D (19).

Interestingly, we found that retinopathy was associated with an increased incidence of microalbuminuria, and this was following a previous follow-up study of adults with T1D (20). In the current study group, hypertension was detected in 26 cases, and 25 (37.90%) of cases with microalbuminuria were hypertensive. Our findings are in agreement with the previous study which proves that the prevalence of hypertension increases with advanced diabetic nephropathy and defines hypertension as the most significant risk factor for microalbuminuria (14).
Additionally, consistent with other studies (14,15), we found that with an incremental rise in hbA1c, the risk of microalbuminuria is imminent in these patients. Similarly, Wadén *et al.* demonstrated that higher levels of hbA1c predict not only incident microalbuminuria and progression of established DKD but also CVD events in patients with T1D (16).

Our results showed that there is a significant increase in hs-CRP levels among patients with microalbuminuria. Comparable findings regarding increased plasma markers of inflammation such as hs-CRP were associated with the progression of kidney dysfunction in T1D during both short-term and long-term follow-up (21). In addition, other studies have confirmed that soluble molecules involved in inflammation and endothelial damage including hs-CRP are recognized as potential cardiovascular risk markers through the development and progression of the atherosclerotic inflammation process (22).
We also identified that patients with increased UAER and nephropathy accompanying T1D had an atherogenic lipoprotein profile, which was characterized by elevated plasma levels of LDL-cholesterol and triglyceride-rich lipoprotein subclasses, and lower HDL-cholesterol subclasses, these results concord with the literature (14-16).
An important observation of our study was the association of an increased UAER with high serum TSH levels in patients with T1D. Our findings echo with the observations made by Das *et al.* who ascertained a similar correlation between increased prevalence of microalbuminuria and elevated TSH quartiles (23). Meanwhile, our previous study confirmed that elevated serum TSH levels are characterized by a higher atherogenic index, which implies to be a risk factor for atherosclerosis (24).

Taking into account the strong correlation between UAER and elevated levels of TC/HDL-C, LDL/HDL-C, and TG/HDL-C in our study we can assume that higher UAER in diabetic type 1 patients may indicate an increased cardiovascular risk. Gender difference is one of the utmost outstanding characteristics of CVD. Several studies have reported the impact of gender dissimilarity in the prevalence of CVD risk factors (25,26). In the present study, we found that male subjects with microalbuminuria had hyperlipidaemia (higher LDL, TC, and TG) and higher values of lipid ratios, indicators of atherosclerosis and stroke (TC/HDL, LDL/HDL, and TG/HDL). In recent epidemiological studies, higher levels of proteinuria and microalbuminuria have been associated with an increased risk of cardiovascular mortality, heart failure, coronary disease, and stroke (27). Based on the results of the present study, the association of TG/HDL-C with increased UAER and DKD was stronger in patients with microalbuminuria. It is thus possible that TG/HDL-C could represent the progression of kidney insufficiency even in the early stage of lipid metabolism abnormity. There are several reasons why the level of TG/HDL-C may be superior to that of other lipid parameters in increased UAER and DKD identification. Elevated TG levels and decreased HDL-C levels have been most strongly associated with an increased risk of atherosclerosis and renal dysfunction (28).

Like any research, there are some limitations in the current study. First, the sample size contained a low prevalence of microalbuminuria, which limited our ability to establish the full outcome of diabetic nephropathy. Second, the retrospective nature of the present study and how we have collected the data does not allow making a clear, conclusive decision about the atherosclerosis disease in T1D concerning microalbuminuria. Nevertheless, regardless of these limitations, we believe that our conclusions would remain reliable and valid. Our study also has multiple strengths, including a significant correlation of lipid profiles and lipid ratios with UAER levels, which after adjustment for age, gender, disease duration, and HbA1c, reinforces the importance of our investigation. This study also showed epidemiological evidence from a specific population-based study using nationally representative data reflecting a single ethnicity. To the best of our knowledge, this is the first study establishing the relationship between microalbuminuria and dyslipidemia in type 1 diabetic subjects with an atherogenic lipid profile in Algerian individuals.

Conclusion

In summary, our results indicate that an increase in UAER is associated with an increased risk of atherosclerosis and dyslipidemia. This shows the importance of controlling the lipid index as a method of preventing atherosclerotic cardiovascular disease.

Acknowledgements

We are beholden to the patients of the current study for their persistent and tremendous support and to our colleagues for their precious assistance.

Research funding

No funding.

Competing interests

The authors declared no conflicts of interest.

