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Original Article

Relationship between lipid profile, inflammatory and endothelial dysfunction biomarkers, and type 1 diabetes mellitus: a case-control study

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Abstract: Objective: Inflammation is a major factor in endothelial dysfunction (ED) which is the earliest predictor of cardiovascular disease and premature mortality in type 1 diabetes mellitus (T1DM) patients. This study aimed to describe the possible relationship between plasma lipids and inflammatory and ED biomarkers in young Emirati patients with and without T1DM. Methods: This case-control study included 158 patients with T1DM and 157 healthy controls from the local population of the United Arab Emirates (UAE). Anthropometric data, clinical variables, lipid profiles, liver enzymes, HbA1c, inflammatory, and ED biomarkers were measured for all participants using sophisticated techniques and assays. Results: The mean ages ± SD of patients with T1DM and healthy controls was 19.3 ± 6.4 years (59.5% females) and 9.2 ± 6.8 years (61.5% females), respectively. The mean duration of T1DM was 9.3 ± 5.7 years, with HbA1c of 8.9 ± 2.1%. BMI, WC, SBP, and DBP significantly differed between the two groups. The mean lipid profiles (HDL, TG, TC, ApoA, and ApoB), liver enzymes (GGT, ALT), inflammatory (IL-6, adiponectin, TNF-α, hs-CRP), and ED biomarker levels (ICAM-1, VCAM-1, selectin, and ET-1) were also significantly different between patients and controls. Based on Spearman's rank and logistic regression analysis, there was a significant association between elevated lipid profile, liver enzymes, inflammatory markers, and ED markers in T1DM patients compared to controls. Among the biomarkers studied, ApoA, ApoB, and TC were significantly increased in T1DM patients compared to controls. Conclusion: This study revealed a strong association between an elevated lipid profile and inflammatory and ED markers with T1DM, which could lead to cardiovascular events in the UAE population.

Keywords: Type 1 diabetes mellitus, lipid profile, inflammation, endothelial dysfunction, cardiovascular risk

Introduction

Type 1 diabetes mellitus (T1DM) is caused by T-cell-mediated autoimmune destruction of pancreatic β-cells, leading to absolute insulin deficiency. T1DM is the predominant form of diabetes mellitus in childhood and adolescence, with typical symptoms of polyuria, polydipsia, and weight loss [1]. The combined effects of genetic susceptibility, environmental factors, and dietary deficiencies are known to contribute to T1DM. Over the past decades, the prevalence of cardiovascular risk factors, such as central obesity, hypertension, and dyslipidemia has markedly increased in patients with T1DM, regardless of glycemic control [2]. Despite significant advances, individuals with T1DM are at risk of comorbidities, particularly vascular complications [3]. Patients with T1DM have a 4-to-10-fold greater risk of cardiovascular disease (CVD) than healthy controls [4-7].

Inflammation and endothelial dysfunction (ED) have been identified as early markers of vascu-

lar disease in T1DM [8]. Further, the appearance of a pro-inflammatory state at a young age may be a major contributor to the development of CVD later in life by accelerating the formation of atherosclerotic plaques. The pathogenesis of ED in T1DM is complex, with metabolic and hormonal changes impacting insulin deficiency, which leads to decreased nitric oxide levels, increased oxidative stress, and decreased ability to promote vessel dilatation. Oxidative stress is mainly observed as a reactive oxygen species (ROS) that overcomes the scavenging abilities of antioxidants and may be due to a genetic lack of antioxidant enzymes or environmental triggers, such as viral infections [9].

The International Diabetes Federation (IDF) Atlas (2019) estimated that the UAE had a diabetes prevalence of 16.3% in the 20-79 age group. However, data on T1DM prevalence in the UAE population are not available [10, 11]. In a previous local study, dyslipidemia, DM, and hypertension were reported in 34%, 29.5%, and 35% of the cohort, respectively. In the same sample, peripheral vascular disease, history of coronary artery disease and CVD were present in 11.6%, 14.4%, and 3.5% of participants, respectively [12]. A national survey revealed the presence of at least one cardiovascular risk factor in 62.2% of Emirati men younger than 30 years, and at least two factors were present in 24% of these men [13].

