Lipid ratios as a predictive marker of Subclinical Atherosclerosis inflammation among Type 1 Diabetic patients with Thyroid Dysfunction

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ABSTRACT

Background and Objectives: Epidemiological inquiries on the subclinical atherosclerotic disease in type 1 diabetes associated with autoimmune thyroid disease are scarce. Our aim was to evaluate the risk of developing atherosclerosis via lipid ratios by comparing two groups of patients according to their TSH (Thyroid-stimulating hormone) status.

Methods: A retrospective study including 190 patients (13-74 years) with confirmed type 1 diabetes divided into the following groups (patients with serum TSH < 2.5 μIU/mL vs. patients with serum TSH ≥ 2.5 μIU/mL). Autoimmune thyroid disease was classified according to clinical biological, and follow up data.

Results: Our study showed a slight predominance of females (50.50%), with an average age of 29.25±11.39 years. The prevalence of hypothyroidism was 14.7%, hyperthyroidism 6.3%, and anti-TPO 16.31%. Significant differences were observed between lipid profiles such as LDL and TG (p>0.008, p=0.04, respectively). The results showed that the 3rd (OR= 2.28 [0.72-7.20]; p=0.15) and the fourth quartiles (OR= 1.9 [0.61-5.83]; p=0.26) of TC/HDL ratio were higher in patients with serum TSH ≥ 2.5 μIU/mL group. Similarly, we noticed higher concordant values on the last quartile (4th) of LDL/HDL ratio with p values of 0.06 as well as the two quartiles (2nd and 4th) of TG/HDL ratio with p values of 0.03 and 0.04, respectively. In both groups, lipid ratios were slightly higher in males compared to females' patients.

Conclusion: The risk of atherosclerosis was higher in patients with elevated TSH concentrations. Therefore, early detection of thyroid dysfunction and associated dyslipidemia is essential for effective prevention of premature cardiovascular morbidity and mortality.

Keywords: Subclinical atherosclerotic disease, autoimmune thyroid disease, TSH, type 1 diabetes

INTRODUCTION

Approximately 4.2 million persons aged between 20–79 years are estimated to die as a result of diabetes and its complications in 2019 1. In the same year, the International Diabetes Federation (IDF) estimated that 463 million people around the world aged 20–79 years had diabetes, and by 2035 this number is expected to rise to 587.4 million 1.

Type 1 diabetes (T1D) is an auto-immune disease leading to absolute insulin deficiency 2, with prevalence estimated to be 207 cases per 100,000 equivalents to 1 T1D for 462 children under 15 3. It can be related to other auto-immune disorders that may affect the control of diabetes by disrupting the function of some organs 2. Commonly known, this disease is closely associated with autoimmune thyroid disease (AITD) in clinical practice because these endocrinopathies are linked by the same pathophysiological mechanism 4,5. They share an autoimmune predisposition, and some genetic factors might contribute to the coexistence of AITD and T1D 6, and indeed up to a third of patients with T1D ultimately develop thyroid dysfunction at an early age compared with the general population 7.

It has also been reported that AITD occurs in 17% to 30% of individuals with T1D, and these patients are at higher risk of both autoimmune-induced hyperthyroidism (Graves’ disease) as well as hypothyroidism (Hashimoto’s thyroiditis) 8. Thyroid autoantibodies can be detected at the initial diagnosis or may be detected over time, after diagnosis 2. The prevalence of positive antithyroid peroxidase antibodies (anti-TPO) is estimated to be ranged between 2% and 10% in the general population, whereas in the population of T1D patients it is much higher, reaching the level from 15% to 30% 9.

According to some of the recognized associations, global guidelines currently recommend routine screening for...
thyroid function and anti-TPO in patients with T1D. Specifically, the American Diabetes Association (ADA) guideline document advises screening for anti-TPO and thyroid function soon after diagnosis and then to consider rechecking thyroid function every two years.

Undiagnosed thyroid disorder may impair metabolic control in patients with T1D including the synthesis, mobilization, and catabolism of lipids which may amplify the risk of atherosclerosis disease. Diabetes mellitus, in particular T1D, which is highly associated with lipid abnormalities, was also known to dramatically increasing the risk of atherosclerotic cardiovascular disease especially to those at a younger age due to their long duration of diabetes.

