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Original Research

Inflammatory Atherosclerosis Risk and Lipid Ratios Markers in Type 1 Diabetic Patients: The Role of Ketosis as a Metabolic State

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Abstract

Introduction: Epidemiological inquiries on the subclinical atherosclerotic inflammatory disease in ketosis-onset type 1 diabetes (T1D) are scarce. Our objective was to evaluate the risk of developing atherosclerosis via lipid ratios by comparing two groups of patients according to their ketosis status. **Material and Methods:** We performed a comparative retrospective study, including 351 patients (13–74 years) with confirmed T1D divided into the following groups: patients with inaugural diabetic ketosis (IDK) vs. patients with diabetic ketosis (DK). Clinical, biological and pathophysiological patients' data were compared. Main lipid ratios have been assessed according to the patients' ketosis status and gender. The multivariate logistic regression test was applied to evaluate the association of lipid ratios quartiles with the diabetic ketosis status. **Results:** Our study showed a slight predominance of males (50.43%), with an average age of 25.77 years. Comparing to IDK, DK patients had a higher body mass index. No significant differences were observed between fasting plasma glucose and HbA1C and lipid levels. The results showed that the third (OR= 2.14 [0.81–5.61]; p=0.12) and the fourth quartiles (OR= 0.9 [0.35–2.33]; p=0.83) of TC/HDL ratio were higher in both groups. We noticed higher concordant values on the last two quartiles (third and fourth) of the LDL/HDL ratio with p values of 0.07 and 0.39, respectively. In both groups, TC/HDL and TG/HDL were slightly higher in males compared to female T1D patients except for the LDL/HDL ratio, which showed a slight ascendant median in females compared to males with IDK. **Conclusions:** The prevalence and risk of atherosclerosis inflammatory disease were higher in newly and formerly diagnosed patients with ketosis-onset T1D. Thus, medical awareness initiatives and a routine thorough endothelial function are needed to reduce the prevalence of the risk of atherosclerotic inflammatory disease.

Keywords: Atherosclerosis risk, lipid ratios, ketosis, type 1 diabetes.

Introduction

In a global picture, the number of patients diagnosed with diabetes increased up to 463 million among the population aged between 20 and 79 years. If these tendencies remain by 2045, 700.2 million people will be living with diabetes [1].

Multiple epidemiological investigations have shown that the incidence rate of type 1 diabetes (T1D) has been escalating to 2–5% annually [2]. This increase in the number of cases is particularly felt in low and middle-income countries, and children are not spared by the spread of the disease [3].

In Algeria, the disease's prevalence is continuously increasing, which will lead to a financial burden for the government budget [4].

Unlike other types of diabetes, T1D is characterized by immune-interfered destruction of pancreatic β cells, which negatively affects the secretion of insulin [5]. This leads over time to major microvascular complications like neuropathy, retinopathy, and nephropathy,

among other macrovascular complications like peripheral artery and cardiovascular diseases [6].

Several studies show that up to 40% of patients with new-onset T1D have diabetic ketoacidosis (DKA) [7, 8], which is a serious, potentially deadly T1D complication [9]. The mortality rate associated with DKA depends on the experience of the treating hospital in dealing with this condition [10]. Thus, it is crucial that patients detect DKA and get medical care immediately.

Although the metabolic dysfunction and autoimmune implication in ketosis T1D have been well documented [11, 12], slightly is known regarding the prevalence, clinical and biological features of atherosclerosis in ketosis T1D, which is defined as a persistent, progressive inflammatory process that initiates with lipid deposits and fatty streaks on the arterial intima leading to atherosclerotic plaques [13].

T1D is often associated with the early manifestation of atherosclerosis, representing the morphological basis for macrovascular diabetic complications and shows certain specific features that result from different proportions of risk factors [14].

Recent studies have shown that patients with T1D are at higher risk for endothelial dysfunction and atherosclerosis [15, 16]. However, few studies have inspected the possibilities of influencing and detecting the atherosclerotic process in subjects with ketosis T1D.

Thus, the objective of this scientific study is to assess and to compare the biological, clinical and pathophysiological characteristics of T1D patients with inaugural diabetic ketosis and with diabetic ketosis in order to evaluate the potential atherosclerosis risk, as a preliminary cardiovascular complication, by evaluating blood lipid ratios in a population from northwestern Algeria.

