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Association between Lipoprotein (a) Concentration, Glycemic Control and Diabetes Complications in Moroccan Patients with Type 2 Diabetes Mellitus

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Abstract

Objective: The objective of this prospective study was to investigate the relationship of the levels of Lp(a) in Moroccan patients with type 2 diabetes mellitus (T2DM) with other metabolic factors related to the severity of T2DM.

Material and methods: 231 T2DM patients aged over 18-years-old were analyzed. Fasting plasma glucose, lipid profile, liver and renal tests, glycated hemoglobin test (HbA1c), and Lp(a) level were measured. Sociodemographic data, clinical characteristics and anthropometric measures were reported by the patient's endocrinologists. Our results were analyzed using SPSS software.

Results: The prevalence of Lp(a) > 75 nmol.L^{-1} was 31.2% with a median of 105.3 nmol.L^{-1} (IQR 87.4-154). Compared to the group without hyper lipoprotein (a), hyper lipoprotein (a) patients were more likely to be older (median 61 years [IQR 29-83] vs. 58 years [17-85]; $P = 0.014$), obese or overweight (21% vs. 2%; $P < 0.05$), have a longer duration of diabetes (11 years (6-19.5) vs. 10 (6-15), $P = 0.053$), and have a higher prevalence of previous myocardial infarction (22.2% vs. 5%; $P < 0.001$). In contrast, there were no significant differences in sex ratio, nephropathy, retinopathy, lipid profiles, and glycemic control between the two groups ($P > 0.05$). The higher Lp(a) tertile (T3) had significantly higher BMI, Waist circumference and overall macrovascular complications $P < 0.05$. There was a weak positive correlation between Lp(a) with total cholesterol concentration ($r = 0.137$, $P = 0.037$), and LDL-c ($r = 0.17$, $P < 0.01$).

Conclusion: we suggest measuring Lp(a) in routine evaluation in T2DM patients.

Keywords

Lipoprotein (a) [Lp(a)], Diabetes Mellitus Type 2, Lipid profile, Prevalence, Atherogenic Index of Plasma (AIP), Diabetes complications

Introduction

Diabetes mellitus Type 2 (T2DM) is a multifactorial metabolic disorder characterized by chronic hyperglycemia [1,2]. For individuals with T2DM, atherosclerotic cardiovascular disease (ASCVD) is the leading causes of morbidity and mortality [3,4] and Lipoprotein (a) [Lp(a)] was recognized in the 2019 ESC/EAS guidelines as a risk enhancer [5-12]. Several studies have shown that an increased risk of T2DM has been associated with a very low Lp(a) molar concentration [13-17]. We conducted an observational prospective study of demographic and biochemical data from patients with T2DM who were admitted to Avicenne Military Hospital, Marrakech, Morocco, from July 2018 to January

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2019, the objective was to investigate the relationship of Lp(a) with other metabolic factors related to the severity of diabetes mellitus in Moroccan T2DM patients.

Materials and Methods

Patient description

From July 2018 to January 2019, a total of 231 consecutive patients with confirmed T2DM who were admitted to Avicenne Military Hospital, Marrakech, Morocco, were analyzed. Inclusion criteria were patients aged over 18-years-old with confirmed T2DM defined according to the American Diabetes Association (ADA) criteria [18]: repeated fasting plasma glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L), fasting is defined as no caloric intake for at least 8 hours or glycated hemoglobin A1c (HbA1c) ≥ 6.5%, the test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay and/or under current treatment of insulin or oral hypoglycemic medicine. Exclusion criteria include patients who refuse to participate in the study or with other types of diabetes and patients with comorbidities that could increase the amount of Lp(a), such as severe liver and/or renal failure, thyroid dysfunction and malignant disease.

Data collection

The purpose of the present study was explained to the patients, and informed consent was obtained from all participants with respect to confidentiality and anonymity. A detailed questionnaire was obtained from all patients, including sociodemographic data such as age, sex, weight, height, disease status (duration of diabetes, comorbidity), current medications, and smoking status (defined as current tobacco use). Clinical data, body mass index (BMI), waist circumference (WC), and blood pressure were reported by the patient's endocrinologists. BMI was calculated as the weight (kg)/height $(m)^2$. Obesity was defined as a BMI ≥ 30 kg/m^2 [19] and overweight as BMI ≥ 25 kg/m^2 [20]. Hypertension was defined as systolic blood pressure (BPS) ≥ 140 mmHg and/or diastolic blood pressure (BPD) ≥ 90 mmHg at least two blood pressure measurements per visit and on at least two visits [21] or subjects with antihypertensive drugs treatments. Dyslipidemia was diagnosed with fasting total cholesterol (TC) ≥ 200 mg/dL, triglyceride (TG) ≥ 150 mg/dL and/or high density lipoprotein cholesterol (HDL-c) < 40 mg/dL (for men) or 50 mg/dL (for women) and/or patients with lipids-lowering therapy consistent with the previous studies [22].