To that end, we aimed in this scientific study to assess and to compare the prevalence of known and undiagnosed thyroid disease and to analyze the thyroid autoantibody profile among patients with T1D in order to investigate the potential atherosclerosis risk, which has greater predictive power for a cardiovascular complication, by evaluating blood lipid ratios in Algerian type 1 diabetic patients since no similar studies have been performed before.

PATIENTS AND METHODS

Our transverse retrospective observational study was performed using a database of 190 patients ≥13 years with a confirmed T1D according to the WHO criteria who had been referred to the University Hospital Center in Sidi-Bel-Abbes, northwestern Algeria in the years 2009 to 2019 and remained under the care of the Endocrinology Department of the hospital thereafter. Patients' medical records were reviewed for medical history, other associated diseases, biochemical parameters, and complications of the diabetic disease. All patients with previously diagnosed with T1D, aged more than 13 years with no history of any cardiovascular disease were involved in the analysis. Though, patients with T1D aged less than 13 years, missing the medical records of the disease, and missing informed consent were excluded. Ethical approval for the study was granted by the Ethics Committee of the University Hospital Center in which the study was carried out.

For all patients, anthropometric parameters (body weight and height, body mass index “BMI” and waist circumference) were available on the patient’s medical record. Blood pressure was measured with a sphygmomanometer in a supine position followed by a second measurement (after a few minutes) in a standing position. Hypertension was defined by blood pressure (BP) in the spine position of 140/90 mmHg or more or by current anti-hypertensive treatment. The latest biochemical assessment including fasting blood glucose, glycated hemoglobin (HbA1c), high-sensitivity C-reactive protein (hs-CRP) (< 6 mg/L), urea (0.15-0.45 g/L), serum creatinine (4-10 mg/L) and lipid parameters, namely; total cholesterol (TC) (1.5-2 g/L), high-density lipoprotein cholesterol (HDL) (≥ 0.45 g/L), low-density lipoprotein cholesterol (LDL) (0.5-1.5 g/L) and triglycerides (TG) (0.5-1.5 g/L), microalbuminuria (> 30 mg/24h), thyroid-stimulating hormone (TSH) (0.27-4.25 μIU/mL), Anti-thyroid peroxidase antibodies (Anti-TPO) (< 30 μIU/mL) were taken from patients’ medical records. Anti-TPO was defined as positive (>30 μIU/mL) in at least one sample obtained within the period of hospitalization. Moreover, lipid ratios as indicators of atherosgenic risk were calculated; TC/HDL, LDL/HDL, and TG/HDL.

Statistical analysis

Concerning the statistical analytical study, the data were summarized using mean and standard deviation values with its respective 95 % confidence intervals (95% CI) for continuous variables and percentages (%) and relative frequencies for qualitative variables.

Chi-square test and Student’s t-test were used to compare qualitative and quantitative variables between the two groups. Significant differences were established when the p-value is less than or equal to 0.05 (p ≤ 0.05).

To explore the differences of categorical variables such as serum lipid ratios and to assess their clinical utility to identify the atherosclerosis risk in patients with T1D according to their TSH status multivariate logistic regression was applied. All data were computed and analyzed using SPSS software (SPSS 22, IBM Corporation; Chicago, IL August 2013).

RESULTS

We identified 190 type 1 diabetic patients (49.50% males and 50.50% females) with a male-to-female ratio of 0.98. Among all the involved patients, 73 (38.4%) patients presented with TSH < 2.5 μIU/mL while 117 (61.6%) patients with TSH ≥ 2.5 μIU/mL. The mean age of the sample was 29.25 ± 11.39 years (range 13-74) and mean duration of diabetes was 12.20 ± 8.45 years. Meanwhile, the mean age of patients with TSH < 2.5 μIU/mL was significantly lower than that of patients with TSH ≥ 2.5 μIU/mL (25.60 ± 10.11 years vs. 31.52 ± 11.59 years, p<10^-3) (Table 2). The most affected age group was the “20-29 years” with a rate of (38.40%), followed by the “30-39 years” group with (22.60%). However, the least affected age group was the “≥60 years”. The overall prevalence of underweight, normal weight, overweight, and obesity was (22.10%), (65.30%), (11.10%), and (1.50%), respectively (Table 1).