The blood levels of various inflammatory and ED biomarkers have been demonstrated to be elevated in different T1DM populations. However, to date, the role of lipid profile, inflammation, or ED in T1DM among the UAE local population has not been reported. Therefore, this study aimed to determine the association between different biomarkers of lipid profile, inflammation, and ED in young patients with type 1 diabetes. This case-control study was conducted to determine the relationship between (1) serum lipid levels [(high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), total cholesterol (TC), lipoprotein-(Aa) (ApoA), and lipoprotein-B (ApoB))]; (2) markers of inflammation [(Interleukin-6 (IL-6), adiponectin, tumor necrosis factor-α (TNF-α), and C-reactive protein (hs-CRP))]; and (3) ED biomarkers [(intracellular adhesion molecule-1 (ICAM), vascular cell adhesion molecule-1 (VCAM), selectin, and endothelin-1 (ET-1))] in cases with and without T1DM.

Materials and methods

Study participants

This is a case control study including 158 T1DM patients and 157 healthy controls. Patients were enrolled from two centers: Sheikh Khalifa Medical City (SKMC) and Tawam Hospital. T1DM was diagnosed according to the 1985 World Health Organization (WHO) diagnostic criteria (WHO Technical Report Series 727; Geneva 1985). All participants were unrelated UAE nationals residing in the Emirate of Abu Dhabi.

Inclusion criteria: patients diagnosed with T1DM based on clinical and laboratory findings (C-peptide levels <0.3 mmol/l) and treated with insulin therapy since diagnosis.

Exclusion criteria: patients diagnosed with other types of diabetes, including maturity-onset diabetes of the young (MODY), T2DM, polyendocrinopathies, and other autoimmune or concomitant diseases.

This study was approved by the Ethics Committee of SKMC (RS-445) and Tawam Hospital, Al-Ain Medical District Human Research Ethics Committee (AAMDHREC): ERH-2016-4255 16-002. The study was conducted in accordance with the Declaration of Helsinki and the institutional ethical committee review. All participants provided written informed consent before participating in the study.

Methods

The plasma levels of lipid profile and hemoglobin A1c (HbA1c) were measured using an automated analyzer Integra 400 Plus (Roche Diagnostics, Germany). Absorbance photometry, turbidimetry, and fluorescence polarimetry were also employed. ApoA, ApoB, and hs-CRP were measured using electrochemiluminescence (ECL) for immunoassay analysis on Cobas e411 (Roche Diagnostic, Mannheim, Germany). Enzyme-linked immunosorbent assays (Invitrogen, Thermo Fischer Scientific Systems) were used to measure IL-6 (EH2IL6), TNF-α (KHC3011), sICAM-1 (BMS 201), VCAM-1

Table 1. Anthropometric and clinical variables for the study participants

	All study subjects (n=315)	Cases (T1DM) (n=158)	Control (n=157)	*p-value*
Age (y)	19.3 ± 6.6	19.3 ± 6.4	19.2 ± 6.8	
Gender, n (%)				
Female	190 (60.3)	94 (59.5)	96 (61.2)	0.764
Male	125 (39.7)	64 (40.5)	61 (38.9)	
Diabetes duration (y)	-	9.3 ± 5.7	-	
BMI (kg/m^2)	24.2 ± 5.5	24.8 ± 5.3	23.7 ± 5.7	0.007
WC (cm)	79.2 ± 15.6	80.6 ± 13.7	77.9 ± 17.2	0.033
SBP (mm Hg)	116.0 ± 10.9	118.0 ± 10.8	114.0 ± 10.6	<0.001
DBP (mm Hg)	72.3 ± 8.8	73.0 ± 10.1	71.5 ± 7.3	0.005

Data are presented as mean ± SD unless otherwise indicated.

(KHT0601), selectin (BMS 205), adiponectin (BMS2032-2), and ET-1 (EIAET-1) following the manufacturers' protocols.

