Is subclinical atherosclerosis associated with visceral fat and fatty liver in adolescents with type 1 diabetes?

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Abstract

Introduction: There is a 3-fold higher prevalence of cardiovascular complications in patients with type 1 diabetes. The aim was to assess the relationship between subclinical atherosclerosis and visceral fat and fatty liver in diabetic adolescents.

Material and methods: The study was performed on 110 adolescents with type 1 diabetes (T1D) attending the Pediatric Diabetes Clinic of the University Hospital, Ismailia, Egypt. Their mean age was 14.2 ±0.7 years with a mean duration of diabetes 6 ±0.3 years. They were divided into group 1 which consisted of 55 adolescents with T1D and normal carotid intima media thickness (cIMT) and the second group which included 55 adolescents with T1D and subclinical atherosclerosis. All adolescents were normotensive, normo-albuminuric and had no retinopathy. Visceral fat thickness was measured as the distance between the anterior wall of the aorta and the posterior surface of the rectus abdominis muscle. Hepatic steatosis was diagnosed based on enlarged liver size and evidence of diffuse hyper-echogeneity of liver relative to kidneys.

Results: The mean visceral fat was significantly higher in adolescents with increased cIMT (4.8 ±1.6) than in the normal thickness group (3.9 ±1.4). Liver size was also significantly larger in the former group (13.73 ±2.26 versus 12.63 ±2.20) (p = 0.022). After adjusting for other variables, logistic regression demonstrated that glycated hemoglobin (HbA₁c) and fatty liver are independent factors affecting cIMT, OR = 1.426 (p < 0.05) and OR = 4.71 (p < 0.05).

Conclusions: In the present study, fatty liver and HbA₁c were associated with subclinical atherosclerosis in lean adolescents with T1D.

Key words: subclinical atherosclerosis, type 1 diabetes, fatty liver, visceral fat area.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is rapidly becoming the most common liver disease worldwide [1]. The prevalence of non-alcoholic fatty liver disease in the general population of Western countries is 20–30% [1]. A meta-analysis by Anderson et al. reported that the pooled mean prevalence of NAFLD in children/adolescents from general population studies was 7.6% (95% CI: 5.5–10.3%) and 34.2% (95% CI: 27.8–41.2%)
in studies based on child obesity clinics [2]. Prevalence of NAFLD in type 1 diabetes (T1D) is 4.7% [3].

Early assessment of the arterial damage is important to prevent future vascular risk since subclinical atherosclerosis can be reversible if detected early and intervention is provided [4]. A systematic review and meta-analysis of 7 cross-sectional studies confirmed that NAFLD is strongly associated with increased cIMT and an increased prevalence of carotid atherosclerotic plaque. Individuals identified with carotid disease should be evaluated for NAFLD and vice versa [5]. Most studies of NAFLD and subclinical atherosclerosis are conducted on obese adolescents.

There has been a great deal of controversy regarding the accuracy of ultrasound diagnosis of fatty liver, but many encouraging results have validated the use of ultrasound. A sensitivity of 91.7% and a specificity of 100% for ultrasound fatty liver detection were reported by Hamaguchi et al. [6]. Similarly, Palmentieri et al. [7] compared ultrasound with liver biopsy findings in 235 patients and found that the sensitivity, specificity, positive predictive value and negative predictive value for calculating at least 30% steatosis were 91%, 93%, 89% and 94%, respectively.

This study was undertaken to evaluate the relationship between subclinical atherosclerosis and visceral fat and fatty liver in diabetic adolescents.

Material and methods

The study was performed on 110 adolescents with T1D (diagnosis according to International Society for Pediatric and Adolescent Diabetes (ISPAD) Consensus Guidelines 2014 criteria) attending the Pediatric Diabetes Clinic of Suez Canal University Hospital, Ismailia. Their mean age was 14.2 ±0.7 years. Their mean duration of diabetes was 6 ±3 years. The goal was to assess the relationship between subclinical atherosclerosis and visceral fat and fatty liver. This study was a case-control study. Group 1 consisted of 55 adolescents with T1D and normal carotid intima media thickness (cIMT). The second group included 55 adolescents with T1D and subclinical atherosclerosis. There was no significant difference between the two groups as regards weight, height, body mass index (BMI) or waist circumference. Subclinical atherosclerosis was defined as two standard deviations (SD) above the normal Egyptian value. Normal cIMT for females was considered 0.46 ±0.1 and for males 0.52 ±0.07 [8–10]. The two groups were matched in age, sex and height. All studied adolescents had a BMI value between the 25th and the 85th centile. Height, weight, and BMI were measured according to the Egyptian growth curves for children and adolescents [11]. All adolescents were normotensive, normo-albuminuric and had no retinopathy. Adolescents who were only on insulin therapy were included; any adolescents on other medications were excluded. There were no participants included who had been previously diagnosed with metabolic syndrome. Both groups were matched for Tanner staging.