In the current study, significant differences were found concerning the well-known complications of diabetes. The differences were most pronounced for diabetic nephropathy, diabetic retinopathy, hypothyroidism, hyperthyroidism and hypertension which all differed significantly between the two groups (16.30%, p<10^-5; 21.00%, p=0.04; 14.70%, p<10^-3; 6.30%, p=10^-3; and 15.80%, p=0.02; respectively) (Table 1).

Concerning the Laboratory data for both groups, there were no significant differences between them in terms of age at first diagnosis, anthropometric measurement (body weight, height, and waist circumference), fasting plasma glucose, HbA1c level, Total cholesterol (TC), LDL-c/TC/HDL-c ratio, LDL/HDL-c ratio (all p > 0.05) (Table 2). However, significantly higher systolic blood pressure (SBP) (p=0.001) and diastolic blood pressure (DBP) (p=0.01) was found in TSH ≥ 2.5 μIU/mL compared to TSH < 2.5 μIU/mL T1D patients, on the other hand, high-sensitivity C-Reactive Protein (hs-CRP) was lower in subjects with serum TSH < 2.5 μIU/mL than that with serum TSH ≥ 2.5 μIU/mL (6.6±14.02 mg/L vs. 36.45±58.21 mg/L, p=0.003; respectively). With regard to lipid levels, as shown in (Table 2) when the t-test was applied to the HDL-c and triglycerides for both groups, p-value was 0.008, 0.04 respectively which was statistically significant. Further, it was found that TG/HDL-c ratio was significantly higher in the group with serum TSH ≥ 2.5 μIU/mL (p=0.03) (Table 2).

With respect to renal function, patients with serum TSH ≥ 2.5 μIU/mL had increased plasma levels of creatinine and urea and microalbuminuria (17.07±22.12 μg/L, p=0.002; 0.53±0.48 g/L, p<10^-3; and 218.42±553.14 mg/24h, p=0.05; respectively).

Regarding patients who had both T1D and thyroid dysfunction, Anti-TPO antibodies were higher in patients...
with serum TSH ≥ 2.5 μIU/mL than that with serum TSH < 2.5 μIU/mL (99.42±123.66 IU/mL vs. 7.9±10.04 IU/mL, respectively, p = 0.006).

For the whole study population, the multivariate regression between lipid ratios quartiles, as powerful predictors of atherosclerosis, plotted that the 3rd (OR= 2.28 [0.72-7.20]; p=0.15) and the fourth quartiles (OR= 1.9 [0.61-5.83]; p=0.26) of TC/HDL ratio were higher in both groups as described in (Table 3). Furthermore, we noticed higher discordant values in the 4th quartile of the LDL/HDL ratio with p-value 0.06. Likewise, there were a higher significant differences in the [2nd and 4th] quartiles of the TG/HDL ratio disclosed an Odd ratio of 0.26 [0.07-0.89] (p=0.03) and (OR= 0.28 [0.08-0.97]; p=0.04), respectively.

As shown in Figure 1, in males and females, when comparing lipid ratios between the two groups, TC/HDL, LDL/HDL, and TG/HDL ratios were slightly higher in males compared to females’ type 1 diabetic patients. In addition, higher TC, LDL, and TG levels were observed in males compared to females with serum TSH < 2.5 μIU/mL. Meanwhile, females with serum TSH ≥ 2.5 μIU/mL had high levels of TC and LDL compared to male patients. Similarly, TG levels were higher in males compared to females with serum TSH ≥ 2.5 μIU/mL.

Concerning the subgroups divided by the TSH cut-off level of 2.5 μIU/mL (Figure 2). There was a higher prevalence of anti-TPO in patients with TSH ≥ 2.5 μIU/mL (64.44% vs. 35.56%). Likewise, we did observe a statistically significant difference in the prevalence of anti-TPO among patients with serum TSH below 2.5 μIU/mL (93.33% vs. 6.67%).