Material and Methods

Population and study design

We underwent a transverse retrospective observational study that involved all patients newly and formerly diagnosed with T1D and aged from 13 to 74 years. The study was carried out between January 2009 and December 2019 at the Diabetes-Endocrinology Department of the University Hospital Center in Sidi-Bel-Abbes, northwestern Algeria. Patients' medical records were reviewed for medical history, symptoms and signs, biochemical parameters, and complications of the diabetic disease. All T1D patients with Inaugural Diabetic Ketosis (IDK) and Diabetic Ketosis (DK) with complete and adequate medical records were involved in the analysis. Diabetic ketoacidosis (DKA) was defined according to the latest biochemical criteria for the DKA identification published by the American Diabetes Association (ADA) [17]. However, T1D patients without confirmed ketosis were excluded.

For all patients, anthropometric parameters (body weight, body mass index "BMI" and waist circumference) were available on the patient's medical record. Blood pressure was determined by a sphygmomanometer in a supine position followed by a second measurement (after a few minutes) in a standing position. Hypertension was defined by systolic blood pressure (SDP) of 140 mmHg and diastolic blood pressure (DBP) of about 90 mmHg or more. The latest biochemical assessment including fasting blood glucose, glycated hemoglobin (HbA1c), hemoglobin, urea, creatinine and lipid parameters, namely total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and triglycerides (TG), were taken from patients' medical records. Moreover, lipid ratios as indicators of atherogenic risk were calculated - TC/HDL, LDL/HDL, and TG/HDL.

Ethical considerations

Complete confidentiality of vital patient information was maintained for ethical purposes, and ethical approval was obtained from the department in which the study was carried out.

Statistical analyses

Descriptive analyses were conducted after the data were summarized using percentages and

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relative frequencies for qualitative variables and means±SD with its respective 95% confidence intervals (95% CI) for continuous variables.

Qualitative categorical variables were compared using the Chi-square test, while quantitative variables were compared using the Student t-test. Significant differences were maintained when the p-value was less than or equal to 0.05 ($p < 0.05$).

Multivariate logistic regression was applied to evaluate differences of categorical variables while adjusting for serum lipid ratios and exploring their clinical usefulness to identify the atherosclerosis risk in T1D patients with IDK or DK. All data were computed and analyzed via the SPSS software (SPSS 22, IBM Corporation; Chicago, IL. August 2013).

Results

The basic characteristics of the studied patients are summarized in Table 1. A total of 351 patients with type 1 diabetes (50.43% males and 49.57% females) were admitted to the University Hospital Center from January 2009 to December 2019. Among all the involved patients, 155 patients (44.2%) presented DKA at first diagnosis of diabetes (inaugural diabetic ketosis "IDK"), while 196 DKA patients (55.8 %) had long-established T1D (diabetic ketosis "DK").

At diagnosis, the age of patients was more than 13 years old in all of them with a mean age of 25.77 years. Meanwhile, the mean age of patients with diabetic ketosis (DK) was

Table 1: Basic characteristics of the participants.

