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Association of Lipid Ratios and Neutrophil-lymphocyte Ratio in Type 2 Diabetic Moroccan Patients Without Chronic Kidney Disease

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Abstract: Background: Atherogenic dyslipidemia and currently chronic inflammation are among the factors of atherosclerosis in type 2 diabetes mellitus patients (T2DM). This retrospective study conducted at Mohammed VI University Hospital, Morocco, from January 2020 to June 2021, aimed to investigate the association between the lipid profile, lipid ratios and neutrophil to lymphocyte ratio (NLR), among T2DM Moroccan patients without chronic kidney disease and to find out the possible correlation between these parameters and glycated hemoglobin (HbA1c). Methods: 274 T2DM patients and 88 non-diabetic controls aged over 40 years old were analyzed. Fasting plasma glucose, lipid profile tests, liver and renal function tests, and HbA1c test were measured. The NLR and lipid ratios including total cholesterol / HDL-c, non- HDL-c and atherogenic index of plasma were calculated. Results: There was no significant difference in median level of all lipid profile parameters between the poor controlled T2DM group (HbA1c > 7%) compared to the well controlled group (HbA1c ≤ 7%) and control group (all $P > 0.05$). All lipid ratios were lower in the good controlled group compared to the poor controlled diabetes group, but the difference did not reach statistical significance (all $P > 0.05$). HbA1c was correlated with FPG, and neutrophils (r = 0.655, r = 0.263, $P < 0.001$ respectively). NLR was weekly correlated with HDL (r = -0.14, $P = 0.01$). By using multivariate logistic regression, FPG was the only factor significantly predictive of well diabetic control. Conclusion: This study did not show significant association between HbA1c, lipid ratios and NLR.

Keywords: Diabetes Mellitus Type 2, Lipid Ratios, Neutrophil-to-lymphocyte ratio, Glycated Hemoglobin, Morocco

1. Introduction

Diabetes mellitus Type 2 (T2DM) is characterized by chronic hyperglycemia due to a progressive loss of adequate β-cell insulin secretion frequently on the background of insulin resistance [1, 2] and is usually associated with lipoprotein disorders [3]. Atherogenic dyslipidemia is one of the major risk factors for cardiovascular disease (CVD) in DM patients [4], the United Kingdom Prospective Diabetes Study [5] showed that low density lipoprotein cholesterol (LDL-c) was the main lipid predictor of coronary disease and the American Diabetes Association [2] have recommended that in lipid-lowering therapy, the main priority is to decrease LDL-c. The use of lipid ratios such as the total cholesterol/ high-density-lipoprotein cholesterol ratio (TC/HDL-c), the total cholesterol minus HDL-c (non-HDL) and Atherogenic Index of Plasma (AIP) is rarely applied. These indexes were

strong indicators of the CVD risk by its expressions of imbalance between atherogenic and antiatherogenic lipoproteins [6]. AIP is a parameter proposed by Dobiasova and Froehlich [6] as a predictive marker for plasma atherogenicity and is strongly correlated with CVD risks [7, 8]. Furthermore, atherosclerosis is a systemic, lipid-driven immune-inflammatory disease, several studies have suggested that chronic subclinical inflammation has also been linked to risk factors such as hyperlipidemia and endothelial dysfunction [9], the ratio of neutrophil count to lymphocyte count (NLR) has received attention due to its role as an independent prognostic factor for coronary artery disease [10], it can be easily calculated from differential white blood cell count (WBC). In the present retrospective study, the objective was to investigate the association between the lipid profile, the lipid ratios and the NLR, among T2DM Moroccan patients without chronic kidney disease and to find out the possible correlation between these parameters and HbA1c as an indicator of glycemic control.

2. Materials and Methods

The present retrospective study was conducted from January 2020 to June 2021, a total of 274 consecutive patients with T2DM who routinely perform glycemic control in the biochemistry laboratory of Mohammed VI University Hospital, Marrakech, Morocco were analyzed, the patients' medical records were reviewed to extract the demographic and clinical data. Inclusion criteria were patients aged over 40 years old with confirmed T2DM defined according to the American Diabetes Association criteria [11]: repeated fasting plasma glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L), or glycated hemoglobin A1c (HbA1c) ≥ 6.5%. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay [7]. Exclusion criteria included patients with chronic kidney disease (Diabetes chronic kidney disease has been definitively linked to chronic inflammation), clinical evidence of active infection (WBC over $10*10^9$/l), hematologic disease, systemic inflammatory conditions, and liver disease. In the same period, 88 non -diabetic control subjects aged over 40 years with the same exclusion criteria were enrolled from subjects that applied to our laboratory for a routine check-up.