Laboratory examination

Venous blood samples from 12h fasting participants were analyzed, the conventional lipid profile including total cholesterol (TC), triglyceride (TG), and HDL-c, was evaluated by the standard enzymatic methods. LDL-c levels were calculated using Friedewald's formula, unless TG ≥ 4 mmol/L, where a direct LDL-c measurement was performed. Fasting plasma glucose (FPG) was measured by the enzymatic hexokinase method. Other parameters including serum creatinine, blood urea nitrogen, thyroid-stimulating hormone (TSH) were also evaluated by routine methods. Atherogenic Index of Plasma (AIP) was calculated by using the following formula: $\log_{10}$ (TG/HDL-c) measured in mmol/L. It has been suggested that an AIP value of under 0.11 is associated with low risk of cardiovascular disease, the values between 0.11 to 0.21 and upper than 0.21 are associated with intermediate and increased risks, respectively [23]. Lp(a) was measured using a latex turbid metric method with antibodies specific to apo(a), using a calibration of 5 levels (Cobas 6000 (Roche diagnostics). In our study, the normal reference value was less than 75 $nmol.L^{-1}$. Glycated hemoglobin A1 (HbA1c) was analyzed by using the HPLC assay with a cation exchange column (Variant II Turbo, BIORAD). The normal values of HbA1c in our laboratory ranged from 4% to 6%. All tests were measured using commercial assays on Roche Cobas 6000 automated analyzer (Roche Diagnosis, Germany) immediately after sampling. The patients enrolled were subsequently divided into two groups based on Lp(a) levels: Patients with Lp(a) lower or equal than 75 $nmol.L^{-1}$ were defined as non-hyperlipoprotein (a) group, others with Lp(a) greater than 75 $nmol.L^{-1}$ were grouped as hyper lipoprotein (a) group.

Statistical analysis

All statistical analysis was performed with SPSS version 10.0 (SPSS, Chicago, IL). Categorical variables were summarized as numbers and percentages and continuous variables were expressed as median values and interquartile range (IQR). Statistical significant differences between the groups were determined by the Mann-Whitney test for categorical variables. Continuous variables without normal distribution were conducted with non- parametric statistics Kruskal-Wallis. Correlation between Lp(a) and study parameters was done with spearman's correlation analysis. Bivariate logistic regression was performed to test the association between diabetic complications status, Lp(a) and glycemic/metabolic control status. The *P*-value < 0.05 was considered statistically significant.

Results

During the study period, 231 T2DM patients were eligible and included in our analysis, the median age was 59 years (IQR 53-64) and 134 (58%) of the patients were men with median duration of diabetes was 10 years (IQR 6-15), the male-to-female ratio was 1.38. Among 97 women, 76.2% were in menopause. Demographic data and clinical characteristics of the study subjects are presented in Table 1. The median BMI was 21.4 kg/m^2 (IQR 19.5-25.4) and 10% of the patients were obese (BMI > 30 kg/m^2). 44.2% of the patients had diabetes for more than 10 years and more than 37% of the patients had hypertension. With regard to current diabetic management, 51.5% of the patients were treated with oral hypoglycemic agents, and 17.7% of the patients had insulin-dependent T2 diabetes mellitus. The incidence proportion of atherosclerotic cardiovascular disease was 18.6% with 10.4% having coronary heart disease, 4.3% had cerebrovascular disease, and 3.9% had peripheral arterial disease. When 231 T2DM patients were separated into two groups according to Lp(a) levels, 72 (31.2%) patients were diagnosed as having high level of Lp (a) ≥ 75 $nmol.L^{-1}$, in this group median Lp(a)

Table 1: Demographic data and clinical characteristics of type 2 diabetic patients by the level of Lp(a).