### Table 1: Basic characteristics of the participants

| Variables                             | All Patients | TSH < 2.5 (μIU/mL) | TSH ≥ 2.5 (μIU/mL) | p-value |
|---------------------------------------|--------------|--------------------|--------------------|---------|
|                                       | n=190        | n=73               | n=117              |         |
|                                       | Number (%)   | Number (%)         | Number (%)         |         |
| Gender, n (%)                         | Male         | 94 (49.50)         | 30 (41.10)         | 64 (54.70) | 0.069 |
|                                       | Female       | 96 (50.50)         | 43 (58.90)         | 53 (45.30) |         |
| Age group, years                     | [13-19]      | 38 (20)            | 24 (32.90)         | 14 (12.00) | <10^-7*|
|                                       | [20-29]      | 73 (38.40)         | 25 (34.30)         | 48 (41.00) |         |
|                                       | [30-39]      | 43 (22.60)         | 16 (21.90)         | 27 (23.10) |         |
|                                       | [40-49]      | 22 (11.60)         | 6 (8.20)           | 16 (13.70) |         |
|                                       | [50-59]      | 12 (6.30)          | 2 (2.70)           | 10 (8.50)  |         |
|                                       | ≥ 60         | 2 (1.10)           | 0 (0.00)           | 2 (1.70)   |         |
| Smoking history, n (%)                | Male         | 23 (21.10)         | 7 (9.60)           | 16 (13.70) | 0.40   |
|                                       | Female       | --                 | --                 | --         |         |
| Prevalence of weight categories, n (%)| Underweight, BMI<18.5 Kg/m² | 42 (22.10) | 19 (26.00) | 23 (19.70) | 0.45 |
|                                       | Normal weight, BMI=18.5–25.0Kg/m² | 124 (65.30) | 45 (61.60) | 79 (67.50) |         |
|                                       | Overweight, BMI=25.0–29.9Kg/m² | 21 (11.10) | 8 (11.00) | 13 (11.10) |         |
|                                       | Obesity, BMI ≥30 Kg/m² | 3 (1.50) | 1 (1.40) | 2 (1.70) |         |
| Other associated diseases, n (%)      | Low visual acuity | 63 (33.20) | 14 (19.20) | 49 (41.90) | <10^-7* |
|                                       | Diabetic retinopathy | 40 (21.00) | 11 (15.10) | 29 (24.80) | 0.04*   |
|                                       | Diabetic nephropathy | 31 (16.30) | 1 (1.40) | 30 (25.70) | <10^-7* |
|                                       | Hypertension | 30 (15.80) | 6 (8.20) | 24 (20.50) | 0.02*   |
|                                       | Hyperthyroidism | 20 (10.70) | 0 (0.00) | 20 (17.20) | <10^-7* |
|                                       | Hypothyroidism | 6 (3.60) | 12 (16.40) | 0 (0.00) |         |
|                                       | Anemia | 60 (31.60) | 22 (30.10) | 38 (32.50) | 0.73   |
|                                       | Dyslipidemia | 7 (3.70) | 2 (2.70) | 5 (4.30) | 0.58   |
| Symptoms and signs, n (%)             | Weight loss | 81 (42.60) | 30 (41.10) | 51 (43.60) | 0.73   |
|                                       | Polyuria-Polydipsia | 171 (90.00) | 65 (98.90) | 106 (90.60) | 0.54   |
|                                       | Asthenia | 54 (28.40) | 15 (20.50) | 39 (33.30) | 0.05*   |
|                                       | Overeating | 107 (56.30) | 32 (43.80) | 75 (64.10) | 0.03*   |
| Medical care, n (%)                   | Diabetic foot | 29 (15.30) | 5 (6.80) | 24 (20.50) | <10^-7* |
|                                       | Ketosis on inaugural diabetes | 25 (13.20) | 13 (17.80) | 12 (10.30) | 0.09   |
|                                       | Ketosis on diabetes | 41 (21.60) | 14 (19.20) | 27 (23.10) | 0.64   |
|                                       | Severe hyperglycemia | 14 (7.40) | 6 (8.20) | 8 (6.80) | 0.58   |
|                                       | Severe hypoglycemia | 6 (3.20) | 3 (4.10) | 3 (2.60) | 0.50   |
| Family history, n (%)                 | Hypertension | 32 (16.80) | 11 (15.10) | 21 (17.90) | 0.60   |
|                                       | Type 1 diabetes | 22 (11.60) | 8 (11.00) | 14 (12.00) | 0.73   |
|                                       | Type 2 diabetes | 79 (41.60) | 25 (34.20) | 54 (46.20) | 0.10   |
|                                       | Gout | 8 (4.20) | 5 (6.80) | 3 (2.60) | 0.15   |