Laboratory examination: venous blood samples from 12 h fasting participants were analyzed for fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG), HDL-c, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen and creatinine serum. All tests were measured using commercial assays on a Roche Cobas 6000 automated analyzer (Roche Diagnosis, Germany) immediately after sampling. LDL-c was calculated using the Friedewald formula: LDL-c: TC - HDL-c - (TG/5) in mg/dL or when high TG values (>340 mg/dL), the formula cannot be used and was measured directly using enzymatic techniques [12]. Plasma non-HDL-c is a measure of TC carried by all atherogenic ApoB-containing lipoproteins, including TG-rich particles in VLDL and their remnants [13] and was calculated as TC - HDL-c. AIP was calculated 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 CVD, the values between 0.11 to 0.21 and upper than 0.21 are associated with intermediate and increased risks, respectively [14]. The TC/ HDL-c ratio was calculated by dividing TC by HDL-c, measured in mmol/L. Dyslipidemia was diagnosed with TC ≥200 mg/dL, TG ≥150 mg/dL and/or HDL-c <40 mg/dL (for men) or 50 mg/dL (for women) [15]. A complete blood count, including WBC count, neutrophil count, lymphocyte count, hemoglobin, hematocrit and platelet count were analyzed in the hematology unit using an automated blood cell counter Sysmex XE-5000MC. The NLR was calculated by dividing the neutrophil count by the lymphocyte count. Hb A1c was analyzed using the HPLC assay with a cation exchange column (Tosoh Automated Glycohemoglobin Analyzer), the normal values of Hb A1c in our laboratory ranged from 4% to 6%. The patients enrolled were subsequently divided into two groups based on HbA1c levels: patients with HbA1c lower than or equal to 7% were defined as well controlled T2DM, others with HbA1c greater than 7 were grouped into poorly controlled T2DM group.

Statistical analysis: All statistical analysis was performed with SPSS version 10.0 (SPSS, Chicago, IL). The Kolmogorov-Smirnov test was used for each parameter to assess whether a data set was normally distributed. Categorical variables were summarized as numbers and percentages, and continuous variables were expressed as median values and interquartile range (IQR). Statistically significant differences between groups were determined by the chi-square test for categorical variables. Continuous variables without normal distribution were performed with non parametric statistics (Kruskal–Wallis). The correlation between HbA1c and the study parameters was done with Pearson's correlation analysis. Univariate logistic regression and multivariate analysis were performed to test the independent impact of HbA1c on the dependent variables. The P value <0.05 was considered statistically significant.

3. Results

The study groups include 274 T2DM patients without chronic kidney disease (188 women (68.6%) and 86 men (31.3%) and 88 non-diabetic controls (38 women (43.1%) and 50 men (56.8%), the median age of the T2DM patients was 62 years (IQR 55-67) aged 40 to 93 years, including 177 (64.5%) non elderly (<65 years) and 97 (35.4%) elderly (≥65 years), similarly, of the 88 controls subjects, the median age was 56 years (IQR 46-65) aged 40 to 79 years, including 62 (70.4%) non elderly (<65 years) and 26 (29.5%) elderly (≥65

years). Demographic data and biochemical variables of the study subjects are shown in Table 1. Among 274 patients, the HbA1c of 112 (40.8%) T2DM patients was below or equal to 7% with median HbA1c levels of 6.2% (IQR 5.9– 6.7) and 162 (59.1%) patients had poor controlled diabetes with median HbA1c levels of 8.4% (IQR 7.6-9.5) ($P < 0.001$). The most commonly observed lipid abnormalities in the study were hypertriglyceridemia (30.6%), hypercholesterolemia (23.3%) and low HDL cholesterolemia (21.1%) for T2DM patients. Hyper LDL cholesterolemia (40%) followed by hypercholesterolemia (36%) and low HDL cholesterolemia (34.7%) were reported in control subjects. The results of conventional lipid profile showed for the TG, the poor controlled T2DM group has a higher level compared to the participants in well controlled T2DM and control groups, but the difference was not significant with (1.25 g/L (IQR 1.01-1.64) vs (1.09 g/L (IQR (0.78-1.67) vs (1.04 g/L (IQR (0.91-1.4)), P=0.99) respectively. Abnormality of other conventional lipid markers was not significantly different among the groups as shown in Table 1. However, the lipid ratios between atherogenic lipoproteins and HDL-c (AIP, and TC/ HDL-c ratio) were lower in the group with good controlled diabetes as compared to the poor controlled group, but the difference did not reach statistical significance (P>0.05). When 274 T2DM patients were separated into three groups according to AIP ratio, 166 (60.5%) had low risk of atherosclerosis (AIP < 0.11), 52 (18.9%) had intermediate risk (AIP=0.11-0.21) and 56 (20.4%) had increased risk (AIP > 0.21), from the demographic characteristics of the subjects there were no significant differences in the age and gender between groups with different AIP ratio (P>0.05). FPG was higher in the group with intermediate risk of atherosclerosis compared with other groups (P=0.07). Except for TG and HDL-c (P<0.01) as expected, there were no significant differences between the groups with a different AIP ratio regarding TC (P=0.75), LDL-c (P=0.87) and non- HDL-c (P=0.51), the details of the finding are presented in Table 2. The correlation of AIP with other variables in T2DM patients are shown in Table 3. The result shows a significant positive correlation between AIP and TC, TG, LDL-c, non -HDL and TC/HDL (all P<0.001), and a negative correlation with HDL-c (r=-0.64; P<0.001). On the contrary, no significant correlation was observed with FPG (P=0.93), HbA1c (P=0.18) and NLR (P=0.10). In the inflammation profile, the median NLR of the T2DM group was elevated in poor controlled T2DM patients compared to well controlled T2DM, but the difference was not significant (1.70 (IQR 1.22-2.35) vs 1.49 (IQR 1.15-2.1)) (P=0.8). Similarly, the neutrophil count was higher in T2DM group with poor controlled diabetes than in the patients with good controlled diabetes (P=0.75) (Table 1). According to their AIP as shown in Table 2, the NLR of the increased risk group among T2DM patients was higher than those with intermediate and low risks with (1.69 (IQR 1.14-2.35) vs 1.62 (IQR 1.33-2.04) vs 1.66 (IQR 1.14-2.24) P=0.93), respectively. A Pearson's correlation test revealed that NLR was weekly positive correlated with age (r=0.13, P=0.03) and negative correlated with HDL (r=- 0.14, P=0.01). However, NLR was not associated with other parameters (Table 3). In this study, HbA1c was used as an indicator of glycemic control, Pearson correlation analysis showed that there is a significant positive correlation with FPG (r=0.655, P< 0.001) and neutrophils (r=0.263, P < 0.001), but not with AIP, TC, TG, non- HDL-c and TC/ HDL ratio (all P >0.05) as shown in Table 3.