Statistical analysis

Statistical analysis was performed using Stata 16.1 (Stata Corp, College Station, TX, USA). Descriptive statistics were performed to present and compare the characteristics of T1DM patients to those of controls. Continuous variables are presented as means and standard deviations, while categorical variables are presented as counts and percentages. Pearson chi-squared or Fisher's tests were used to compare proportions for categorical variables, and Student's t-test was used to compare means for continuous variables. Lipid profile parameters and inflammatory and ED biomarkers were log-transformed to achieve a normal distribution. Spearman's rank correlations were determined to evaluate the relationships between various parameters and biomarkers among T1DM cases and controls. Univariate and multivariate logistic regression models were used to quantify the association between T1DM and the different parameters and biomarkers. Crude and adjusted (for age, sex, and BMI) odds ratios (ORs) and 95% confidence intervals (CIs) were reported for each one-standard-deviation increase in the levels of parameters and biomarkers. Statistical significance was set at $P \leq 0.05$.

Results

The overall mean age of participants was 19.3 ± 6.6 years, and both groups comprised about 60% women and 40% men. The mean duration of T1DM was 9.3 ± 5.7 yrs. **Table 1** shows the anthropometric measurements of both groups. Body mass index (BMI) (P=0.007), waist circumference (WC) (P=0.033), systolic blood pressure (SBP) (P<0.001), and diastolic blood pressure (DBP) (P=0.005) were greater in the T1DM group than in the control group. Of the control participants, 18.5% and 2.5% were overweight and obese, respectively. In contrast, 50% of the T1DM patients were overweight but none were obese.

According to the lipid profile, HDL, TG, TC, ApoA, and ApoB levels were significantly higher in patients with T1DM than in controls. LDL levels did not differ between the two groups (**Table 2**). As expected, HbA1c was significantly higher among patients with T1DM than controls (8.9 ± 2.1 and 4.9 ± 0.4%, respectively, P<0.001). Further, the liver enzymes GGT and ALT, were significantly different between the groups (P<0.001). The levels of three inflammatory biomarkers, IL-6, TNF-α, and hs-CRP, were significantly higher in patients with T1DM. Among the ED biomarkers, soluble levels of ICAM-1 and VCAM-1 were significantly higher in patients with T1DM than controls. However, selectin levels were significantly lower in the T1DM group than the control group. Significantly higher adiponectin levels and lower ET-1 levels were found in patients with T1DM.

Spearman correlation analysis in the T1DM group revealed a significant positive correlation between LDL and WC, TG, and HbA1c, and a negative correlation between ApoA/ApoB and HbA1c. Diabetes duration also had a significant negative correlation with TG levels in the patient group. However, in healthy controls, BMI and WC had significant positive correla-

Table 2. Lipid profile values, liver enzymes, and inflammatory and endothelial dysfunction biomarker levels in the T1DM and control groups