Laboratory investigations

Venous blood samples were taken in the morning and after an overnight fast (10–12 h). Serum total cholesterol and triglyceride concentrations were measured using standard enzymatic methods (Kuksis and Myher 1984). Glycosylated hemoglobin was determined using a fully automated Electro-Chemiluminesence Cobas e 411 (Roche Diagnostics, Germany) [9]. Good metabolic control was considered at glycated hemoglobin (HbA1c) < 7.5%. The American Diabetes Association currently recommends that adolescents under the age of 18 diagnosed with T1D strive to maintain an HbA1c level lower than 7.5%. An adolescent was considered to have a poor metabolic control if HbA1c was > 8.5%. Recent evidence has shown that there is a greater risk of harm from prolonged hyperglycemia that would occur if adolescents maintained an HbA1c of 8.5% [12, 13].

Imaging studies

Each participant in the study was subjected to carotid, visceral fat volume assessment and ultrasoundography to detect fatty liver.

Carotid

Doppler ultrasound on carotid artery using a Philips HD11, linear array probe 12 MHz was performed. The estimation of cIMT was done in the radiology department at Suez Canal University Hospital with the adolescent in a supine position. The same experienced doctor scanned all the adolescents using the same equipment. He was blinded to study subjects concerning their clinical and laboratory characteristics. All studies were done following a predetermined, standardized scanning protocol for the right and left carotid arteries, using images of the far wall of the distal common carotid arteries and carotid bulbs according to the Mannheim common cIMT consensus [14]. Each common carotid artery segment was measured. Four measurements of the intima-media thickness were averaged together, in order to give the mean common carotid intima-media thickness for each side.

Visceral fat volume

Sonography measurements were performed using a linear-array probe (Philips Ultrasound

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Imaging System, Italy) (7.5 MHz and 42 mm) in a supine position. It was kept perpendicular to the skin on the upper median abdomen, and a longitudinal scan was done at the midpoint between the xiphoid appendix and the navel along the alba line with regard to the surface of the liver, to be almost parallel to the skin. Subcutaneous fat thickness and area were measured on the xipho-umbilical line in both longitudinal and transverse views. Measurements were taken 3 times directly from the screen using the electronic calipers at the inner edge of the skin and at the outer edge of the alba line and the fat-muscle interfaces for area. Pre-peritoneal fat thickness or visceral-fat thickness and area were measured at the same sites and views. In this case, measurements were taken at the inner edge of the alba line and at the peritoneal line for thickness and area. Visceral fat thickness was measured as the distance between the anterior wall of the aorta and the posterior surface of the rectus abdominis muscle [15].

Fatty liver

Hepatic ultrasonography scanning was performed by an experienced radiologist who was blinded to clinical data by using an abdominal convex 3.5–5 MHz transducer. Hepatic steatosis was diagnosed by characteristics sonographic features, i.e. enlarged liver size, diffuse hyper-echogenicity of liver relative to kidneys, ultrasound beam attenuation and poor visualization of intrahepatic vessel borders and diaphragm [16]. Liver size ≥ 95th centile for age and sex was reported as hepatomegaly [17].

Ethical considerations

This study was performed after obtaining signed informed parental consent. A signed consent form was also obtained from each adolescent above 12 years. The bioethics committee of the University Hospital approved the protocol.

Statistical analysis

Comparisons between groups were made using Student’s t-test. Statistical correlations were determined by the non-parametric Spearman’s test. Multivariate logistic regression models were used to identify independent factors associated with subclinical atherosclerosis in patients with T1D. Factors were considered independently associated with outcome parameters if \( p < 0.05 \).