Table 1. *Demographic data and biochemical variables of the study subjects.*

Variables	All T2DM Patients	T2DM Patients with HbA1C ≤7	T2DM Patients with HbA1C > 7	Non-diabetic controls	P value
n (%)	274	112 (40.8)	162 (59.1)	88	-
Age (years) *	62 (55-67)	60 (54-68)	62 (56.7-66.2)	56 (46 -65)	0.002
Sex ratio (M/W) *	0.45	0.52	0.42	1.31	< 0.001
Hypercholesterolemian (%)*	64 (23.3)	29 (26.1)	35 (21.8)	26 (36)	0.05
Hypertriglyceridemian (%)*	84 (30.6)	31 (27.9)	53 (33.1)	20 (27.7)	0.5
Hyper LDL cholesterolemia n (%)*	15 (5.4)	8 (7.2)	7 (4.3)	35 (40)	0.1
Low HDL cholesterolemia n (%)*	58 (21.1)	24 (21.6)	34 (21.2)	25 (34.7)	0.05
FPG g/L*	1.2 (1.08-1.7)	1.1 (0.9-1.2)	1.5 (1.2-2)	0.9 (0.8-0.99)	0.02
HbA1c (%) **	7.4 (6.4 -8.7)	6.2 (5.9– 6.7)	8.4 (7.6-9.5)	5.4 (5.2 -5.9)	< 0.001
Neutrophils** (10^9/L)	3.7 (2.8-5.2)	3.4 (2.6 - 4.5)	4.1 (3.1-5.5)	4.3 (2.9- 4.9)	0.75
Lymphocytes** (10^9/L)	2.3 (1.8-2.8)	2.2 (1.7- 2.7)	2.4 (1.9-2.9)	2.02 (1.6-2.3)	0.51
NLR**	1.66 (1.16- 2.27)	1.49 (1.15-2.1)	1.70 (1.22-2.35)	2.04 (1.42 -2.55)	0.80
Total cholesterol (g/L) **	1.77 (1.52-1.9)	1.75 (1.50- 2)	1.80 (1.56 -1.96)	1.65 (1.47-1.8)	0.99
Triglycerides (g/L) **	1.21 (0.89-1.64)	1.09 (0.78-1.67)	1.25 (1.01-1.64)	1.04 (0.91-1.4)	0.99
HDL-c (g/L) **	0.49 (0.41-0.58)	0.51 (0.41-0.62)	0.47 (0.41-0.55)	0.45 (0.38-0.51)	0.69
LDL-c (g/L) **	0.98 (0.79-1.2)	0.97 (0.82-1.21)	0.99 (0.78-1.2)	1.05 (0.71 - 1.31)	0.94
AIP**	0.04 (-0.14 -0.18)	-0.02 (-0.19- 0.16)	0.06 (-0.05-0.19)	0.04 (-0.06- 0.19)	0.93
Non- HDL**	1.25 (1.02-1.46)	1.23 (1.01-1.44)	1.27 (1.04 -1.46)	1.35 (1.09 -1.61)	0.75
TC/HDL-c**	3.5 (2.9 – 4.2)	8.7 (7.2 – 10.7)	9.36 (7.8 - 11)	10.2 (8.4-11.8)	0.48

Data are presented as the median (interquartile range [IQR]). *Chi-square test. **Kruskal–Wallis. 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; NLR: Neutrophil–Lymphocyte ratio.