Items	Lp (a) ≥ 75 nmol/L	Lp (a) < 75 nmol/L	All T2DM patients	*P* value
n (%)	72 (31.2)	159 (68.8)	231	-
Age (years)	61 (55-65)	58 (53-63)	59 (53-64)	0.014
Sex ratio (M/W)	1.76	1.23	1.38	0.141
Current smokers, n (%)	13 (18.1)	11 (6.9)	24 (10.4)	0.012
Postmenopausal status n (%)	22 (84.6)	52 (73.2)	74 (76.2)	0.186
Body mass index (kg/m²)	26.8 (22.6-31.4)	20.4 (19.2-22.7)	21.4 (19.5-25.4)	< 0.001
≤ 30 n (%)	51 (70.8)	157 (98.7)	208 (90)	
> 30 n (%)	21 (29.2)	2 (1.3)	23 (10)	< 0.001
Waist circumference (cm) Men	94 (89-101)	89 (82-93)	90 (85-98)	0.001
Waist circumference (cm) women	90 (78-98)	78 (72-84)	78 (73.5-89)	< 0.001
Diabetes duration (years)	11 (6-19.5)	10 (6-15)	10 (6-15	0.053
< 5 years n (%)	15 (20.8)	39 (24.5)	54 23.4)	0.327
6 à 10 years n (%)	20 (27.8)	55 (34.6)	75 (32.5)	
> 10 years n (%)	37 (51.4)	65 (40.9)	102 (44.2)	
Hypertension n (%)	39 (54.2)	48 (30.2)	87 (37.7)	< 0.001
Metabolic syndrome n (%)	33 (45.8)	33 (20.8)	66 (28.5)	< 0.001
Nephropathy n (%)	6 (8.3)	10 (6.3)	16 (6.9)	0.377
Retinopathy n (%)	16 (22.2)	25 (15.7)	41 (17.7)	0.156
Foot ulcer n (%)	10 (13.9)	2 (1.3)	12 (5.2)	< 0.001
Neuropathy n (%)	33 (45.8)	42 (26.4)	75 (32.5)	0.003
Previousmyocardial infarction n (%)	16 (22.2)	8 (5.0)	24 (10.4)	< 0.001
Cerebrovascular accident n (%)	8 (11.1)	2 (1.3)	10 (4.3)	0.002
Peripheral arterial disease n (%)	8 (11.1)	1 (0.6)	9 (3.9)	< 0.01
Treated with oral drugs	41 (56.9)	78 (49.05)	119 (51.5)	0.07
Treated with Insulin	7 (9.7)	34 (21.4)	41 (17.7)	0.03

Data is shown as median and IQR (interquartile range) or proportions (%).

(*N*: Number of patients tested). Lp(a): Lipoprotein (a). Significant ($P < 0.05$)

levels was 105.3 nmol.L^{-1} (IQR 87.4-154) vs. 21.3 nmol.L^{-1} (IQR 7.6-36.2) in the other group (Lp(a) levels < 75 nmol. L^{-1}). Compared to the group without hyperlipoprotein (a), hyperlipoprotein (a) patients were more likely to be older (61 years [IQR = 55-65] vs. 58 years [IQR = 53-63]; $P = 0.014$), obese or overweight (21% vs. 2%; $P < 0.05$), have a longer duration of diabetes (11 years (6-19.5) vs. 10 (6-15), $P = 0.053$), diagnosed with hypertension (54.2% vs. 30.2%; $P < 0.001$), diagnosed with dyslipidemia (55.6% vs. 30.2%; $P < 0.01$), and have a higher prevalence of previous myocardial infarction (22.2% vs. 5%; $P < 0.001$). On the contrary, there was no significant difference regarding sex ratio, nephropathy and retinopathy between the two groups ($P > 0.05$). The results of conventional lipid profile showed that hyper lipoprotein (a) group has a higher level of LDL-C and AIP compared to the patients with normal lipoprotein (a), but the difference was not significant with ((2.5 mmol/L (IQR 2-3.3) vs. ((2.3 mmol/L (IQR (1.8-3.1), $P = 0.124$) and (-0.28 (IQR -0.45-(-0.08)) vs. (-0.31 IQR (-0.4-(-0.07)), $P = 0.524$) respectively. Furthermore, there were no statistically significant differences between the groups regarding TC, HDL-C, triglycerides, FPG, and HbA1c ($P > 0.05$) as shown in Table 2. Notably, according to the glycemic control status, diabetic patients were divided into three subgroups based on HbAlc levels (< 7% (n = 91); 7-9% (n = 99); ≥ 9% (n = 41)), when we compared Lp(a) levels between each diabetic subgroup, we noticed that T2DM patients with HbA1c levels higher than 9% have the higher Lp(a) level with a median 40.3 nmol.L^{-1} (IQR 7.9-98.2) than in the 7-9% group (32.4 nmol.L^{-1} (IQR 11.8-84) or in the ≥ 9% group (36.5 nmol.L^{-1} (IQR 17.6-84.1)), but the difference between the groups did not reach statistical significance ($P = 0.812$). The characteristics of the T2DM patients by Lp(a) tertiles is summarized in Table 3. The median Lp(a) level for each tertile group was T1 (7.6 nmol.L^{-1} (IQR 3-14.6), n = 78); T2 (34.4 nmol. L^{-1} (IQR 25.3-45.8), n = 76) and T3 (102.2 nmol.L^{-1} (IQR 84.5-151.7), n = 77). There were no differences between groups regarding sex ratio, diabetes duration, diabetic nephropathy, diabetic retinopathy and insulin therapy ($P > 0.05$). The higher tertiles Lp(a) (T3) group had significantly higher BMI and waist circumference in both men and women with $P < 0.05$. Overall macrovascular complications was markedly and significantly more prevalent in higher Lp(a) tertiles (T3) patients (P < 0.05),