	All study subjects (n=315)	Cases (T1DM) (n=158)	Control (n=157)	*P-Value*
Lipid Profiles				
HDL (mmol/L)	1.4 ± 0.5	1.5 ± 0.5	1.3 ± 0.4	<0.001
LDL (mmol/L)	2.6 ± 0.8	2.6 ± 0.8	2.6 ± 0.8	0.558
TG (mmol/L)	1.2 ± 1.7	1.4 ± 2.3	0.9 ± 0.5	0.003
TC (mmol/L)	4.8 ± 1.5	5.3 ± 1.9	4.3 ± 0.9	<0.001
ApoA (g/L)	1.9 ± 0.7	2.3 ± 0.8	1.6 ± 0.4	<0.001
ApoB (g/L)	1.1 ± 0.5	1.2 ± 0.5	0.9 ± 0.2	<0.001
Glycemic Profile				
HbA1c (%)	7.1 ± 2.5	8.9 ± 2.1	4.9 ± 0.4	<0.001
Liver Enzymes				
GGT (IU/L)	16.0 ± 8.8	12.9 ± 7.1	19.2 ± 9.3	<0.001
ALT (IU/L)	19.1 ± 15.3	22.0 ± 19.3	16.2 ± 9.1	<0.001
Inflammatory Biomarkers				
IL-6 (pg/mL)	2.5 ± 2.3	3.1 ± 2.8	1.9 ± 1.3	0.003
Adiponectin (ng/mL)	9.5 ± 6.1	10.7 ± 6.5	8.4 ± 5.4	<0.001
TNF-α (pg/mL)	6.9 ± 5.4	7.9 ± 5.8	6.1 ± 4.8	0.012
hs-CRP (mg/dL)	3.5 ± 5.3	4.3 ± 5.3	2.8 ± 5.2	<0.001
Endothelial Dysfunction Biomarkers				
ICAM-1 (ng/mL)	472.0 ± 275.0	538.0 ± 258.0	406.0 ± 276.0	<0.001
VCAM-1 (ng/mL)	759.0 ± 365.0	795.0 ± 310.0	722.0 ± 412.0	<0.001
Selectin (ng/mL)	45.7 ± 30.7	38.8 ± 30.9	52.6 ± 28.9	<0.001
ET-1 (pg/mL)	10.2 ± 8.1	7.5 ± 6.6	12.7 ± 8.6	<0.001

Table 3. Spearman's rank correlation between different lipid profiles and liver enzymes in the T1DM and control groups

		BMI	WC	HbA1c	Duration of diabetes
HDL	T1DM	-0.051	-0.080	-0.126	0.077
	Control	-0.283**	-0.305**	0.003	-
LDL	T1DM	0.123	0.267**	0.138	-0.021
	Control	0.220**	0.267**	0.113	-
TG	T1DM	-0.056	0.046	0.370**	-0.237**
	Control	0.157*	0.272**	0.109	-
TC	T1DM	0.068	0.032	0.076	0.008
	Control	0.278**	0.207**	0.083	-
ApoA	T1DM	0.008	-0.076	-0.048	0.013
	Control	-0.239**	-0.120	0.008	-
ApoB	T1DM	0.063	0.064	0.135	0.023
	Control	0.230**	0.248**	0.016	-
ApoA/ApoB	T1DM	-0.083	-0.159	-0.195*	-0.031
	Control	-0.373**	-0.357**	0.022	-
GGT	T1DM	-0.105	0.033	0.003	-0.006
	Control	-0.224**	-0.032	0.098	-
ALT	T1DM	0.043	0.104	0.060	0.030
	Control	0.348**	0.527**	0.105	-

*P<0.05, **P<0.01.

tions with LDL, TG, TC, ApoB, and ALT, and negative correlations with HDL and ApoA/ApoB (**Table 3**).

In the T1DM group, inflammatory biomarkers (IL-6, TNF-α, and hs-CRP) had significant positive correlations with TC (P=0.003, P=0.001, P= 0.001), ApoA (P=0.002, P=0.040; P=0.001), and ApoB (P<0.001; P=0.024; P<0.001). Further, TNF-α levels showed a significant positive correlation with BMI (P=0.006) and SBP (P=0.039). In the control group, IL-6, TNF-α, and hs-CRP levels had significant positive correlations with WC (P=0.019, P<0.001, and P< 0.001, respectively). Further, TNF-α had a significant positive correlation with BMI (r=0.535, P<0.001), DBP (P=0.010), TC (P=0.044), and ApoB (P=0.003); and a negative correlation with HDL (P=0.026). hs-CRP was positively correlated with BMI (P<0.001) and WC (P<0.001), and

Table 4. Spearman's rank correlation between participant characteristics, lipid profile, and liver enzymes with inflammatory & ED biomarkers in the T1DM and control groups