Table 2. *Demographic data and biochemical variables of the T2DM patients according to AIP risk of atherosclerosis groups.*

Variables	Low Risk (AIP < 0.11)	Intermediate Risk (AIP=0.11-0.21)	Increased Risk (AIP > 0.21)	P value
n (%)	166 (60.5)	52 (18.9)	56 (20.4)	
Age (years) *	62 (56- 67)	59.5 (53.7- 66.2)	61 (55 – 67)	0.64
Sex ratio (M/W) *	0.39	0.5	0.64	0.29
FPG (g/L) **	1.26 (1-1.6)	1.53 (1-1.2)	1.28 (1.1-1.4)	0.07
Neutrophils** (10^9/L)	3.6 (2.8- 5.2)	3.90 (3.15-5.24)	3.82 (2.89 -5.24)	0.44
Lymphocytes** (109/L)	2.28 (1.79 -2.83)	2.55 (2.03- 3.2)	2.44 (2.02-2.75)	0.42
NLR**	1.66 (1.14-2.24)	1.62 (1.33-2.04)	1.69 (1.14-2.35)	0.93
HbA1c (NGSP %) **	7.2 (6.4-8.40)	7.95 (6.7-9.3)	7.67 (6.47-9.1)	0.13
Total Cholesterol (g/L) **	1.74 (1.53-1.96)	1.78 (1.44-2.03)	1.76 (1.61-2)	0.75
Triglyceride (g/L) **	0.96 (0.74-1.19)	1.50 (1.27-1.71)	2.05 (1.72-2.53)	0.002
HDL-c (g/L) **	0.55 (0.46-0.64)	0.455 (0.39-0.52)	0.4 (0.34-0.43)	0.01
LDL-Cc (g/L) **	0.99 (0.78-1.18	0.99 (0.79 - 1.27)	0.97 (0.81-1.25)	0.87
Non- HDL (g/L) **	1.18 (0.96-1.36)	1.27 (1.06- 1.55)	1.38 (1.21-1.6)	0.51

Data are presented as the median (interquartile range [IQR]). (*n*: Number of patients tested)
*Chi-square test. **Kruskal–Wallis. Significant (P<0.05). FPG: Fasting Plasma Glucose; HDL-c: High Density Lipoprotein Cholesterol; LDL-c: Low Density Lipoprotein Cholesterol; NLR: Neutrophil–Lymphocyte ratio.

Table 3. *Pearson's correlation between lipid ratios, NLR and HbA1c in T2DM patients.*

Variables	HbA1c		AIP		NLR		TC/HDL Ratio		Non-HDL	
	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*
Age	-0.01	0.85	0.005	0.94	0.13	0.03	-0.67	0.26	-0.61	0.315
FPG	0.655	<0.001	0.009	0.935	- 0.013	0.84	0.009	0.9	0.052	0.444
HbA1c	1	-	0.091	0.181	0.079	0.247	-0.074	0.22	0.005	0.932
AIP	0.091	0.181	1	-	0.09	0.10	0.424	<0.001	0.49	<0.001
NLR	0.079	0.247	0.09	0.10	1	-	0.037	0.54	0.053	0.382
Neutrophils	0.263	<0.001	0.121	0.265	0.63	<0.001	0.36	0.55	0.075	0.217
Lymphocytes	0.146	0.031	0.081	0.459	-0.43	<0.001	-0.029	0.62	0.011	0.860
TC	-0.079	0.245	0.5	<0.001	0.01	0.85	0.84	<0.001	0.9	<0.001
TG	0.074	0.277	0.885	<0.001	0.00	0.99	0.37	<0.001	0.489	<0.001
LDL-c	-0.089	0.191	0.505	<0.001	0.04	0.51	0.879	<0.001	0.923	<0.001
HDL-c	- 0.031	0.649	-0.644	<0.001	-0.14	0.01	-0.251	<0.001	-0.28	<0.001
Non HDL	-0.072	0.288	0.49	<0.001	0.05	0.38	0.85	<0.001	1	-
TC/HDL-c ratio	-0.074	0.221	0.42	<0.001	0.03	0.54	1	-	0.85	<0.001

r: correlation coefficient; Significant (P <0.05); FPG: Fasting plasma Glucose; HbA1c: glycated hemoglobin; AIP: atherogenic index of plasma; NLR: Neutrophil–Lymphocyte ratio; TC: total cholesterol; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol; TG: triglyceride.