Table 2: Laboratory parameters of type 2 diabetic patients by the level of Lp(a).

Laboratory parameters	Lp (a) ≥ 75 nmol/L	Lp (a) <75 nmol/L	All T2DM patients	P Value
Lp(a) nmol.L^{-1}	105.3 (87.4-154)	21.3 (7.6-36.2)	34.4 (14.4-84.5)	-
FPG (mmol.L^{-1})	8.4 (6.7-9.9)	7.6 (6.2-8.9)	7.8 (6.4-9.4)	0.104
Total cholesterol (mmol.L^{-1})	4.1 (3.7-5.2)	4.1 (3.5-4.8)	4.1 (3.6-4.9)	0.136
Triglycerides (mmol.L^{-1})	1.2 (1-1.8)	1.32 (1- 1.8)	1.3 (1-1.8)	0.958
HDL-c (mmol.L^{-1})	1.09 (0.9-1.3)	1.16 (0.9-1.4)	1.1 (0.9-1.4)	0.182
LDL-c (mmol.L^{-1})	2.5 (2-3.3)	2.3 (1.8-3.1)	2.4 (1.9-3.2)	0.124
AIP	-0.28 (-0.45- (-0.08))	-0.31 (-0.4-(-0.07))	-0.4 (-0.3 -(-0.08))	0.524
HbA1c (%)	7.6 (6.8-8.7)	7.3 (6.8- 8.5)	7.4 (6.8-8.6)	0.407

Note: Data are presented as the median (interquartile range [IQR]). Significant *(P* < 0.05). FPG: Fasting Plasma Glucose; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; AIP: Atherogenic Index of Plasma; HbA1c: Glycated Hemoglobin;

Table 3: Characteristics of the T2DM patients by Lp(a) tertiles.