(*) percentages were compared with Chi-square test, p≤0.05 was considered as significant; BMI: body mass index.
Table 2: Comparison of clinical characteristics between patients’ serum TSH levels subgroups

| Variables                             | All Patients, n=351 | TSH < 2.5 (μIU/mL), n=155 | TSH ≥ 2.5 (μIU/mL), n=196 | p-value |
|---------------------------------------|---------------------|----------------------------|----------------------------|---------|
| **Mean±SD**                           | 95% CI              | **Mean±SD**               | 95% CI                     |         |
| Mean age (years)                      | 29.25 ± 11.39       | 27.62-30.88               | 25.60 ± 10.11              | 23.24-27.96 | 31.52 ± 11.59 | 29.40-33.64 | <10−7* |
| Diabetes duration (years)             | 12.20 ± 8.45        | 10.99-13.41               | 9.48 ± 8.01                | 7.61-11.35 | 13.90 ± 8.30 | 12.38-15.42 | <10−7* |
| Age at 1st diagnosis (years)          | 17.07 ± 9.04        | 15.77-18.36               | 16.15 ± 9.16               | 14.01-10.29 | 17.64 ± 8.95 | 16.00-19.20 | 0.27   |
| Body height (m)                       | 1.66 ± 0.07         | 1.65-1.68                 | 1.65 ± 0.07                | 1.64-1.67 | 1.67 ± 0.08 | 1.66-1.69 | 0.12   |
| Body weight (Kg)                      | 58.63 ± 11.67       | 56.85-60.40               | 57.01 ± 11.71              | 54.16-59.87 | 59.68 ± 11.58 | 57.41-61.96 | 0.14   |
| BMI (Kg/m²)                           | 21.00 ± 3.55        | 20.46-21.54               | 20.82 ± 3.65               | 19.93-21.71 | 21.12 ± 3.50 | 20.43-21.01 | 0.59   |
| Waist circumference (cm)              | 81.72 ± 10.41       | 78.88-84.56               | 78.63 ± 6.55               | 75.13-82.12 | 83.03 ± 11.40 | 79.25-86.80 | 0.15   |
| SBP (mmHg)                            | 113.1 ± 13.4        | 111.2-115.0               | 109.2 ± 10.7               | 106.7-111.7 | 115.6 ± 14.3 | 113.8-118.2 | 0.001* |
| DBP (mmHg)                            | 65.7 ± 9.3          | 64.4-67.1                 | 63.6 ± 9.1                 | 61.4-65.7 | 67.1 ± 9.2 | 65.4-68.8 | 0.01* |
| Fasting plasma glucose (g/L)          | 2.92 ± 1.32         | 2.73-3.11                 | 2.77 ± 1.21                | 2.48-3.05 | 3.02 ± 1.38 | 2.76-3.27 | 0.20   |
| HbA1c (%)                             | 9.69 ± 2.21         | 9.34-10.04                | 9.31 ± 2.15                | 8.75-9.87 | 9.93 ± 2.22 | 9.47-10.38 | 0.09   |
| hs CRP (mg/L)                         | 18.55 ± 40.76       | 9.17-27.93                | 6.61 ± 14.02               | 2.40-10.02 | 3.64 ± 50.21 | 14.71-58.19 | 0.001* |
| Total cholesterol (g/L)               | 1.60 ± 0.35         | 1.54-1.66                 | 1.61 ± 0.32                | 1.52-1.70 | 1.59 ± 0.37 | 1.51-1.67 | 0.77   |
| HDL-c (g/L)                           | 0.43 ± 0.12         | 0.41-0.46                 | 0.47 ± 0.12                | 0.44-0.51 | 0.41 ± 0.11 | 0.38-0.44 | 0.008* |
| LDL-c (g/L)                           | 0.95 ± 0.28         | 0.89-1.00                 | 0.98 ± 0.26                | 0.90-1.07 | 0.92 ± 0.30 | 0.85-1.00 | 0.31   |
| Triglycerides (g/L)                   | 0.92 ± 0.62         | 0.82-1.02                 | 0.79 ± 0.45                | 0.67-0.91 | 1.00 ± 0.70 | 0.85-1.15 | 0.04* |
| TC/HDL-c                              | 3.83 ± 1.14         | 3.61-4.04                 | 3.61 ± 0.91                | 3.30-3.91 | 3.95 ± 1.23 | 3.65-4.24 | 0.14   |
| LDL/HDL-c                             | 2.30 ± 0.85         | 2.14-2.46                 | 2.16 ± 0.75                | 1.91-2.40 | 2.38 ± 0.89 | 2.16-2.60 | 0.19   |
| TG/HDL-c                              | 2.45 ± 2.25         | 2.02-2.88                 | 1.93 ± 1.36                | 1.49-2.38 | 2.73 ± 2.57 | 2.12-3.35 | 0.03* |
| Creatinine (mg/L)                     | 13.62 ± 18.48       | 10.76-16.48               | 7.69 ± 5.93                | 6.16-9.23 | 17.07 ± 22.12 | 12.75-21.40 | 0.002* |
| Urea (g/L)                            | 0.42 ± 0.41         | 0.36-0.49                 | 0.24 ± 0.10                | 0.22-0.27 | 0.53 ± 0.48 | 0.44-0.63 | <10−7* |
| Microalbuminuria (mg/24h)             | 146.55 ± 436.96     | 54.51-238.60              | 40.75-70.50               | 14.19-67.32 | 218.42-553.14 | 65.95-370.88 | 0.05* |
| TSH (μIU/mL)                          | 4.79 ± 9.45         | 3.44-6.15                 | 1.65 ± 0.79                | 1.46-1.83 | 6.76 ± 11.62 | 4.63-8.89 | <10−7* |
| Anti-TPO (IU/mL)                      | 76.57 ± 114.11      | 47-109-106.05             | 7.99 ± 10.04               | 2.43-13.56 | 99.42 ± 123.66 | 62.77-136.58 | 0.006* |