In T2DM patients, univariate logistic regression analysis were performed as shown in Table 4, we can see that FPG, neutrophil count and TC/ HDL-c ratio were predictors for determining well diabetic control with (B=1.704 [95% CI (1.642- 5.585)], *P*<0.001), (B=0,239 [95% CI (0,077- 0,400)], *P*=0.004) and (B=-0.172 [95% CI (-0.335 -0.009)], *P*=0.039) respectively. Multivariate logistic regression analysis was performed where the HbA1c was used as the dependent variable, while FPG, NLR, lymphocyte counts, TG, TC, HDL-c, LDL-c, TC/HDL-c, AIP, non- HDL-c and neutrophil counts were used as independent variables. The result revealed that FPG was the only factor significantly predictive of well diabetic control (OR=1.637 [95% CI (1.61- 2.68)] and *P*<0.001).

Table 4. *Univariate and multivariate logistic regression analysis of predictors for determining well diabetic control.*

Parameters	Univariate Logistic Regression Analysis			Multivariate Logistic Regression Analysis		
	B	95% C.I Lower- Upper	*P* value	OR	95% C.I Lower- Upper	*P* value
FPG	1.704	1.642- 5.585	<0.001	1.637	1.61 - 2.68	<0.001
Neutrophils	0.239	0.077 - 0.400	0.004	0.25	-0.20 - 0.70	0.296
Lymphocytes	0.035	0.011 - 0.382	0.842	0.03	-0.89 - 0.83	0.396
NLR	-0.125	-0.339- 0.089	0.250	0.39	-0.30 - 1.09	0.592
TG	0.223	-1.024 - 1.469	0.725	1.98	-1.53 - 2.51	0.857
HDL-c	-0.225	-3.185- 2.735	0.881	1.850	-1.447- 1.59	0.216
LDL-c	0.961	-0.691- 2.613	0.253	2.218	1.45-2.54	0.356
TC/HDL ratio	-0.172	-0.335 -0.009	0.039	-0.072	-0.035-0.24	0.320
AIP	0.682	-2.714 - 4.079	0.693	1.630	-9.15 - 5.92	0.309
Non-HDL-c	-0.571	-2.192 - 1.050	0.488	-2.250	- 2.350- 1.13	0.352

B: coefficient for the constant; CI: confidence interval; OR: odds ratio; significant (*P* < 0.05); FPG: Fasting Plasma Glucose; HDL-c: High Density Lipoprotein Cholesterol; LDL-c: Low Density Lipoprotein Cholesterol; NLR: Neutrophil–Lymphocyte ratio; AIP: Atherogenic Index of Plasma; TC: Total Cholesterol.

4. Discussion

The present study was carried out to explore the lipid-driven inflammatory state in 274 T2DM patients without chronic kidney disease through the correlation between HbA1c, NLR, and lipid ratios in well and poorly controlled diabetes. In our results, gender was statistically different in the study groups (P<0.001), the number of enrolled females was higher than that of males (68.6% vs. 31.3%), this may be due to regularly follow-up of women with their doctor visits more carefully than men. We have a high control rate of HbA1c in T2DM patients (40.8%); this finding is consistant with previous studies in China (30%) [16] and in Europe (37.4%) [17]. This study showed a no significant increase in TC, and TG in diabetic patients compared to the control group (P>0.05) and there was a similar median concentration of LDL-c in both groups, similar finding was reported by Jan SS et al [18] and by Moon J et al. [19] who showed that there is no statistically significant difference in serum TC and LDL-c concentration in diabetic patients compared to control groups, in contrast to our results, Khan AH et al. [20], investigating differences in lipid profile in 2,220 T2DM patients showed lipid profile parameters for TC, TG, HDL-c, and LDL-c, which is higher in patients with poor compared to good glycemic control (P<0.05). Whilst absolute LDL-c values in diabetes are often quantitatively similar to those without diabetes, the LDL particles themselves are qualitatively different and more likely to be glycated [21], this is due to the fact that hyperinsulinemia is associated with increased hepatic production of highly atherogenic VLDL with longer half-lives resulting in smaller more dense LDL particles and dysfunctional HDL [21-23]. Hypertriglyceridemiae was the major lipid parameter disorder in this study in both groups with good and poor controlled diabetes [27.9% vs 33.1%), this finding is consistent with previous studies in Ethiopia (63.5%) [24] and Sudan (48.8%) [25]. In the literature, abnormal lipid metabolism in diabetic patients is often manifested by elevated TG, and reduced HDL levels [26, 27], therefore, these abnormalities are not always revealed by conventional lipid measures, as LDL-c levels may remain within the normal range [28, 29]. It may be better revealed by the lipid ratios; our data revealed high median levels of AIP (0.06 vs -0.02), non-HDL-c (1.27 g/L vs 1.23) and TC/ HDL-c (9.36 vs 8.7) in the poor controlled group compared to the controlled diabetes groups, but the difference was not statistically significant (P>0.05). Furthermore, the outcome indicated that the majority of the T2DM patients fell into the low risk AIP group (60.5% with AIP < 0.11), AIP was positively higher correlated with TG (r=0.885, P <0.001) and negatively correlated with HDL-c (r=-0.644, P<0.001). Therefore, in this study, we did not find a correlation between AIP and HbA1c (r=-0.091, P=0.18), in contradiction to previous studies that reported a positive association between AIP and T2DM. Zhu XW et al. [27] reported during a meta-analysis containing 1727 cases and 2283 controls that subjects with T2DM had significantly higher AIP values, compared to subjects without T2DM. Previous studies suggested that AIP was negatively correlated with insulin sensitivity in diabetic patients [30]. Therefore, the use of the AIP in diabetic patients can not only describe the comprehensive situation of blood lipids, but also reflect the degree of insulin resistance [31]. Regarding the TC/HDL-c ratio and non-HDL cholesterol, we don't found a correlation between these ratios and HbA1c. On the contrary, a strong correlation was observed between LDL-c and the TC/HDL ratio (r=0.879, P<0.001) and between LDL-c and non HDL-c (r=0.923, P<0.001). In the other hand, non–HDL-c is the combination of LDL-c and VLDL, and is more atherogenic than either lipoprotein alone [3, 32], in the Strong Heart Study [33], the predictive value of non-HDL-c for clinical endpoints in a diabetic population was demonstrated. Furthermore, substantial evidence indicates that glycated hemoglobin predicts cardiovascular risk in people with diabetes [34], in the present data, HbA1c was positively and significantly correlated with FPG (r=0.655, P < 0.001), and neutrophils (r=0.263, P < 0.001), but not with other parameters of lipid parameters. In literature, the results of studies are quite inconsistent, Mullugeta Y et al. [35] reported that HbA1c was positively associated with TC while not with LDL-c; the same finding was reported by Wang S et al [23], however, some studies showed a positive correlation between HbA1c, LDL and TC [36]. The level of HbA1c is a relevant indicator of long-term glycemic control and therefore indicative of the severity of diabetes [37], in the Women's Health Study cohort [38], the authors reported that diabetes, but not HbA1c, significantly predicted significantly increased risk of cardiovascular events.