		Inflammatory Biomarkers				ED Biomarkers			
		IL-6	TNF-α	hs-CRP	Adiponectin	ICAM-1	VCAM-1	Selectin	ET-1
BMI	T1DM	0.020	0.219**	-0.067	-0.117	0.090	-0.120	-0.103	0.111
	Control	0.110	0.535**	0.323**	-0.181**	-0.133	-0.078	0.156	-0.095
WC	T1DM	-0.001	-0.033	-0.012	-0.043	-0.112	-0.121	0.015	-0.098
	Control	0.187*	0.532**	0.282**	-0.183*	0.011	-0.043	0.179*	-0.022
SBP	T1DM	-0.066	0.165*	-0.120	-0.117	0.287**	-0.137	-0.193*	0.250**
	Control	0.003	0.113	0.120	-0.187*	-0.014	-0.068	0.109	-0.057
DBP	T1DM	-0.069	0.041	-0.121	-0.006	-0.054	-0.118	-0.082	-0.002
	Control	0.089	0.205**	0.100	0.067	0.069	-0.028	0.060	0.211**
HDL	T1DM	-0.073	0.093	-0.127	0.185*	0.168*	-0.003	-0.090	0.130
	Control	-0.062	-0.177*	-0.394**	0.471**	0.220**	0.209**	-0.041	0.018
LDL	T1DM	0.150	-0.104	0.128	0.005	-0.182*	0.075	0.036	-0.113
	Control	0.024	0.092	0.094	-0.133	-0.082	-0.178*	-0.011	-0.114
TG	T1DM	0.016	-0.040	0.062	-0.121	-0.145	-0.018	0.079	-0.168*
	Control	0.083	0.152	0.038	-0.156	0.180*	-0.092	0.131	-0.023
TC	T1DM	0.239**	0.254**	0.255**	0.131	0.214**	0.109	-0.015	0.076
	Control	0.024	0.161*	0.137	-0.144	-0.031	-0.119	-0.040	-0.165*
ApoA	T1DM	0.248**	0.165*	0.266**	0.113	0.123	0.072	-0.032	0.130
	Control	-0.028	0.042	-0.085	0.186*	0.297**	0.066	0.069	0.083
ApoB	T1DM	0.297**	0.181*	0.325**	0.090	0.159*	0.127	0.017	0.074
	Control	0.061	0.236**	0.094	-0.089	0.042	-0.037	0.004	-0.002
ApoA/ApoB	T1DM	-0.177*	-0.088	-0.217**	0.044	-0.088	-0.021	0.020	-0.034
	Control	-0.073	-0.224**	-0.137	0.215**	0.147	0.043	0.048	0.014
GGT	T1DM	0.107	-0.330**	0.266**	0.000	-0.203*	0.181*	-0.148	0.308**
	Control	0.083	-0.286**	-0.014	-0.199*	0.127	-0.025	0.123	-0.049
ALT	T1DM	0.162*	-0.055	0.250**	-0.042	-0.020	0.111	-0.033	0.094
	Control	0.157*	0.292**	0.344**	-0.265**	-0.032	-0.145	-0.099	0.030

*P<0.05, **P<0.01.

negatively correlated with HDL (P<0.001). TNF-α was the only inflammatory biomarker that positively correlated with DBP (P=0.010) and ApoB (P=0.003) levels.

In the T1DM group, the ED biomarker, VCAM-1, was correlated with any of the weight status and lipid profile parameters. ICAM-1 had a significant positive correlation with some lipid levels, HDL (P=0.035), TC (P=0.007), and ApoB (P=0.048); and a negative correlation with LDL (P=0.022). ET-1 had a significant negative correlation with TG level (P=0.040) and a positive correlation with SBP (P=0.002). Selectin levels had a significant negative correlation with SBP (P=0.016). Similar to ICAM-1, adiponectin levels were positively correlated with HDL levels (P=0.020). Among the controls, ICAM-1 was significantly positively correlated with HDL (p=0.006), TG (P=0.024), and ApoA (P<0.001). VCAM-1 was positively correlated with HDL (P=0.009) and negatively correlated with LDL (P=0.026) levels. Selectin levels showed a significant positive correlation with WC (P=0.026). ET-1 negatively correlated with DBP (P=0.008) and TC (P=0.039). Adiponectin was significantly negatively correlated with BMI (P=0.0243), WC (P=0.022), and SBP (P=0.019), but positively correlated with HDL (P<0.000) and ApoA (P=0.020) levels (**Table 4**).