Variables	All Patients n=351	Inaugural Diabetic Ketosis n=155	Diabetic Ketosis n=196	*p* value*
		Gender, n (%)		
Male	177 (50.43)	100 (64.52)	77 (39.29)	$<10^{-3}$
Female	174 (49.57)	55 (35.48)	119 (60.71)	$<10^{-3}$
		Age groups, years		
[13–19]	102 (29.10)	53 (34.20)	49 (25.00)	
[20–29]	148 (42.20)	75 (48.40)	73 (37.20)	$<10^{-3}$
[30–39]	81 (23.10)	27 (17.40)	54 (27.60)	
[40–49]	15 (4.30)	0 (0.00)	15 (7.70)	
[50–59]	3 (0.90)	0 (0.00)	3 (1.50)	
≥ 60	2 (0.60)	0 (0.00)	2 (1.00)	
		Smoking history, n (%)		
Male	53 (15.10)	34 (21.93)	19 (9.69)	$<10^{-3}$
Female	–	–	–	–
		Prevalence of weight categories, n (%)		
Underweight, BMI <18.5 Kg/m^2	119 (33.90)	67 (43.22)	52 (26.53)	
Normal weight,	163 (46.40)	70 (45.16)	93 (47.45)	0.009
BMI=18.5–25.0Kg/m^2	20 (5.70)	5 (3.22)	15 (7.65)	
Overweight, BMI=25.0–29.9Kg/m^2	9 (2.60)	5 (3.22)	4 (2.04)	
Obesity, BMI ≥30 Kg/m^2				
		Precipitating factors, n (%)		
Angina	17 (4.80)	9 (5.80)	8 (4.08)	0.45
Influenza syndrome	33 (9.40)	7 (4.50)	26 (13.27)	**0.005**
Pregnancy	13 (3.70)	0 (0.00)	13 (6.63)	**0.001**
Urinary infection	73 (20.80)	25 (16.14)	48 (24.49)	**0.05**
Dental abscess	8 (2.28)	1 (0.66)	7 (3.57)	0.06
Insulin omission	16 (4.57)	0 (0.00)	16 (8.16)	**$<10^{-3}$**
Diabetic foot	3 (0.90)	0 (0.00)	3 (1.53)	0.12
Alcohol abuse (in males)	10 (2.84)	7 (4.51)	3 (1.53)	0.09
Unknown	178 (50.71)	106 (68.39)	72 (36.74)	–

(continued)

Table 1: Basic characteristics of the participants.

Variables	All Patients n=351	Inaugural Diabetic Ketosis n=155	Diabetic Ketosis n=196	*p* value*
Other associated diseases, n (%)				
Low visual acuity	44 (12.50)	8 (5.16)	36 (18.37)	$<10^{-3}$
Diabetic retinopathy	13 (3.70)	0 (0.00)	13 (6.63)	$<10^{-3}$
Hypertension	9 (2.60)	0 (0.00)	9 (4.59)	$<10^{-3}$
Hypothyroidism	13 (3.70)	2 (1.29)	11 (5.16)	0.03
Hyperthyroidism	6 (1.70)	4 (2.58)	2 (1.02)	0.26
Anemia	76 (21.70)	24 (15.48)	52 (26.53)	0.01
Gastroenteritis	8 (2.30)	1 (0.65)	7 (3.57)	0.06
Symptoms and signs, n (%)				
Signs of dehydration	87 (24.80)	44 (28.38)	43 (21.94)	0.16
Abdominal pain	67 (19.10)	18 (11.61)	49 (25.00)	0.001
Vomiting and nausea	98 (27.90)	14 (11.61)	84 (42.86)	10^{-3}
Dyspnea	18 (5.10)	7 (9.03)	11 (5.61)	0.64
Transit disorder (diarrhea)	15 (4.30)	2 (1.29)	13 (6.63)	0.01
Epigastric	21 (6.00)	1 (0.65)	20 (10.20)	0.001
Headaches	25 (7.10)	13 (8.39)	12 (6.12)	0.41
Dizziness	27 (7.70)	17 (10.97)	10 (5.10)	0.04
Edema	5 (1.40)	1 (0.65)	4 (2.04)	0.27
Micturition burn	22 (6.30)	6 (3.87)	16 (8.16)	0.1
Cardinal syndrome, n (%)	245 (69.80)	129 (83.23)	116 (5.61)	$<10^{-3}$
Weight loss	349 (99.40)	155 (100.00)	194 (98.97)	0.20
Polyuria-Polydipsia	186 (53.00)	84 (54.19)	102 (52.04)	0.98
Asthenia	258 (73.50)	140 (90.32)	118 (60.20)	0.01
Overeating				
Family history, n (%)				
Hypertension	82 (23.36)	37 (23.87)	45 (22.96)	0.84
Type 1 diabetes	56 (15.95)	22 (14.19)	34 (17.35)	0.42
Type 2 diabetes	195 (55.55)	89 (57.42)	106 (54.08)	0.53
Goiter	20 (5.69)	9 (5.80)	11 (5.61)	0.93

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

significantly higher than that of patients with inaugural diabetic ketosis (IDK) (27.83±9.93 years vs. 23.16±5.74 years, p<0.001) (Table 2). The most affected age group by both IDK and DK was the 20–29 age group, with a rate of 42.2%, followed by the 13–19 age group with 29.1%. However, the least affected age group was the >60 years group (Table 1). The overall prevalence of underweight, normal weight, overweight, and obesity was 33.90%, 57.80%, 5.70%, and 2.60%, respectively.