Reference

1. Papadopoulou-Marketou N, Paschou SA, Marketos N, Adamidi S, Adamidis S, Kanaka-Gantenbein C. Diabetic nephropathy in type 1 diabetes. Minerva Med 2017;109:218-28.
2. American Diabetes Association (ADA). Standard of medical care in diabetes. Diabetes Care 2017;40: S4-128.
3. Hovind P, Tarnow L, Rossing P, et al. Predictors for the development of microalbuminuria and macroalbuminuria in patients with type 1 diabetes: inception cohort study. BMJ 2004;328:1105.
4. Koroshi A. Microalbuminuria, is it so important?. Hippokratia 2007;11:105-7.
5. Bjornstad P, Pyle L, Nguyen N, et al. Achieving International Society for Pediatric and Adolescent Diabetes and American Diabetes Association clinical guidelines offers cardiorenal protection for youth with type 1 diabetes. Pediatr Diabetes 2015;16:22-30.
6. Pálsson R, Patel UD. Cardiovascular complications of diabetic kidney disease. advances in chronic kidney disease. Adv Chronic Kidney Dis 2014;21:273-80.
7. Ellis EN, Warady BA, Wood EG, et al. Renal structuralfunctional relationships in early diabetes mellitus. Pediatr Nephrol 1997;11:584–91.
8. Jensen JS, Feldt-Rasmussen B, Borch-Johnsen K, Jensen KS, Nordestgaard BG. Increased transvascular lipoprotein transport in diabetes: association with albuminuria and systolic hypertension. J Clin Endocrinol Metab 2005;90:4441-5.
9. Jha JC, Ho F, Dan C, Jandeleit-Dahm K. A causal link between oxidative stress and inflammation in cardiovascular and renal complications of diabetes. Clin Sci 2018;132:1811-36.
10. Brischetto R, Leonardi V, Amore MG, et al. Significance of microalbuminuria in atherosclerotic vascular disease. Arch Gerontol Geriatr 1996; 22:173-7.
11. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation. Geneva, 2006. Pp 9-10.
12. Flack JM., Adekola B. Blood pressure and the new ACC/AHA hypertension guidelines. Trends in cardiovascular medicine 2020;30:160-4.
13. Jenkins AJ, Lyons TJ, Zheng D, et al. Lipoproteins in the DCCT/EDIC cohort: associations with diabetic nephropathy. Kidney Int 2003;64:817–828.
14. Lithovius R, Harjutsalo V, Forsblom C, Saraheimo M, Groop PH. Antihypertensive treatment and resistant hypertension in patients with type 1 diabetes by stages of diabetic nephropathy. DiabetesCare 2014;37:709-17.
15. Saraheimo M, Forsblom C, Thorn L, et al. Serum adiponectin and progression of diabetic nephropathy in patients with type 1 diabetes. Diabetes care 2008;31:1165-9.
16. Wadén J, Forsblom C, Thorn LM, Gordin D, Saraheimo M, Groop PH. A1C variability predicts incident cardiovascular events, microalbuminuria, and overt diabetic nephropathy in patients with type 1 diabetes. Diabetes 2009;58:2649-55.
17. Galler A, Haberland H, Näke A,et al. Natural course of untreated microalbuminuria in children and adolescents with type 1 diabetes and the importance of diabetes duration and immigrant status: longitudinal analysis from the prospective nationwide German and Austrian diabetes survey DPV. Eur J Endocrinol 2012;166:493-501.
18. Gambaro G, Bax G, Fusaro M, et al. Cigarette smoking is a risk factor for nephropathy and its progression in type 2 diabetes mellitus. Diabetes NutrMetab 2001;14:337-42.
19. Odermarsky M, Andersson S, Pesonen E, Sjöblad S, Ylä-Herttuala S, Liuba P. Respiratory infection recurrence and passive smoking in early atherosclerosis in children and adolescents with type 1 diabetes. Eur J Clin Invest 2008;38:381-8.
20. Agardh CD, Agardh E, Torffvit O. The association between retinopathy, nephropathy, cardiovascular disease and long-term metabolic control in type 1 diabetes mellitus: a 5 year follow-up study of 442 adult patients in routine care. Diabetes Res Clin Pract 1997;35:113-21.
21. Baker NL, Hunt K.J, Stevens DR, et al. Association between inflammatory markers and progression to kidney dysfunction: examining different assessment windows in patients with type 1 diabetes. Diabetes Care 2018;41:128-35.

23. Das G, Taylor PN, Abusahmin H, et al. Relationship between serum thyrotropin and urine albumin excretion in euthyroid subjects with diabetes. Ann Clin Biochem 2019;56:155-62.
24. Hamri WH, Diaf M, Harir N, Hadj Habib M. Lipid ratios as a predictive marker of Subclinical Atherosclerosis inflammation among Type 1 Diabetic patients with Thyroid Dysfunction. J Drug DelivTher 2020;10:112-29.

25. Leening MJ, Ferket BS, Steyerberg EW, et al. Sex differences in lifetime risk and first manifestation of cardio-vascular disease: prospective population based cohort study. BMJ 2014;349:g5992.
26. Lin CC, Tang KT, Li CI, Liu CS, Lai MM, Lin WY. Gender Difference in the Relationship of Albuminuria and Arterial Stiffness in Chinese Adults - a 6.6-Year Follow-Up Longitudinal Study. Kidney Blood Press Res 2018;43:1479-87.
27. Nakhjavani M, Morteza A, Jenab Y, et al. Gender difference in albuminuria and ischemic heart disease in type 2 diabetes. Clin Med Res 2012;10:51–6.
28. Muntner P, Coresh J, Smith JC, Eckfeldt J, Klag MJ. Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. Kidney Int 2000;58:293–301.