The crude and adjusted ORs for the associations between different values, biomarkers, and T1DM are presented in **Table 5**.

Based on logistic regression analysis, T1DM patients were more likely to have higher levels of the lipid markers, HDL, TG, TC, ApoA, and

Table 5. Crude and adjusted ORs of the associations between T1DM and the different lipid profile values and inflammatory and endothelial dysfunction biomarkers

Case Control	Crude ORs				Adjusted ORs#			
	ORs	95% CI		*p*-value	ORs	95% CI		*p*-value
Lipid profile Values								
HDL	1.56	1.23	1.99	<0.001	1.82	1.39	2.38	<0.001
LDL	0.92	0.73	1.14	0.437	0.90	0.71	1.13	0.354
TG	1.43	1.13	1.81	0.003	1.44	1.12	1.83	0.004
TC	2.18	1.65	2.88	<0.001	2.23	1.67	2.96	<0.001
ApoA	4.56	3.12	6.67	<0.001	5.23	3.47	7.90	<0.001
ApoB	2.47	1.84	3.31	<0.001	2.52	1.86	3.40	<0.001
ApoA/ApoB	1.08	0.87	1.35	0.480	1.12	0.89	1.42	0.331
Liver Enzyme								
GGT	0.24	0.17	0.35	<0.001	0.21	0.14	0.32	<0.001
ALT	1.65	1.28	2.12	<0.001	1.62	1.25	2.12	<0.001
Inflammatory Biomarkers								
IL-6	1.47	1.16	1.86	0.001	1.48	1.16	1.87	0.001
Adiponectin	1.43	1.13	1.80	0.003	1.60	1.24	2.06	0.000
TNF-α	1.21	0.97	1.52	0.089	1.16	0.90	1.49	0.257
hs-CRP	1.57	1.24	1.98	0.000	1.58	1.24	2.01	<0.001
Endothelial Dysfunction Biomarkers								
ICAM-1	1.79	1.41	2.27	<0.001	1.80	1.40	2.30	<0.001
VCAM-1	1.36	1.08	1.71	0.010	1.39	1.09	1.77	0.007
Selectin	0.47	0.36	0.63	<0.001	0.47	0.35	0.63	<0.001
ET-1	0.32	0.23	0.44	<0.001	0.32	0.23	0.44	<0.001

Adjusted for age, gender and BMI.

ApoB than controls. In addition, the liver enzymes, ALT, inflammatory markers (IL-6), adiponectin, hs-CRP, and ED biomarkers ICAM-1, VCAM-1, selectin, and ET-1 were likely to be higher in T1DM patients than controls. Patients with T1DM were likely to have decreased levels of LDL, selectin, and ET-1 compared to the controls.

The adjusted ORs according to the sex basis of different markers and logistic regression analysis are presented in **Table 6**. Although the results were similar, LDL displayed a significant correlation in men, but not in women, whereas TG displayed a significant correlation in women compared to men. The liver enzyme, GGT, displayed a significant correlation between the male and female groups. Among the inflammatory markers, IL-6 in females, adiponectin in males, and hs-CRP in both sexes had a significant association. The ED markers ICAM-1, ET-1, and selectin showed significant associations in both sexes, whereas VCAM-1 showed an association in women but not in men (**Table 6**).

Discussion

The present study reports the extensive correlation of different biomarkers in patients with T1DM and compares these correlations to age- and sex-matched controls in a local population of UAE, Emiratis. We observed significant associations between elevated plasma lipid profile and inflammatory and ED biomarkers, which were significantly higher in patients with T1DM. T1DM patients are exposed to various cardiovascular risk factors as well as signs of increased degradation of both inflammatory and ED status.