(*) means were compared with independent sample Student’s t-test; a p<0.05 was considered as significant; SD: standard deviation; CI: confidence interval; HbA1c: glycosylated hemoglobin; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; hs-CRP: high-sensitivity C-reactive protein; TC: total cholesterol; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TG: triglycerides; TSH: thyroid-stimulating hormone; Anti-TPO: anti-thyroid peroxidase antibodies.
Table 3: Crude “Odds Ratio” of blood lipid ratios quartiles associated with serum TSH levels

| Variables | TSH < (2.5 μIU/mL), n=73 | TSH ≥ 2.5 (μIU/mL), n=117 | Odds ratio (95% CI OR) | p-value |
|-----------|---------------------------|-----------------------------|------------------------|---------|
| TC/HDL ratio |                           |                             |                        |         |
| 1<sup>st</sup> quartile (2.09-3.00) | 12 (31.6) | 15 (21.4) | Reference | --- |
| 2<sup>nd</sup> quartile (3.01-3.63) | 11 (28.9) | 16 (22.9) | 1.61 [0.39-3.42] | 0.78 |
| 3<sup>rd</sup> quartile (3.64-4.34) | 7 (18.4) | 20 (28.6) | 2.28 [0.72-7.20] | 0.15 |
| 4<sup>th</sup> quartile (4.35-8.10) | 8 (21.1) | 19 (27.1) | 1.90 [0.61-5.83] | 0.26 |
| LDL/HDL ratio |                           |                             |                        |         |
| 1<sup>st</sup> quartile (0.73-1.74) | 13 (34.2) | 14 (20.3) | Reference | --- |
| 2<sup>nd</sup> quartile (1.85-2.13) | 10 (26.3) | 16 (23.2) | 1.48 [0.49-4.43] | 0.47 |
| 3<sup>rd</sup> quartile (2.14-2.74) | 9 (23.7) | 19 (27.5) | 1.96 [0.65-5.85] | 0.22 |
| 4<sup>th</sup> quartile (2.75-5.14) | 6 (15.8) | 20 (29) | 3.09 [0.94-10.11] | 0.06 |
| TG/HDL ratio |                           |                             |                        |         |
| 1<sup>st</sup> quartile (0.45-1.27) | 13 (34.2) | 15 (21.4) | Reference | --- |
| 2<sup>nd</sup> quartile (1.28-1.85) | 8 (21.1) | 18 (25.7) | 0.26 [0.07-0.89] | 0.03* |
| 3<sup>rd</sup> quartile (1.86-2.63) | 12 (31.6) | 15 (21.4) | 0.51 [0.14-1.83] | 0.30 |
| 4<sup>th</sup> quartile (2.64-14.95) | 5 (13.2) | 22 (31.4) | 0.28 [0.08-0.97] | 0.04* |