On the other hand, this current study demonstrated a higher NLR in the patients with poor controlled diabetes than in those with good controlled diabetes, but the difference wasn't statistically significant. NLR was weekly correlated with age (r=0.13, P=0.03) and negatively correlated with HDL-c (r=-0.14, P=0.01) which has anti-inflammatory activity, but no correlation was detected between NLR and HbA1c levels (r=0.079, P=0.24). Diabetes is associated with a pro-inflammatory state, mediated in part by increased expression of cell adhesion molecules and inflammatory cytokines [21, 39-43]. Unlike our results, Satilmis Bilgin [10] reported in a retrospective study that the HbA1c level was significantly and positively correlated with NLR (r=0.47, P < 0.001).

On the contrary, HbA1c was positively and significantly correlated with neutrophils (r=0.263, P < 0.001), the abnormal activation of blood neutrophils has been reported in diabetic patients [44]. Neutrophils influx is usually the results of an acute response to injury or inflammation. The interaction between neutrophils and endothelial tissue has been hypothesized to cause increased damage to the endothelium [45]. Neutrophil secreting proteolytic enzymes, arachidonic acid derivatives, and superoxide radicals can damage the local microenvironment and lead to tissue injury [46, 47].

This study has some limitations. First, it was carried involves one single institution and included patients referred to a tertiary center and cannot be generalized for general population. Second, we did not assess changes in other inflammatory markers in this study. Lastly, the absence of data regarding type of treatment, and disease status (duration of diabetes, comorbidity), can be a bias that could affect glycemic control in T2DM patients.

5. Conclusion

The present study did not show significant association between HbA1c, lipid ratios and NLR. Lipid profiles (TC, TG, HDL-c, LDL-c) and lipid ratios (AIP, Non- HDL-c, TC/HDL-c) did'nt show probable markers that can be used in predicting glycemic control in patients with T2DM without chronic kidney disease. In contrast, we have a positive significant correlation between NLR and age and a negative significant correlation between NLR and HDL-c.

References

[1] Zimmet PZ. Diabetes and its drivers: the largest epidemic in human history? Clin Diabetes Endocrinol. 2017. 18; 3: 1.

[2] American Diabetes Association. Standards of medical in diabetes- 2021. Diabetes Care 2021 Jan; 44 (Supplement 1): S125-S150.

[3] 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020; 41: 111-188.

[4] Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low- density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017; 38: 2459-2472.

[5] Turner RC, Millns H, Neil HAW, Stratton IM, Manley SE, Matthews DR et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom prospective diabetes study (UKPDS 23). Br Med J. 1998; 316: 823–828.

[6] Dobiásová M, Frohlich J. The new atherogenic plasma index reflects the triglyceride and HDL-cholesterol ratio, lipoprotein particle size and the cholesterol esterification rate: changes during lipanor therapy. Vnitr Lek. 2000. Mar; 46 (3): 152-6.