Patients with T1DM have an imbalance in serum lipids with diabetes duration, leading to macrovascular dysfunction. The occurrence of subclinical inflammation and ED has been reported previously in a similar population of young patients with type 1 and type 2 diabetes. The study emphasized the impact of obesity and dyslipidemia on cardiovascular health in adolescents with small sample sizes among different ethnicities in the UAE [14]. However, in

Table 6. Logistic regression analysis showing the adjusted ORs for different markers in males and females

	Adjusted ORs#							
	Male				Female			
	ORs	95% CI		*p*-value	ORs	95% CI		*p*-value
Lipid Profile								
HDL	2.12	1.33	3.39	<0.001	1.66	1.19	2.31	<0.001
LDL	2.12	1.33	3.39	<0.001	1.03	0.77	1.37	0.856
TG	1.36	0.91	2.03	0.136	1.46	1.07	1.98	0.017
TC	1.98	1.24	3.17	<0.001	2.37	1.64	3.43	<0.001
ApoA	6.91	3.15	15.20	<0.001	4.68	2.88	7.62	<0.001
ApoB	2.17	1.32	3.56	0.002	2.72	1.84	4.01	<0.001
ApoA/ApoB	1.21	0.83	1.78	0.327	1.08	0.80	1.46	0.604
Liver Enzymes								
GGT	0.20	0.11	0.35	<0.001	0.21	0.12	0.36	<0.001
ALT	1.00	0.68	1.49	0.982	2.45	1.62	3.71	<0.001
Inflammatory Markers								
IL-6	1.22	0.85	1.75	0.290	1.69	1.23	2.32	<0.001
Adiponectin	2.48	1.58	3.90	<0.001	1.26	0.92	1.72	0.157
TNF-α	1.00	0.67	1.48	0.983	1.31	0.94	1.84	0.109
hs-CRP	1.58	1.07	2.35	0.023	1.61	1.18	2.19	0.002
Endothelial Dysfunction Biomarkers								
ICAM-1	1.57	1.07	2.30	0.020	1.99	1.43	2.79	<0.001
VCAM-1	1.03	0.73	1.47	0.853	1.74	1.24	2.44	0.001
ET-1	0.28	0.16	0.49	<0.001	0.33	0.22	0.50	<0.001
Selectin	0.31	0.17	0.56	<0.001	0.55	0.39	0.76	<0.001

Adjusted for age and BMI.

the present study, the control group had overt complications. In fact, T1DM patients were in the first decade after diagnosis together with controls, providing an opportunity to address the objectives of the study early in the disease process. This cohort allowed us to compare the inflammatory and ED profiles in the two groups at several levels and examine the mediators for biological relevance.

Similar to our findings, the SEARCH case-control study with and without diabetes reported an association between inflammation and obesity, hyperglycemia, and dyslipidemia in youths. Increased systemic inflammation was found in youths with diabetes compared with youths without diabetes, with similarities in age and Tanner stage, independent of race/ethnicity, sex, hyperglycemia, and obesity. Increased hs-CRP, fibrinogen, and leptin levels were reported to be associated with being overweight or obese, and this relationship did not differ between youths with and without T1DM [14].

In the present study, all values known to promote inflammation and ED were higher in patients with T1DM than the controls. The overall lower levels of ED biomarkers among the controls may explain the lack of association between cardiovascular risk factors and the probability of having higher levels of ED biomarkers. ApoB and blood pressure were the factors most associated with the probability of higher levels of pro-inflammatory proteins in both controls and patients with T1DM. The infiltration of ApoB-rich LDL in the endothelium is well known to initiate the inflammatory process, leading to arterial injuries and ED [15]. Blood pressure determines the probability of a higher TNF-α level. TNF-α a and blood pressure are tightly related [16]. TNF-α is not only involved in inflammation, but also interferes with vascular function in several ways, including promoting the formation of reactive oxygen species, downregulating nitric oxide production, and stimulating vasoconstrictor proteins. Therefore, TNF-α is also a pro-atherogenic mol-

ecule that might stimulate vasoconstriction of vessels, leading to increased blood pressure.