In the current study, multiple factors contributed to DKA, including infection, poor drug compliance, pregnancy, diabetic foot, and alcohol abuse. The most commonly known precipitating factor for DKA was urinary infection 20.8%, followed by the influenza syndrome – 9.4%, angina – 4.8% and insulin omission – 4.57%. Anemia was the most common complication (21.7%), its frequency being higher in the DK group (26.53%, p=0.01), followed by low visual acuity, diabetic retinopathy, hypothyroidism, and hypertension.

As mentioned in the patients' medical files, the typical symptoms were mostly vomiting and nausea – 27.9%, followed by signs of dehydration – 24.8% and abdominal pain – 19.1% as the presenting symptoms. Other symptoms defined by cardinal syndrome were also present and patients had one or more of them, including polyuria polydipsia, overeating, weight loss, and asthenia.

Family history (grandparents, parents, and siblings) of T1D was present in 15.95% of cases, while the majority (84.6%) reported having a family history of other complications (T2D, hypertension, and goiter).

Laboratory data for the two groups are recapitulated in Table 2. Concerning the

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Table 2: Comparison of biochemical characteristics between ketosis patients' subgroups.

Variables	All Patients n=351		Inaugural Diabetic Ketosis n=155		Diabetic Ketosis n=196		*p* value*
	Mean±SD	95% CI	Mean±SD	95% CI	Mean±SD	95%CI	
Mean age (years)	25.77±8.65	24.86–26.67	23.16±5.74	22.25–24.07	27.83±9.93	26.43–29.23	**$<10^{-3}$**
Diabetes duration (years)	5.92±7.57	5.13–6.72	0.11±0.07	0.10–0.12	10.52±7.4	9.48–11.56	**$<10^{-3}$**
Age at 1st diagnosis (years)	19.95±7.82	19.13–20.78	23.15±5.75	22.24–24.06	17.43±8.31	16.26–18.6	**$<10^{-3}$**
Body weight (Kg)	56.86±12.12	55.51–58.21	57.53±11.66	55.63–59.43	56.26±12.53	54.33–58.19	0.35
BMI (Kg/m^2)	19.96±3.60	19.56–20.36	19.36±3.47	18.80–19.93	20.50±3.63	19.93–21.06	**0.005**
Waist circumference (cm)	78.37±10.19	76.50–80.23	78.18±10.77	75.29–81.06	78.54±9.72	76.05–81.03	0.84
SBP (mmHg)	110.60±11.66	109.40–111.90	110.80±10.84	109.10–112.50	110.50±12.30	108.80–112.20	0.83
DBP (mmHg)	66.70±8.31	65.80–67.60	67.40±8.21	66.10–68.70	66.20±8.38	65.00–67.30	0.15
Fasting plasma glucose (g/l)	3.76±0.91	3.66–3.85	3.69±0.93	3.54–3.84	3.81±0.89	3.68–3.94	0.22
HbA1c (%)	11.42±2.08	11.16–11.69	11.67±2.12	11.28–12.07	11.22±2.03	10.87–11.56	0.08
Haemoglobin(g/l)	13.04±2.05	12.76–13.31	13.66±2.05	13.26–14.06	12.48±1.89	12.13–12.83	**$<10^{-3}$**
Total cholesterol (g/l)	1.58±0.41	1.52–1.65	1.60±0.44	1.50–1.71	1.56±0.38	1.48–1.65	0.54
HDL–c (g/l)	0.40±0.11	0.38–0.42	0.39±0.08	0.37–0.41	0.40±0.13	0.37–0.44	0.48
LDL–c (g/l)	0.93±0.34	0.87–0.98	0.95±0.35	0.87–1.04	0.90±0.32	0.83–0.98	0.36
Triglycerides (g/l)	1.05±0.65	0.95–1.15	1.08±0.67	0.92–1.23	1.02±0.63	0.88–1.16	0.58
TC/HDL–c	4.01±1.21	3.80–4.21	4.10±1.15	3.82–4.38	3.92±1.26	3.63–4.22	0.39
LDL/HDL–c	2.39±0.98	2.23–2.55	2.51±0.98	2.27–2.75	2.29±0.97	2.06–2.51	0.18
TG/HDL–c	2.82±2.04	2.47–3.16	2.93±1.88	2.47–3.39	2.71±2.18	2.20–3.22	0.52
Creatinine(mg/l)	12.58±9.95	9.75–15.41	10.78±10.24	5.68–15.87	13.60±9.80	10.07–17.13	0.34
Urea (g/l)	0.49±0.38	0.38–0.59	0.37±0.26	0.23–0.50	0.55±0.42	0.40–0.71	**0.05**

