**Abstract**

**Aim:** This study aimed to investigate the association between carotid intima-media changes that play a part in the atherosclerotic process in childhood obesity and fibrin monomers as an important indicator of fibrin plaque.

**Methods:** This is a cross-sectional study of obese children and non-obese healthy control subjects. Height, weight, body mass index, waist/hip ratio, systolic/diastolic blood pressures were recorded, in addition, biochemistry, hemogram, fibrin monomers and d-dimer were measured in both groups. Right and left common carotid intima-media thicknesses were measured by ultrasonography and mean carotid intima-media thickness was calculated.

**Results:** Obese children (n=89, 46.1% girls, median age: 12.6±2.3 years) and healthy control group (n=40, 52.5% girls, median age: 13.2±2.2 years) were comparable in terms of gender, age and puberty stage. Mean carotid intima-media thickness was higher in obese children than the healthy control group (p=0.002). There was no difference between the two groups in terms of fibrin monomers and D-dimer levels. In obese children, there was a weak negative correlation between mean carotid intima-media thickness and fibrin monomers (p=0.030, r=-0.233).

**Conclusion:** In obese children, mean carotid intima-media thickness was determined higher, as an early indicator of atherosclerosis. We want to emphasize that obese children are at risk for cardiovascular disease and should be evaluated in terms of atherosclerosis. This study investigates the relation between increased carotid intima-media thickness and fibrin monomers, in children, the first time in Literature.

**Key Words:** Carotid intima-media thickness, obese children, Fibrin monomers,

What's already known about this topic?

It is possible to reveal the early period of the atherosclerosis process by showing carotid intima medial thickness. Fibrin is a major component of many atherosclerotic plaques.

What does this article add?

Our study investigated the relationship between mean carotid intima-media thickness in
childhood obesity and fibrin monomers. But no positive correlation was found between
fibrin monomers and the carotid intima-media thickness.

**Introduction:**

Obesity, which comes out with excessive fat deposition in the body, is a serious
disease that can be the underlying cause of many diseases and has many psychosocial and
economic consequences. It is considered a public health disease of this century and the
prevalence has been increasing gradually.[1]The prevalence of overweight and obesity among
children and adolescents aged 5-19 has risen dramatically from just 4% in 1975 to just over
18% in 2016. Over 340 million children and adolescents aged 5-19 were overweight or obese
in 2016.[2]Obesity in children and adolescence have major importance because although mostly
preventable, usually tends to track into adulthood by further increasing the risk of late-term
complications. Pediatric obesity is associated with an increased risk of cardiovascular disease
and death related to this.[3] The most important cardiovascular complication of pediatric obesity
is the development of early atherosclerosis.[4]

Fibrin is a major component of many atherosclerotic plaques.[4]Fibrin and fibrin
degradation products, and thrombin could contribute to atherogenesis by their chemotactic
(attracting monocytes/macrophages) mitogenic (stimulating cell proliferation) properties.
Rupture-related plaque progression due to luminal thrombosis and/or plaque haemorrhage is
the most important mechanism underlying the unpredictable rapid progression of coronary
lesions responsible for acute coronary syndromes. Both platelets and fibrin play a role in the
dynamic thrombotic response to plaque rupture.[5]Soluble fibrin monomer appears in the

bloodstream during the early stage of blood coagulation and can provide information regarding the state of thrombotic diseases. Elevated plasma fibrin monomers were suggested to be an early indicator of thrombotic events in the coronary artery of myocardial infarction patients.[6]Another fibrin degradation product 180 kDa D-dimer is also known to be associated with cardiovascular events.[7,8]

It is possible to reveal the early period of the atherosclerosis process by showing carotid intima medial thickness (CIMT). Carotid intima medial thickness measurement is the correct proof of estimating the size of atherosclerotic lesions attempted using the non-invasive technique of B mode real-time imaging.[9]It is a simple and non-invasive clinical tool to evaluate atherosclerosis and predict coronary artery disease.[10]Most studies report a significantly increased CIMT in obese children and adolescents compared with normal-weight controls.[11]

Although early atherosclerosis risk is increased in obese children, the relation of fibrin monomers in atherosclerosis was not studied. It is aimed to determine whether any differences in the coagulation system in terms of fibrin and fibrin degradation products exist between obese and normal weighed children by measurement fibrin particles. It is also aimed to investigate the association between fibrin monomers and carotid intima-media changes considered to play a part in the atherosclerotic process.

**Methods**

The study included 89 obese children and 40 non-obese healthy children as controls. Obese children were enrolled in the Pediatric Endocrinology Department. Healthy children with no health problems admitted for routine check-up or immunization (as the control group) were enrolled at Pediatric Outpatient Clinics.

At enrollment, obese and control subjects underwent physical examination including weight (kg), standing height (cm), body mass index (BMI), weight standard deviation score (SDS), BMI-SDS, waist-to-hip ratio (waist circumference/hip circumference), systolic (SBP) and diastolic blood pressure (DBP) measurements. None of the patients had any concomitant disease (e.g., hypothyroidism, Cushing syndrome). Neither the patients nor the controls were on drugs affecting the insulin action or insulin secretion, lipid metabolism and/or homeostasis (e.g. glucocorticoid therapy) or a history of medication use that could affect the carotid artery IMT.