Serum apolipoprotein levels have been reported to be stronger biomarkers of DN than traditional lipid measures. In fact, the associations between serum apolipoproteins (ApoA, ApoB, and the ApoB-to-ApoA ratio) and the presence and severity of diabetic retinopathy in people with diabetes have been reported to be better biomarkers of DN than traditional lipid measures [17]. In the present study, SBP, TC, and ApoB were positively associated with ICAM-1 levels. Further, LDL and GGT levels showed a significant negative correlation with ICAM-1 levels.

hs-CRP, which is a strong predictor of CVD [18], was particularly high among patients with T1DM. According to the American Heart Association, 2 mg/L and 3 mg/L hs-CRP are two levels associated with intermediate and high risks of CVD, respectively. Based on these guidelines, 50% of patients in our study were at an intermediate risk for CVD and 43% were at high risk [19]. Elevated hs-CRP is known to be related to BMI and WC in children with T1DM, healthy controls, and obese children [20].

Similar to HDL, high adiponectin levels have been associated with a lower risk of CVD. However, similar to our study, high levels have also been associated with T1DM [21, 22]. This apparent paradox could be explained by a decrease in adiponectin during puberty [23]. As the age distribution among patients with T1DM shifted toward higher ages relative to the controls, such shift may help to explain the difference between the two groups. Dysregulation of adiponectin secretion and function is possible and may be due to the relationship between adiponectin levels, weight status, and lipid parameters. Adiponectin is known to be inversely correlated with weight status, body composition, and waist circumference, and positively correlated with HDL [24, 25].

In the present study, the controls and patients with T1DM had the same average BMI. Further, waist circumference was greater among the patients. However, the association of adiponectin with weight status parameters was only found among controls. A similar breaking of the relationship between adiponectin and body composition has been described in other studies where the increase in adiponectin with T1DM was not dependent on body composition but rather on other factors, such as HDL [22, 26]. Such findings indicate that changes in the regulation of adiponectin secretion might occur in patients with T1DM, independent of weight status and the main role of HDL, as supported by the greater HDL levels observed among patients with T1DM, and the positive correlation between adiponectin and HDL in the present work. In patients with T1DM, the contribution of HDL was not significant, suggesting that other perturbations may be associated with T1DM. Compensatory mechanisms have been proposed to explain the increase in adiponectin levels in patients with T1DM. Due to its insulin-sensitizing effect, an increased adiponectin level could stimulate glucose uptake in peripheral tissues and suppress glucose production in the liver, thereby contributing to better control of glycemia [26, 27]. Further studies are required to clarify the role of adiponectin in T1DM.

In risk estimate models, the T1DM group revealed that TC and HDL were more important than LDL for predicting adverse cardiovascular outcomes [28]. In another observational study, cardiovascular risk in T1DM was predicted by TC/HDL and non-HDL but not LDL [29]. In the INTERHEART study, the non-fasting ApoB/ApoA ratio was a better predictor of myocardial infarction than any single lipid or apolipoprotein concentration, or any other combination or ratio of measurements [30]. In the Finnish Diabetic Nephropathy Study, the ApoB/ApoA ratio was the best predictor of normoalbuminuria and acceptable glycemic control, whereas ApoB levels were the best predictor in patients with macroalbuminuria [31]. In this study, among all the biomarkers studied, HDL, TG, TC, ApoA, ApoB, ratio of ApoA/ApoB, ALT, IL-6, adiponectin, TNF-α, hs-CRP, ICAM-1, and VCAM-1 were significantly increased in T1DM cases compared to healthy controls. Biomarkers, such as LDL, GGT, selectin, and ET-1 appear to decrease in the T1DM group compared with the control group.

Conclusion

Subclinical inflammation and ED were detected in young patients with T1DM compared to controls in the UAE population. This study revealed

that lipid levels, liver enzymes, and inflammatory and ED biomarkers were significantly higher in the T1DM group than the control group. Furthermore, a significant association was found between ApoA, ApoB, and TC, which may support roles as a major risk factor and highlight their importance in the assessment of patients with T1DM in the prevention of CVD.

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Disclosure of conflict of interest

None.

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