(*) 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; TC: total cholesterol; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TG: triglycerides.

anthropometric measurement on admission, there were no significant differences in body weight and waist circumference between the two groups. However, significantly higher BMI (p=0.005) was found in DK comparing to IDK T1D patients. No differences are observed in orthostatic blood pressure (Table 2).

Although the glycemic control was poor, as shown by a mean glycated hemoglobin (HbA1c) level above 10%, no significant differences regarding fasting plasma glucose and HbA1c levels (IDK: 11.67±2.12%, DK: 11.22±2.03 %, p=0.08) between the two groups of diabetes was noted on admission. On the other hand, hemoglobin was lower in DK patients than in IDK patients (12.48±1.89 g/l vs. 13.66±2.05 g/l, respectively, p<0.001). Concerning lipid levels, no significant differences were found between the two groups. In contrast, mean levels of lipid ratios were slightly higher in IDK than in DK without significant differences (Table 2).

With respect to renal function, urea mean±SD was higher in the longstanding T1D group (0.55±0.42 g/l), with a significant difference among the two groups (p=0.05). Meanwhile, no evidence of a difference in creatinine mean±SD was found between the two groups (p=0.34).

Regarding fluid management in the emergency room, the initial insulin requirement was higher in patients with DK than that of IDK (50.51±23.72 IU vs. 45.57±18.66 IU, respectively, p= 0.03).

For the whole study population, the multivariate regression between lipid ratios quartiles, as powerful predictors of atherosclerosis, plotted that the third (OR= 2.14 [0.81–5.61]; p=0.12) and the fourth quartiles (OR= 0.9 [0.35–2.33]; p=0.83) of TC/HDL ratio were higher in both groups as described in Table 3. Furthermore, we noticed higher concordant values in the last two quartiles (third and fourth) of the LDL/HDL ratio with p values of 0.07 and 0.39, respectively.

Table 3: Crude "Odds Ratio" of blood lipid ratios quartiles associated with the type of diabetic ketosis.

Variables	Inaugural Diabetic Ketosis, n=155 Number (%)	Diabetic Ketosis, n=196 Number (%)	Odds ratio (95% CI OR)	*p-value
CT/HDL ratio				
1st quartile (1.56–3.12)	14 (20.89)	20 (27.78)	Reference	–
2nd quartile (3.13–3.92)	13 (19.41)	22 (30.56)	1.81 [0.69–4.73]	0.22
3rd quartile (3.93–4.61)	21 (31.34)	15 (20.83)	2.14 [0.81–5.61]	0.12
4th quartile (4.62–7.96)	19 (28.36)	15 (20.83)	0.90 [0.35–2.33]	0.83
LDL/HDL ratio				
1st quartile (0.35–1.81)	17 (25.37)	18 (25.00)	Reference	–
2nd quartile (1.82–2.25)	13 (19.41)	22 (30.56)	1.51 [0.58–3.91]	0.39
3rd quartile (2.26–2.84)	17 (25.37)	18 (25.00)	2.41 [0.91–6.36]	0.07
4th quartile (2.85–5.93)	20 (29.85)	14 (19.44)	1.51 [0.58–3.19]	0.39
TG/HDL ratio				
1st quartile (1.00–1.40)	14 (20.89)	20 (27.78)	Reference	–
2nd quartile (1.41–2.16)	18 (26.87)	18 (25.00)	1.51 [0.58–3.91]	0.39
3rd quartile (2.17–3.68)	17 (25.37)	17 (23.61)	1.05 [0.41–2.68]	0.90
4th quartile (3.69–13.58)	18 (26.87)	17 (23.61)	1.05 [0.41–2.72]	0.90

(*) multivariate logistic regression significant at $p = 0.05$; CI, confidence interval; OR, Odd ratio; Q, quartiles; TC: total cholesterol; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; TG: triglycerides.