Results

There were no significant differences between the two groups regarding weight, height, BMI, or waist circumference (Table I). The mean HbA\(_1c\) was significantly higher in the increased cIMT group (8.27 ±1.98) compared to the normal cIMT group (7.96 ±1.45), \( p < 0.05 \) (Table I). No significant difference in subcutaneous fat thickness was found between the two groups. The mean visceral fat was significantly higher in the increased cIMT group (4.8 ±1.6) than in the normal cIMT group (3.9 ±1.4), \( p = 0.007 \). Liver size was significantly large in adolescents with increased cIMT (13.73 ±2.26) than those with normal cIMT (12.63 ±2.20), \( p < 0.05 \) (Table I). cIMT correlated with height, to-

| Table I. Anthropometric measurements, baseline laboratory values, measurements of liver size and aortic intimal media thickness in the two study groups |
|---------------------------------|-----------------|-----------------|-----------------|
| Parameter                       | Mean ±2 SD      |                  | P-value         |
|                                 | Normal cIMT     | Increased cIMT  |                 |
| Weight                          | 50 ±9           | 50 ±11          | 0.746           |
| Height                          | 1.47 ±0.11      | 1.49 ±0.12      | 0.409           |
| BMI                             | 23.3 ±4.6       | 22.4 ±4.4       | 0.233           |
| Waist circumference             | 68 ±8           | 69 ±8           | 0.929           |
| HbA\(_1c\)                      | 7.96 ±1.45      | 8.27 ±1.98      | 0.007*          |
| LDL                             | 85 ±29          | 86 ±32          | 0.809           |
| HDL                             | 60 ±15          | 62 ±25          | 0.702           |
| Cholesterol                     | 165 ±36         | 161 ±49         | 0.961           |
| Triglycerides                   | 92 ±26          | 106 ±45         | 0.115           |
| Liver size [cm]                 | 12.63 ±2.20     | 13.73 ±2.26     | 0.022*          |
| Visceral fat [cm]               | 3.9 ±1.4        | 4.8 ±1.6        | 0.007*          |
| Subcutaneous fat [cm]           | 6.5 ±2.8        | 7.1 ±3.1        | 0.07            |

*\( p < 0.05 \) is significant.
tal daily insulin dose, HbA1c, visceral fat, liver size and triglycerides (Table II).

Logistic regression was used to test and estimate the dependence of cIMT based on its relationship with a set of independent variables. After adjusting to other variables, it was shown that HbA1c and fatty liver are independent factors affecting cIMT, where adolescents with fatty liver had higher risk for subclinical atherosclerosis (OR = 4.71, p < 0.05), and higher HbA1c had a substantial risk for subclinical atherosclerosis (OR = 1.426, p < 0.05) (Table III). 

Discussion

The T1D is a known risk factor for arterial atherosclerosis. Individuals with T1D have a three times higher risk of developing atherosclerotic diseases [18]. The cIMT is a strong predictor of future cardiovascular events and is associated with conventional markers of cardiovascular risk such as age, diabetes and serum cholesterol [19, 20]. The cIMT has been considered a screening tool in studies addressing the high risk of cardiac diseases in subjects with and without diabetes and has been correlated with cardiac risk factors [21, 22]. Furthermore, some studies have shown that carotid ultrasonography is more sensitive for detection of subclinical atherosclerosis than the coronary artery calcification score [23]. Age and gender were listed as non-modifiable atherosclerotic risk factors in adults. However, carotid intima media thickness is not influenced by age or gender in the pediatric age group [1], which is in accordance with our results that indicated age as a significant predictor of cIMT [24]. Research investigating risk factors predicting cIMT in pediatric diabetic patients has proven challenging [25]. Scattered follow-up studies indicate that factors such as HbA1c, BMI, disease duration and serum LDL influence progression of cIMT [26]. Our study established the following conditions as cardiac risk factors in adolescents with T1D: HbA1c, fatty liver and visceral fat. The NAFLD has been found in up to 11.3% of children with type 1 diabetes, compared to 2.6% of children in the general population [1, 3]. The possible mechanisms linking NAFLD and cardiovascular disease include inflammation, oxidative stress, insulin resistance, ectopic adipose tissue distribution, dyslipidemia and endothelial dysfunction [5]. This was supported in the current study as the results showed that cIMT increases in patients with poor glycemic control and those with an increased amount of visceral fat and liver size. Although obesity is the most important cause of NAFLD among adolescents, it is important to note that a transient insulin resistant state occurs during puberty [27]. This state worsens the insulin resistance present in obese children and in turn accelerates the progression to metabolic syndrome and type 2 diabetes. In obese individuals, the co-occurrence of obesity and puberty represents a high degree of insulin resistance. The β-cell is not always able

| Table II. Correlation between cIMT and other variables |
|-----------------------------------------------|
| **Parameter** | **r** | **P-value** |
| Duration of diabetes [years] | 0.097 | 0.376 |
| Weight | 0.051 | 0.05 |
| Height | 0.155 | 0.038* |
| BMI | −0.057 | 0.442 |
| Waist circumference | −0.005 | 0.95 |
| Blood pressure | 0.066 | 0.411 |
| Total insulin dose unit | 0.248 | 0.019** |
| Visceral fat | 0.22 | 0.003** |
| Liver size | 0.185 | 0.013** |
| Subcutaneous fat | 0.07 | 0.349 |
| HbA1c | 0.225 | 0.003** |
| LDL | −0.053 | 0.478 |
| HDL | −0.004 | 0.963 |
| Cholesterol | −0.081 | 0.276 |
| Triglycerides | 0.175 | 0.02* |
| ALT | −0.027 | 0.73 |
| AST | −0.118 | 0.132 |