Items	Lipoprotein (a)			P VALUE
	Lower tertile T1	Middle tertile T2	Higher tertile T3	
Number (%)	78 (33.8)	76 (32.9)	77 (33.3)	
Lp(a) nmol/L	7.6 (3-14.6)	34.4 (25.3-45.8)	102.2 (84.5-151.7)	-
Age (years)	58 (53-63.7)	57 (51-63)	61 (55-65)	0.018
Sex ratio M/W	0.95	1.53	1.85	0.107
Diabetes duration (years)	10 (6-16.2)	9 (5-14)	10 (6-18)	0.137
BMI (kg/m^2)	20.2 (19.2-22.2)	20.5 (19.1-23)	26.7 (22.2-31)	< 0.01
WC (cm) Men	87.5 (81.7-93)	90 (85-93)	94 (88-100.2)	0.002
WC (cm) women	78 (73-87.7)	77 (72-79.2)	90 (78-98)	0.001
Hypertensionn (%)	32 (41)	14 (18.4)	41 (53.2)	< 0.01
Dyslipidemia n(%)	28 (35.9)	18 (23.7)	42 (54.5)	< 0.01
Nephropathy n(%)	6 (7.7)	3 (3.9)	7 (9.1)	0.432
Retinopathy n(%)	15 (19.2)	10 (13.2)	16 (20.8)	0.428
Foot ulcer n(%)	1 (1.3)	1 (1.3)	10 (13.0)	0.001
Diabetic Peripheral Neuropathy n(%)	25 (32.1)	17 (22.4)	33 (42.9)	0.026
Previous myocardial infarction n(%)	3 (3.8)	4 (5.3)	17 (22.1)	< 0.01
Cerebrovascular accident n(%)	2 (2.6)	0	8 (10.4)	0.004
Peripheral arterial disease n(%)	1 (1.3)	0	8 (10.4)	0.001
Insulin n(%)	17 (21.8)	15 (19.7)	9 (12.7)	0.325
FPG ((mmol.L^{-1})	7.9 (6.3-10.1)	7.6 (6.2-8.6)	8.2 (6.6-9.9)	0.174
TG (mmol.L^{-1})	1.4 (1-1.9)	1.2 (0.9-1.7)	1.3 (1-1.8)	0.243
TC (mmol.L^{-1})	4.1 (3.3-4.8)	3.9 (3.7-4.8)	4.1 (3.6-5.1)	0.498
HDL-c (mmol.L^{-1})	1.1 (0.8-1.4)	1.2 (0.9-1.4)	1.1 (0.9-1.3)	0.174
LDL-c (mmol.L^{-1})	2.2 (1.6-3.1)	2.5 (1.9-3.1)	2.5 (1.9-3.3)	0.184
AIP	-0.24 (-0.41- (-032))	-0.36 (-0.55-(-0.18)	-0.29 (-0.45-(-0.08))	0.032
HbA1c (%)	7.4 (6.8-8.7)	7.3 (6.5-8.2)	7.6 (6.8-8.6)	0.259

Note: Data are presented as the median (interquartile range [IQR]). Significant (P < 0.05).WC: Waist Circumference; BMI: Body Mass Index; FPG: Fasting Plasma Glucose; AIP: Atherogenic Index of Plasma; TC: Total Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; TG: Triglyceride; Hba1c: Glycated Hemoglobine; Lp(a): Lipoprotein(a)

with coronary heart disease prevalence within T3 to T1 was 22.1% (T3), 5.3% (T2), and 3.8% (T1).

Neuropathy and foot ulcer were also significantly increased in T3 patients with 42, 9% and 13% respectively compared to frequencies within T2 and T1: 22.4% and 1.3% (T2) vs. 32.1% and 1.3% (T1). Regarding the laboratory parameters, the TC, TG, LDL-c, HDL-c and FPG values were not significantly different between the three tertiles groups (all *P* > 0.05 respectively), only AIP values were significantly different between the three groups, T2 group had the lowest median of AIP with *P* < 0.05. The elevated Lp(a) group (T3) did not have a significantly

Table 4: Spearman correlation between different tertiles of Lp(a) with other laboratory parameters of study population.

Laboratory parameters	Lower tertile T1		Middle tertile T2		Higher tertile T3		LP (a)	
	r	*P*	r	*P*	r	*P*	r	*P*
TC	0.113	0.323	0.293	0.010	0.398	0.000	0.137	0.037
LDL-c	0.091	0.430	0.177	0.126	0.309	0.006	0.176	0.007
HDL-c	0.065	0.570	-0.051	0.662	0.005	0.963	-0.018	0.786
AIP	0.004	0.976	0.099	0.452	0.102	0.406	-0.024	0.742
TG	0.038	0.741	0.164	0.158	0.043	0.709	-0.019	0.779
FPG	0.162	0.158	0.180	0.120	0.044	0.703	0.068	0.302
HbA1c	-0.172	0.131	0.053	0.646	0.039	0.736	-0.022	0.736

R: Correlation coefficient; FPG: Fasting Plasma Glucose; AIP: Atherogenic Index of Plasma; TC: Total Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; TG: Triglyceride; Significant (P <0.05); HbA1c: Glycated Haemoglobin

Table 5: Bivariate logistic regression analysis determining the association between diabetic complications status, Lp(a) and glycemic/ metabolic control status.