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Likewise, the fourth quartile of the TG/HDL ratio disclosed an Odd ratio of 1.05 [0.41–2.72] (p=0.90).

As shown in Figure 1, in males and females, when comparing lipid ratios between the two groups of diabetic ketosis, TC/HDL and TG/HDL were slightly higher in males compared to females T1D patients. However, this was not the case for the LDL/HDL ratio, which showed a slight ascendant median in females compared to males with inaugural diabetic ketosis.

Besides, higher TC and LDL levels were observed in females compared to males with IDK. Meanwhile, males with DK had high levels of TC and LDL compared to female patients. Similarly, TG levels were higher in males compared to females with IDK.

Discussion

Ketosis is considered a trait of T1D and one of its most serious acute complications. Its annual incidence is around 4.6 to 8 episodes/1000 diabetic patients [18]. This complication is characterized by increased production of ketones and glucose in the liver precipitated by a total or relative lack of insulin and an increase in catabolic hormone rates [19–21]. In parallel, T1D patients

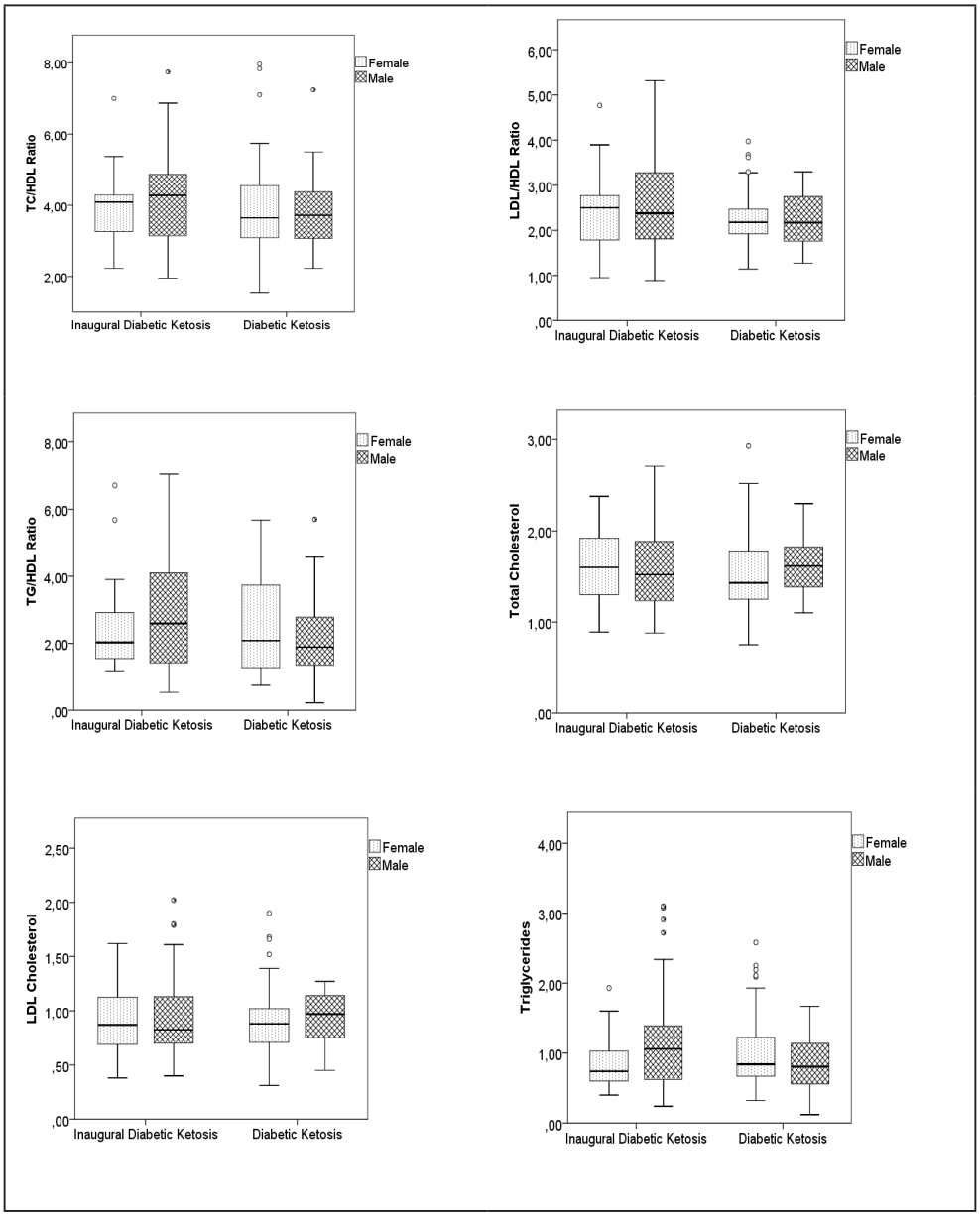

Figure 1: Comparison of lipid ratios levels between patients with Inaugural Diabetic Ketosis and Diabetic Ketosis according to the patients' gender.

are prone to lipid disorders (mainly qualitative abnormalities of the lipoproteins) that can subsequently lead to the onset of atherosclerosis. Hyperglycemia and peripheral hyperinsulinemia, which are likely to play a role in these complications, result from the administration of subcutaneous insulin [22].

The objective of the current study was to evaluate, in T1D patients, the risk of developing atherosclerosis (via lipid ratios) by comparing two groups of patients according to their ketosis status (patients with inaugural diabetic ketosis vs. patients with diabetic ketosis).

Our study's preliminary consequences displayed significant effects of gender, age group, active smoking status, and patients' corpulence on variances between inaugural diabetic ketosis patients and diabetic ketosis ones. The distribution of patients by gender showed a slight predominance of males over females (50.43% – 49.57%), a sex ratio of 1.01. Taieb et al. found that 68% of the population diagnosed with type 1 diabetic ketosis were males versus 32% females with a sex ratio = 2.1 [23]. Our results are in accordance with the same Tunisian study conclusion, where a relatively high proportion of inaugural diabetic ketosis has been described in adolescents and young subjects compared to the older patients [23]. The same observations have been made by Lin et al. in Taiwan [24]. Studies suggesting the relationship between type 1 diabetes, diabetic ketosis and body corpulence are still rare and inconclusive. Low et al. have reported that lean children and adolescents with DK have often type 1 autoimmune diabetes. In contrast, obese children and adolescents with DK have clinical, metabolic, and immunological features of type 2 diabetes [25]. Our findings disclose that most T1D patients with both inaugural diabetic ketosis and diabetic ketosis are either underweight or normal weight with a higher significant effect of body corpulence (p=0.009).

The most common precipitating factors reported in the present study were urinary infection, influenza syndrome, angina, and insulin omission that are significantly more frequent in patients with diabetic ketosis compared to those with inaugural diabetic ketosis. Ahuja et al. reported that infections and insulin omission were the most frequent precipitants factors of DKA [26]. In our series, 4.57% of young patients who had omitted their medications had a family history of omission and/or medication neglecting. One explanation for this behavior may be a patients' misunderstanding of their diabetes management [27].

In our study, vomiting and abdominal pain were the most common presenting symptoms; these results concord with other studies [28, 29]. Moreover, the clinical picture of DK typically involves cardinal syndrome (polyuria, polydipsia, weight loss, asthenia, and weakness).

The diabetic ketosis group required more additional fluid and treatment with the insulin infusion to achieve a ketone-negative status compared with the newly diagnosed group [30].

The comparison between the two ketosis patients' subgroups disclosed some significant differences, especially for mean age, the first age of diabetes diagnosis, and biochemical parameters. The glycated hemoglobin (p=0.08) and hemoglobin (p<0.001) were higher in patients with inaugural diabetic ketosis compared to those with diabetic ketosis. Similarly, the conventional lipid parameters (TC, HDL, LDL, and TG) and their associated ratios (TC/HDL, LDL/HDL, and TG/HDL) were higher in patients with inaugural diabetic ketosis compared to patients with diabetic ketosis indicating a higher cardiovascular risk in new-onset type 1 diabetic patients. There is lacking direct research evaluating the cardiovascular risk (namely of atherosclerosis) in ketosis onset diabetes (inaugural diabetic ketosis) or ketosis-prone diabetes (diabetic ketosis). In their study, Liu et al. showed that patients with inaugural diabetic ketosis do not have absolutely the same clinical characters as patients with diabetic ketosis, and each subgroup showed different rates [31].