[7] Dobiásová M, Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER (HDL)). Clin Biochem. 2001. Oct; 34 (7): 583-8.

[8] Dobiásová M, Urbanová Z, Samánek M. Relations between particle size of HDL and LDL lipoproteins and cholesterol esterification rate. Physiol Res. 2005; 54 (2): 159-65.

[9] Balta S, Celik T, Mikhailidis DP, Ozturk C, Demirkol S, Aparci M, et al. The Relation Between Atherosclerosis and the Neutrophil-Lymphocyte Ratio. Clin Appl Thromb Hemost. 2016 Jul; 22 (5): 405-11.

[10] Bilgin S, Aktas G, Zahid Kocak M, Atak BM, Kurtkulagi O, Duman TT et al. Association between novel inflammatory markers derived from hemogram indices and metabolic parameters in type 2 diabetic men. Aging Male. 2020 Dec; 23 (5): 923-927.

[11] American Diabetes A. Standards of medical care in diabetese 2010. Diabetes Care. 2010; 33 (Suppl. 1): S11e61.

[12] Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 Guideline on the Management of Blood Cholesterol. J Am Coll Cardiol. 2019; 73 (24): e285-350.

[13] Chapman MJ, Ginsberg HN, Amarenco P, Andreotti F, Bore´n J, Catapano AL et al. European Atherosclerosis Society Consensus Panel. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for managment. Eur Heart J. 2011; 32: 1345-1361.

[14] Dobiásová M, Frohlich J, Sedová M, Cheung MC, Brown BG. Cholesterol esterification and atherogenic index of plasma correlate with lipoprotein size and findings on coronary angiography. J Lipid Res. 2011. Mar; 52 (3): 566-71.

[15] Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. J Am Coll Cardiol. 2014; 63: 2889–2934.

[16] Cao YY, Tang X, Sun KX, Liu ZK, Xiang X, Juan J, et al. [Relationship between glycemic control and visceral adiposity index among the patients with type 2 diabetes mellitus]. Beijing Da Xue Xue Bao Yi Xue Ban. 2017 Jun 18; 49 (3): 446-450.

[17] de Pablos-Velasco P, Parhofer KG, Bradley C, Eschwège E, Gönder-Frederick L, Maheux P, el al. Current level of glycaemic control and its associated factors in patients with type 2 diabetes across Europe: data from the PANORAMA study. Clin Endocrinol (Oxf). 2014 Jan; 80 (1): 47-56.

[18] Jan SS, Rehman A, Ahmad R, Khan TM, Ahmad A, Abrar A. Evaluation of pattern of dyslipidemia in type 2 diabetics in swat. Gomal J Medic Sciences. 2011; 9 (2): 243–247.

[19] Moon J, Lee CJ, Lee S-H, Kang S-M, Choi D, Yoo T-H, et al. The Impact of Diabetes Mellitus on Vascular Biomarkers in Patients with End-Stage Renal Disease. Yonsei Med J. 2017; 58 (1): 75-81.

[20] Khan AH. Clinical significance of HBA1c as marker of circulating lipids in male and female type 2 diabetic patients. Acta Diabetol. 2007 Dec; 44 (4): 193-200.

[21] Gonna H, Ray KK. The importance of dyslipidaemia in the pathogenesis of cardiovascular disease in people with diabetes. Diabetes Obes Metab. 2019 Apr; 21 Suppl 1: 6-16.

[22] Avramoglu RK, Basciano H, Adeli K. Lipid and lipoprotein dysregulation in insulin resistant states. Clin Chim Acta. 2006 Jun; 368 (1-2): 1-19.

[23] Wang S, Ji X, Zhang Z, Xue F. Relationship between Lipid Profiles and Glycemic Control Among Patients with Type 2 Diabetes in Qingdao, China. Int J Environ Res Public Health. août 2020; 17 (15): 5317.

[24] Biadgo B, Abebe SM, Baynes HW, Yesuf M, Alemu A, Abebe M. Correlation between Serum Lipid Profile with Anthropometric and Clinical Variables in Patients with Type 2 Diabetes Mellitus. Ethiop J Health Sci. 2017; 27 (3): 215-26.

[25] Elnasri HA, Ahmed A M. Patterns of lipid changes among type 2 diabetes patients in Sudan. EMHJ - Eastern Mediterranean Health Journal. 2008; 14 (2) : 314-324.

[26] Kumar A, Singh V. Atherogenic dyslipidemia and diabetes mellitus: what's new in the management arena? Vasc Health Risk Manag. 2010; 6: 665–9.

[27] Zhu X-W, Deng F-Y, Lei S-F. Meta-analysis of Atherogenic Index of Plasma and other lipid parameters in relation to risk of type 2 diabetes mellitus. Prim Care Diabetes. 2015; 9 (1): 60-7.