Items	Macrovascular complication			Microvascular complication		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
Lp(a)	8.272	3.45-19.79	< 0.001	1.7	0.883-3.272	0.112
Age (years)	1.046	0.994-1.101	0.082	1.039	1.004-1.076	0.028
Male sex	3.220	1.256-8.258	0.015	0.971	0.520-1.812	0.925
Diabetes duration > 10 years	8.661	1.565-47.937	0.013	1.788	0.771-4.148	0.176
Insulin	0.738	0.200-2.728	0.649	0.916	0.418-2.011	0.828
Metabolic syndrome	1.491	0.601-3.702	0.389	1.832	0.923-3.637	0.083
7% > HbA1c < 9%	0.782	0.298-2.056	0.618	3.558	1.456-8.699	0.054
HbA1c > 9%	0.752	0.217-2.601	0.652	3.558	1.456-8.699	0.005

OR: Odds Ratio; CI: Confidence Interval. P < 0.05 was considered statistically significant.

HbA1c: Glycated Hemoglobin

worse glycemic control with HbA1c at 7.6 (IQR 6.8-8.6) vs. 7.4 (IQR 6.8-8.7) in T1 (*P* = 0.259). The correlation between Lp(a) levels and other laboratory parameters was tested using Spearman correlation analysis as shown in Table 4, we found a weak positive correlation with TC concentration (*r* = 0.137, *P* = 0.037) and LDL-c (*r* = 0.17, *P* < 0.01), while a no significant negative correlation was observed between Lp(a) and HbA1c (r = -0.022, *P* = 0.736), and there was no significant correlation between Lp(a) and triglycerides, HDL-c, AIP and FPG (all P > 0.05). We performed statistical analyzes to determine the association of diabetic complications, Lp(a) and glycemic/ metabolic control status. These data are provided in Table 5. The presence of macrovascular complications had a significant association with Lp(a) levels (OR: 8.272 [95% CI 3.45-19.79], *P* < 0.001), age, male sex and diabetes duration > 10 years. In contrast, there were no significant correlations between the development of microvascular complications and Lp(a) levels (OR: 1.7 [95% CI 0.883-3.272], *P* = 0.112). The presence of microvascular complications had a significant association with age and HbA1c > 7%.

Discussion

To our knowledge, for the first time, our study indicated the prevalence of Lp(a) in Moroccan patients with T2DM, and attempted to assess the association between Lp(a) levels and other cardiovascular risk factors. In the atherothrombotic range [8], Lp(a) levels of ≥ 75 nmol.L^{-1} were defined as abnormally high [24], and used to define CVD risk [12]. The prevalence of Lp(a) > 75 nmol.L^{-1} in our study was 31.2%, this *result are in accordance with* previus findings [24-27]. Heller FR, et al. [25] found a prevalence about 20% in 146 patients with Diabetes Mellitus. The control rates of HbA1c for all T2DM patients was 39.3%, this finding is consistent with previous studies in China (30%) [28], and in Europe (37.4%) [29]. T2DM patients with high level of Lp(a) were found to be older and overweight, have a higher WC in both men and women, a higher BPS level and a longer duration of the disease (*P* < 0.05). The duration of the presence of diabetes should be considered, as some data suggest that it only becomes a CVD risk equivalent when it has been present for approximately a decade [30]. WC is an accurate surrogate marker of visceral adiposity in young adults [31], previous study was confirmed this relationship between circulating levels of Lp(a) and subcutaneous abdominal adiposity [32-34]. In a cross-sectional study enrolling 272 subjects, individuals included in the highest tertile of central adiposity indicators

presented higher oxidized -LDL [33], and a strong positive relationship between oxidized phospholipids/apoB level and Lp(a) has been discovered [34].