Many authors agree that atherogenic or Castelli indexes (LDL/HDL and TC/HDL ratios) are the best indicators of vascular risk compared to the traditional lipid parameters [32]. According to the Helsinki study (1992), the LDL/HDL ratio is the most relevant index for cardiovascular health [33]. Our findings disclosed a higher non-significant atherosclerosis risk (evaluated through lipid ratios) in type 1 ketosis-onset diabetics than in

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type 1 diabetic ketosis patients. The same results were reported by Wang et al. [34].

In the present study, all participants were categorized into lipid ratios quartiles, from the highest quartile (fourth) to the lowest one (first) as reference. The comparison of lipid ratios quartiles between patients with inaugural diabetic ketosis and those with diabetic ketosis exposed non-significant differences for all the compared quartiles. Whereas, the Odds ratios increased significantly from the first to the third quartiles of the three studied lipid ratios, regardless of the ketosis subgroup. Our results are in accordance with the conclusions of the Framingham study (2006), where increasing coronary heart disease proportions were observed when the TC/HDL ratio fluctuated from the lower to the higher tertiles [35].

The explanation of DK's role in the inflammatory cascade in diabetic patients has been the subject of several works [36]. It is currently clearer that the acceleration of LDL oxidation, hyperketonemia, and the increased risk of atherosclerosis and CVD in diabetic patients result from the high levels of oxidative stress experienced by these patients. It has also been reported that DK can be independently associated with cardiovascular risk despite the absence of a metabolic history or known sensitivities to cardiovascular pathology [37]. In addition, it has been stated that the elevation level of ketones is proportional to the severity of congestive heart failure [38]. In our study, both patients with inaugural diabetic ketosis and diabetic ketosis have a higher to moderate risk of developing atherosclerosis according to their lipid ratios expressed by quartiles.

Regarding the effect of gender difference on the clinical characteristics and outcomes of diabetic ketosis patients, the availability of data is still very limited. These gender differences must be recognized and taken into account for optimal treatment and diabetes prevention [39]. Our results point out that the TC/HDL ratio was beyond the therapeutic target of 3.5 recognized by several authors for patients with inaugural diabetic ketosis and diabetic ketosis [40]. Likewise, the values of this ratio for men were often high compared to women. The LDL/HDL ratio values were higher in women patients with inaugural diabetic ketosis and almost identical between the two sexes in patients with diabetic ketosis. However, in all studied patients, LDL/HDL and TG/HDL levels were within the normal ranges of 2.5 and 3, respectively [40, 41].

In this study, we haad certain limitations that need to be indicated. First, the observational context of the present investigation does not allow to make a clear, conclusive decision about the atherosclerosis risk in T1D with regard to ketosis. Therefore, further intervention study is preferable to confirm our results. Second, most of the study participants were from the urban area, so this population could not be geographically diverse. Nevertheless, regardless of these limitations, we believe that our conclusions would remain unchanged in the general population despite the study design. The employment of lipid ratios in the evaluation of atherosclerosis risk in T1D patients is a robust method regardless of gender and ketosis status; however, lifestyle factors may undoubtedly change over time. Therefore, data from the present work can be a good support for further research.

Conclusion

Diabetic ketosis or ketoacidosis is the most crucial complication of T1D and can present high morbidity if it is not diagnosed early and managed properly. In patients with type 1 diabetes, the employment of blood lipid ratios for evaluating atherosclerosis threats disclosed a higher risk in both groups of patients with inaugural diabetic ketosis and diabetic ketosis. However, higher frequency and dominance of atherosclerosis risk is observed in the male gender with inaugural diabetic ketosis. Consequently, considering the large prevalence of the associated subclinical conditions, and their consequences for the long-term management, a routinely thorough vascular assessment might be warranted for patients with T1D.

Conflict of Interest

The authors declare no conflict of interest.

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