*P < 0.05 is significant, **p < 0.01 is highly significant.

| Table III. Logistic regression used to test and estimate the dependence of cIMT based on its relationship with a set of independent variables |
|-----------------------------------------------|
| **Parameter** | **Odds ratio** | **P-value** | **Sig.** | **95% CI for odds ratio** |
|----------------|---------------- |------------ |-------- |------------------------|
| Age [years] | 1.109 | 0.338 | NS | 0.898 | 1.369 |
| Visceral fat | 1.324 | 0.085 | NS | 0.962 | 1.823 |
| HbA1c | 1.426 | 0.011 | S | 1.084 | 1.876 |
| Fatty liver | 4.718 | 0.039 | S | 1.083 | 20.542 |
to produce enough insulin to maintain glycemic control [27–31]. Our study showed a significant association between poor glycemic control in T1D adolescents and visceral fat and increased cIMT as an indicator of subclinical atherosclerosis. The accumulation of triglycerides in hepatocytes is predominantly derived from increased free fatty acid efflux from adipose tissue to the liver beside hepatocyte lipotoxicity, stimulation of chronic necro-inflammatory and the fibrogenic response. Most experts believe that fat accumulation in the liver is the first step, but this alone may not be enough to induce progressive liver damage [32]. Al-Hussaini et al. reported that vascular variables were related only to serum triglyceride levels but not to serum HDL cholesterol [26]. This was found in our study to be within normal, probably due mostly to the younger age of the studied adolescents. A systematic review and meta-analysis of seven cross-sectional studies (involving 3497 subjects) confirmed that NAFLD diagnosed on ultrasonography is strongly associated with both increased cIMT and increased prevalence of carotid atherosclerotic plaques [28]. These results are in agreement with the results of the current study, as we reported that liver size and visceral fat were significantly correlated with cIMT. The finding of fatty liver in T1D adolescents may be interpreted by the pathobiological interrelated factors including insulin resistance, increased oxidative stress, altered mitochondrial permeability, hormonal imbalance, proinflammatory cytokines, endothelial dysfunction, increased systolic blood pressure and diastolic dysfunction, among other mediators that are induced by poor metabolic control [33–38]. This study shows that adolescents with increased HbA1c have increased cIMT. This is in accordance with Atwa and Shora, who demonstrated that good glycemic control and normal adiponectin levels may reverse subclinical atherosclerotic change in T1D children [12] and found a mean cIMT of 0.40 mm in children with T1D. On the other hand, Järvisalo et al. found no difference in cIMT in children with T1D in comparison to normal children [38]. These differences may be attributed to the short duration of diabetes in studied groups and the metabolic control states of those patients, any may also be caused by single-gene mutations that alter the course in diabetic patients [39]. In children with NAFLD, an atherogenic lipid profile correlates with severity of liver injury. Several studies have shown evidence of a significant increase of triglycerides with hyperglycemia that is consistent with our study. Bhatia et al. [40] demonstrated in NAFLD an increased level of triglycerides in the form of very low-density lipoprotein (LDL). It is primarily from intrahepatic sources including de novo lipogenesis. Furthermore, delay in triglyceride clearance also contributes to hypertriglyceridemia in NAFLD. Multiple defects in synthesis, secretion and clearance of lipids in patients with NAFLD result in triglyceride deposition in the liver [41]. This study also demonstrated a significant association between visceral fat and cIMT. Several studies have shown the contribution of insulin resistance and hyperactivity of the renin-aldosterone-angiotensin system induced by visceral fat accumulation [41]. A link of subclinical atherosclerosis was found in this study with high visceral adipose tissue in adolescents with T1D compared with control subjects. ectopic fat may have greater lipotoxic effects and is linked with adverse cardiometabolic risks and atherosclerosis [42, 43].

In conclusion, fatty liver and HbA1c could be risk factors for subclinical atherosclerosis in T1D patients, and therefore screening for them is recommended by the authors.

**Conflict of interest**

The authors declare no conflict of interest.

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