Regarding the laboratory parameters, this study showed that patients belonging to the lower tertiles (T1) and to the upper tertiles Lp(a) (T3) did not show significant differences in all conventional lipid profile with respect to the reference category (middle tertile Lp(a)T2)) with (all $P > 0.05$), the median concentrations of LDL-c were similar between the higher Lp(a) tertile (T3) and the middle Lp(a) tertile (T2) with (2.5 mmol.L^{-1} (IQR 1.9-3.3) vs. 2.5 mmol.L^{-1} (IQR 1.9-3.1), $P > 0.05$), the some finding was reported by several sudies [35-38], Qayum, et al. [36] did not find a significant association between Lp(a) and LDL-c in a cohort of 257 children with high risk cardiovascular. In contrast, Meabe YS, et al. [37] found a positive correlation between Lp(a), LDL-c and apo B in a cohort of Spanish children, the same findings were reported by Gannagé-Yared MH, et al. [38]. In our data, only AIP was significantly lower in patient with normal Lp(a) (T2) compared to a group with very-low Lp(a) (T1) and elevated Lp(a) (T3). AIP is a simple parameter proposed as a predictive marker for plasma atherogenicity and atherosclerosis, is strongly correlated with CVD risks and inversely correlated with LDL particle size [7]. Using Spearman correlation, in the total group of patients, Lp(a) levels were weakly correlated with TC (r = 0.137) and LDL-c (r = 0.176), but not with TG (r = -0.019) and HDL-c (r = -0.018). The correlation with LDL-c has also been observed in other studies and can be attributed to the contribution of the Lp(a) cholesterol levels in the calculation of LDL-c using the Friede wald formula [39]. Although this contribution is negligible in individuals with low Lp(a) levels, it can cumulate up to 50% of laboratory-measured cholesterol in the LDL-c fraction in individuals with elevated Lp(a) [40]. However, the levels of serum concentrations of Lp(a) were not significantly related to the degree of glycemic control, Lp(a) did not show a significant correlation with HbA1c (r = -0.022) and, the medians values of serum Lp(a) were not different in patients with differents diabetics status [36.5 nmol.L^{-1} (IQR 1-352) (HbA1c < 7%) vs. 40.3 nmol.L^{-1} (IQR 7-650) (HbA1c > 9%) ($P = 0.812$)], this agrees with results of previous studies showing no association between Lp(a) and diabetic status [41]. In our study, we did not observe any statistically significant correlation between Lp(a) levels and diabetic retinopathy or diabetic nephropathy. Furthermore, the presence of microvascular complications had significant association with age and HbA1c > 7% but not with Lp(a) (OR: 1.7 [95% CI 0.883-3.272], $P = 0.112$). As expected, overall macrovascular complications was significantly more frequent in patients with Lp(a) > 75 nmol.L^{-1}, the group with higher tertils (T3) had a 6-fold increased frequency for previous myocardial infarction suggesting enhanced vulnerability of large vessels at modestly high Lp(a) levels in diabetes. We also found a positive association between Lp(a) and the developement of macrovascular complications (OR: 8.272 [95% CI 3.45-19.79], $P < 0.001$). Several retrospective case-control and prospective studies have evaluated the association of elevated levels of Lp(a) with the risk of CVD [42-44]. In an analysis of European individuals with diabetes from the Biomarkers for Cardiovascular Risk Assessment in Europe (Biomar CaRE) consortium, Lp(a)-associated risk for major coronary events was higher in individuals with diabetes HR = 1.31, (95% CI 1.15-1.50) compared with individuals without diabetes HR = 1.15, (95% CI 1.08-1.21) [43]. Lp(a) contributes to CVD risk through multiple mechanisms, it quantitatively carries all the atherogenic risk of LDL particles, including their propensity to oxidize after entry into the vessel wall, creating highly immunogenic and pro-inflammatory oxidized LDL [8]. However, on an equimolar basis, Lp(a) is more atherogenic than LDL because, by definition, it not only contains all the proatherogenic components of LDL, but also of apo(a). Apo(a) potentiates atherothrombosis through additional mechanisms, including inflammation through its content of oxidized phospholipids, the presence of lysine binding sites that allow accumulation in the arterial wall, and potential antifibrinolytic effects by inhibiting plasminogen activation [45]. Furthermore, hyperglycemia plays a critical role in the pathogenesis of microvascular complications, while atherosclerosis contributes to the pathogenesis of macrovascular complications [24]. Nevertheless, the current study had several limitations, firstly, this is a study among moderate sample size diabetic Morrocan patients, secondly, we measured serum levels of Lp(a) only once and finally, our study was carried involves one single institution and included patients referred to a tertiary center which its patients had more severe complications, hinting at a possible selection bias.

Conclusion

The prevalence of high Lp(a) in our T2DM patients was 31.2%. Lp(a) levels were positively related to BMI, WC and macrovascular complications. In the future, we suggest measuring Lp(a) in the routine evaluation in T2DM patients.

Author Contributions

Siham Aboulmakarim: Statistical analysis, interpretation of data, methodology, article drafting and revising; Latifa Adarmouch: Statistical analysis and interpretation of data; Soumia Hmidouche: Acquisition of data; Hicham Baizri: study conception and design; Abderrahmane Boukhira: Study conception and design, supervision, article revising; Saliha Chellak: Study conception and design, methodology, supervision, article revising. All authors approved the final version of the article.

Statements and Declarations

Acknowledgments

Not applicable.

Declarations of interest

None.

Ethics

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

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