(*) multivariate logistic regression significant at p = 0.05; CI, confidence interval; OR, Odd ratio; Q, quartiles; TSH: thyroid-stimulating hormone (μIU/mL/L); TC: total cholesterol (g/L); LDL: low-density lipoprotein cholesterol (g/L); HDL: high-density lipoprotein cholesterol (g/L); TG: triglycerides (g/L)

Figure 1: Comparison of lipid ratios levels between patients with serum TSH < 2.5 (μIU/mL) and with serum TSH ≥ 2.5 (μIU/mL) according to the patients’ gender
Figure 2: Prevalence of Anti-TPO according to serum TSH concentrations

DISCUSSION

The objective of the present study was to demonstrate, in patients with T1D, through strong predictors like lipids and their related ratios the risk of developing atherosclerosis by comparing two groups of patients according to their TSH status (patients with TSH < 2.5 µIU/mL vs. patients with TSH ≥ 2.5 µIU/mL).

The distribution of patients by gender showed a slight predominance of females over males (50.50% vs 49.50%). Paruk et al (2016) found that 55.50% of the population diagnosed with type 1 diabetic thyroiditis were females versus 44.5% males with a sex ratio of 0.80. The same observations have been made by Umpierrez et al (2003) and Kalktas et al (2015) in longitudinal studies. Our results are in accordance with the European follow-up studies conclusion where thyroid autoimmunity can be associated with increased age, female gender, and long diabetes duration. Another interesting finding of the present study was that there was no significant association between increased TSH levels and BMI status in T1D patients, which is in agreement with certain studies.

In our patients’ group, we have noticed a significant association between blood pressure (SBP or DBP) and hypertension with higher serum TSH levels. Our findings are in agreement with the previous study which demonstrates that thyroid hormone deficiency has serious effects on the cardiovascular system, and overt hypothyroidism leads to substantial alterations of traditional risk factors for cardiovascular disease including diastolic hypertension and increased systemic vascular resistance, decreased cardiac preload and impaired cardiac performance. Hypothyroidism prevalence was similar to that reported by Paruk et al (2016). However, the prevalence from other African countries including Uganda, Egypt, and Libya ranged between 4.2% and 7.3% which is lower than what we reported (20-22), meanwhile, is also known that hypothyroidism generates opposite cardiovascular changes and is associated with the increased risk for coronary atherosclerosis. With regard to the findings of hyperthyroidism, the prevalence reported by Ghwil et al (2011) was 1%. Whereas our data showed that approximately 6.3% of our patients were affected.

In our study, there was no difference between HbA1c levels in both groups. These results are in accordance with reports from the literature.

Our results showed that there is a significant increase in hs-CRP levels among patients with higher TSH concentrations. Comparable findings regarding increased inflammatory markers such as hs-CRP were encountered in diabetic patients (type 1 or type 2 diabetes) with thyroid hormone abnormalities, represented by higher hs-CRP levels. In addition, other studies in people with T1D have confirmed the relationship between elevated hs-CRP and atherosclerotic cardiovascular disease which reflects high grade atherogenic vascular inflammation process.

We also identified that patients with increased TSH levels and AITD accompanying T1D had a worse lipid profile and their HDL-cholesterol level was significantly lower and triglyceride concentration was higher, these results concord with documented literature.

An important observation of our study was the association of high serum TSH concentrations with increased urine albumin excretion in patients with T1D. Our findings echoes with the observations made by Das et al who established a similar relationship between increased prevalence of microalbuminuria and elevated TSH quartiles in British retrospective cross-sectional study.

Microalbuminuria is well documented in T1D and usually represents endothelial dysfunction by increasing the risk of atherosclerotic cardiovascular disease. Therefore, it can be used as a marker of trans-capillary leakage of lipoproteins and systemic vascular damage may play role in accelerating atherosclerosis.

In this study, the overall prevalence of Anti-TPO positivity was 16.31%. These results are similar to those of the literature in particular Paruk’s et al (2015). The prevalence is also similar to the 15%-30% figure reported in the literature for Western countries. However, this rate is higher than the 7.3%, and 9.5%, reported in other African studies.

In the present study, the ability of higher tops quartiles versus 1st quartile of lipids ratios (TC/HDL, LDL/HDL, and TG/HDL) in association with low versus high-atherosclerosis risk in type 1 diabetic patients was determined according to their TSH levels with the calculation of odds ratio (OR) and the corresponding 95% confidence interval using logistic regression.