[28] Mark L, Vallejo-Vaz AJ, Reiber I, Paragh G, Kondapally Seshasai SR, Ray KK. Non-HDL cholesterol goal attainment and its relationship with triglyceride concentrations among diabetic subjects with cardiovascular disease: a nationwide survey of 2674 individuals in Hungary. Atherosclerosis 2015; 241: 62-68.

[29] Ahn SS, Lee LE, Pyo JY, Song JJ, Park YB, Lee SW. Atherogenic index of plasma predicts cerebrovascular accident occurrence in antineutrophil cytoplasmic antibody-associated vasculitis. Lipids Health Dis. 2020 Aug 14; 19 (1): 184.

[30] Tan MH, Johns D, Glazer NB. Pioglitazone reduces atherogenic index of plasma in patients with type 2 diabetes. Clin Chem. 2004; 50: 1184–8.

[31] Qin Z, Zhou K, Li Y, Cheng W, Wang Z, Wang J, et al. The atherogenic index of plasma plays an important role in predicting the prognosis of type 2 diabetic subjects undergoing percutaneous coronary intervention: results from an observational cohort study in China. Cardiovasc Diabetol. 2020; 19 (1): 23.

[32] Gimeno-Orna JA, Faure-Nogueras E, Sancho-Serrano MA. Usefulness of total cholesterol/HDL-cholesterol ratio in the management of diabetic dyslipidaemia. Diabet Med J Br Diabet Assoc. 2005; 22 (1): 26-31.

[33] Lu W, Resnick HE, Jablonski KA, Jones KL, Jain AK, Howard WJ et al. Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes. The Strong Heart Study. Diabetes Care. 2003; 26: 16–23.

[34] Khaw K-T, Wareham N. Glycated hemoglobin as a marker of cardiovascular risk. Curr Opin Lipidol. 2006; 17 (6): 637-43.

[35] Mullugeta Y, Chawla R, Kebede T, Worku Y. Dyslipidemia associated with poor glycemic control in type 2 diabetes mellitus and the protective effect of metformin supplementation. Indian J. Clin. Biochem. 2012, 27, 363–369.

[36] Ozder A. Lipid profile abnormalities seen in T2DM patients in primary healthcare in Turkey: A cross-sectional study. Lipids Health Dis. 2014 Dec 6; 13: 183.

[37] Walton CM, Perry K, Hart RH, Berry SL, Bikman BT. Improvement in Glycemic and Lipid Profiles in Type 2 Diabetics with a 90-Day Ketogenic Diet. J Diabetes Res. 2019 Aug 14; 2019: 8681959.

[38] Blake GJ, Pradhan AD, Manson JE, Williams GR, Buring J, Ridker PM, et al. Hemoglobin A1c level and future cardiovascular events among women. Arch Intern Med. 2004 Apr 12; 164 (7): 757-61.

[39] Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA. 2002; 287 (19): 2570.

[40] Papa A, Emdin M, Passino C, Michelassi C, Battaglia D, Cocci F. Predictive value of elevated neutrophil–lymphocyte ratio on cardiac mortality in patients with stable coronary artery disease. Clin Chim Acta. 2008; 395 (1-2): 27-31.

[41] Gillum RF, Mussolino ME, Madans JH. Counts of neutrophils, lymphocytes, and monocytes, cause-specific mortality and coronary heart disease: the NHANES-I epidemiologic follow-up study. Ann Epidemiol. 2005; 15 (4): 266-271.

[42] Luo W-J, Zhang W-F. The relationship of blood cell-associated inflammatory indices and diabetic retinopathy: a Meta-analysis and systematic review. Int J Ophthalmol. 2019; 12 (2): 312-23.

[43] Ulu SM, Dogan M, Ahsen A, Altug A, Demir K, Acartürk G, et al. Neutrophil-to-lymphocyte ratio as a quick and reliable predictive marker to diagnose the severity of diabetic retinopathy. Diabetes Technol Ther. 2013 Nov; 15 (11): 942-7.

[44] Yu Y, Lin Q, Ye D, Wang Y, He B, Li Y, et al. Neutrophil count as a reliable marker for diabetic kidney disease in autoimmune diabetes. BMC Endocr Disord. 2020; 20 (1): 158.

[45] Gibson PH, Cuthbertson BH, Croal BL, Rae D, El-Shafei H, Gibson G, et al. Usefulness of neutrophil/lymphocyte ratio as predictor of new-onset atrial fibrillation after coronary artery bypass grafting. Am J Cardiol. 2010 Jan 15; 105 (2): 186-91.

[46] Eriksson EE, Xie X, Werr J, Thoren P, Lindbom L. Direct viewing of atherosclerosis in vivo: plaque invasion by leukocytes is initiated by the endothelial selectins. FASEB J. 2001; 15 (7): 1149-1157.

[47] Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM, Blackwell L, Collins R, Keech A, Simes J, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008 Jan 12; 371 (9607): 117-25.