The association of TC/HDL and LDL/HDL with atherosclerosis risk at the two higher quartiles was stronger but non-significant, especially in the group of T1D with TSH ≥ 2.5 µIU/mL. All the same, the 4th and the 2nd quartiles of TG/HDL and ratio were significantly higher in T1D patients with increased levels of TSH, indicating relatively increased dyslipidemia, as evidenced through LDL and HDL levels, and an increased cardiovascular risk mainly in these patients. The same conclusions have been reported in a study done by Shivakrishna et al. (2013). Several case-control studies have also established an association between hypothyroidism and atherosclerosis. In their study of subjects with TSH levels of 4.0 µIU/Liter or more, Tchie et al. reported a higher prevalence of coronary heart disease compared to controls with low TSH levels age-matched.

Undeniably, through lipid metabolism disorder, subclinical hypothyroidism contributes to vascular endothelial dysfunction. The results of a meta-analysis of 27 case-control studies revealed that elevated serum TSH levels were positively correlated with dyslipidemia and markers of thyroid dysfunction.
cardiovascular risk. Most recent studies also indicate a close correlation between hypothyroidism, artery wall thickness, stiffness, endothelial dysfunction, and an increased risk of cardiovascular disease.

In addition, the risk of developing atherosclerosis due to high TSH levels has been identified as related to the patient’s gender. Furthermore, lipid ratio rates were significantly higher in men than in women. Thus, the results of the present study indicate that sex hormones may actively contribute to atherosclerosis disease development. Li et al. and Tognini et al. also found that the gender difference had considerable effects on the association between TSH levels and serum lipid levels, and their conclusions were in agreement with those of the present study.

Several hypotheses explain the mechanism of the effects of sex hormones on lipid metabolism, testosterone and estriol differ in different roles. The lipolytic enzymes LPL and HL remove TG from the bloodstream and lower serum chylomicron levels. Androgens play a stimulating role for HL activity, however, estrogens inhibit HL and LPL activities. Testosterone increases lipolysis by stimulating β-adrenergic activity, regulates the genes responsible for the catabolism of HDL, and increases the activity of hepatic lipase. Estrogen, on the other hand, is capable of increasing cholesterol and LDL levels.

In the current study, we investigated anti-TPO levels according to TSH concentrations. Elevated anti-TPO levels were associated with higher TSH values. Our results could be supported by both Whickham conclusions and Bromfield findings who reported that elevated serum TSH and TPO antibodies levels, separately or together are a risk factor for hypothyroidism.

According to the Rotterdam study conducted by Hak et al., an atherogenic role for thyroid antibodies has been suggested since a higher incidence of atherosclerosis has been noted in hypothyroid anti-TPO positive patients. Chronic inflammation in thyroid antibody-positive patients is one of the mechanisms behind this condition, ultimately leading to atherosclerosis.

In this study, we have certain limitations that need to be considered. First, the lack of genetic analysis and the absence of control subjects were excluded because of cost constraints. Second, the temporal relationship between thyroid dysfunction and the presence of anti-TPO could be more assessed by other laboratory measurements such as free triiodothyronine (FT3 and FT4) concentrations and autoantibodies against thyroglobulin (anti-TG). Therefore, only TSH levels and anti-TPO were used to determine the patients’ thyroid status. Despite these limitations, our conclusions allow us to comment on the employment of lipid ratios in the evaluation of atherosclerosis risk in patients with T1D as a vigorous method regardless of gender and TSH status. Likewise, data from the present investigation can be used as further research given the time period of the studies concerning atherosclerosis in type 1 diabetic patients with thyroid dysfunction.

In conclusion, this study’s findings of border line raised levels of triglycerides and decreased HDL-cholesterol concentrations associated with higher serum TSH levels in patients with T1D make it reasonable to suggest an additional increase of cardiovascular risk for affected patients. AITD may especially affect cardiovascular morbidity and mortality in diabetic patients and deteriorated lipoprotein levels represent potentially modifiable risk factors. Therefore, an early screening of potential thyroid dysfunction and associated dyslipidemia is essential for effective prevention of premature heart failure.

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CONFLICT OF INTEREST
The authors declare no conflicts of interest.

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