Weight was measured to the nearest 0.1 kg on a standard beam scale with the subject dressed only in light underwear and without shoes. Height was measured without shoes using a Harpenden stadiometer (Harpenden, Holtain Ltd., UK) to the nearest 0.1 cm. All the measurements were repeated twice.

The weight status was recorded as BMI, calculated as follows: BMI=weight (kg)/height (m$^2$). A child was considered obese if a BMI exceeded the 95th percentile using population-specific data.[12,13]The BMI-standard deviation score was calculated as follows: BMI-SDS: individual measurement-population mean/population standard deviation.

The distribution of fat mass was expressed by the waist-to-hip ratio (waist circumference/hip circumference). The waist circumference was measured at its smallest point between the iliac crest and rib cage, and the hip circumference was measured at its largest width over the greater trochanters. The resting SBP and DBP were measured twice in

the right arm after a 10-minute (min) rest in the supine position by one investigator using a standard mercury sphygmomanometer and a validated protocol.[14] All subjects were considered hypertensive when the SBP and/or DBP was > 95th percentile for age, sex and height according to a percentiles chart for Turkish children.[15]

All blood tests were conducted in the Hematology Laboratories of the ** Hospital. After 12 hours of fasting, venous blood samples were obtained from both groups. Two millilitres of venous blood were taken in standard tubes containing 0.072 ml of 75% K3-ethylenediaminetetraacetic acid solution (Beckton Dickinson, USA). An automatic and daily-calibrated hemocytometer device (LH-780, Beckman Coulter, USA) was used to measure haematological parameters; on the same day, blood was taken from the children.

Serum concentrations of glucose, insulin, total cholesterol (TC), triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), thyroid-stimulating hormone (TSH), free thyroxin (fT4), lipoprotein a [Lp(a)], homocysteine, fibrin monomers and D-dimer tests were studied in the laboratory, at the same day blood samples were taken from the children. Fasting TC, TGs, and LDL-C HDL-C concentrations were analyzed using original commercial Olympus kits with Olympus AU640 analyzer (Beckman Coulter, USA). Total plasma homocysteine was measured using a commercial "Chromo system" using the Agilent 1100 HPLC system (Rivak, Türkiye).

Lipoprotein (a) was measured by Beckman Coulter Image Immunochemistry analyzer by using original Beckman Coulter kits.

Four mL of blood was taken to test fibrin monomers and D-dimer, into standard tubes, including a 0.5 ml (1 volume) of a 0.109 M trisodium citrate solution. Following daily internal quality control and calibration, the STA-R machine (Stago, France) using each test kits compatible with the device.

The homeostasis model assessment of insulin resistance (HOMA-IR) index was used to determine insulin resistance. The HOMA-IR was calculated with the following formula: HOMA-IR = [fasting insulin (mIU/ml) x fasting glucose (mmol/L)]/22.5. The ratio over 2.7 was assessed as insulin resistance.[16]

The carotid artery intima-media thickness was measured according to a previously described procedure.[17]The radiologist, who was performing the measurements, was blinded to the participant's case status and obesity-related risk factors. The subjects were examined in the supine position with the head turned extension slightly to the left and then the right. B-mode Ultrasonography of the left t and right carotid arteries was performed with a linear 7.5 MHz transducer Toshiba Xario (Tokyo, Japan) machine.

The 10 mm proximal segment of the carotid to the bulbous of the common carotid artery was measured on each side. Three measurements were taken at the far common carotid artery wall in the longitudinal plane. Then, the mean CIMT calculated by the device was recorded.

The study was approved by the local ethics committee. Written informed consent was obtained from all participants, and informed parental consent was obtained for all children.

Statistical analysis of the data was performed using SPSS for Windows 11.5 software package. The distribution of continuous variables was tested for normality with the Shapiro-Wilk test. The descriptive statistics were presented as mean±SD or median (interquartile range) for continuous variables and the number of cases and (%) for categorical variables. The mean difference was assessed using the student's t-test if the variables had a normal distribution, whereas the Mann-Whitney U test assessed the significance of the median difference if the variables did not have a normal distribution. Chi-square test was used to analyze categorical variables.

Wilcoxon signed-rank test was used to assess a statistically significant change between the left and right side CIMT measurements of the patients in the case group. Spearman correlation analysis was used to determine the relationship between mean CIMT and continuous variables.

P-values <0.05 were considered significant. Bonferroni correction method was used to control Type I mistake in all probable multiple comparisons.

**Results:**

The study included 89 obese children and 40 non-obese healthy children. According to age, gender, Tanner stage of puberty (pubertal or pre-pubertal), height or DBP (Table 1), there was no difference between the patient and control groups. Compared to the controls, obese children demonstrated significant differences in a number of clinical risk factors including body weight, BMI, BMI-SDS and waist/hip ratio (p<0.001). Mean SBPs in obese children and control subjects were 115.6±9.7 mmHg and 105.7±11.2 mmHg, respectively (p=0.001) **(Table 1).**

Haematological parameters were compared in obese children and healthy control group **(Table 2)**. Haemoglobin and mean corpuscular haemoglobin (MCV) were significantly lower. In contrast, total leukocyte count, absolute neutrophil count, platelet count and red cell distribution width (RDW) were significantly higher in obese children than the control group **(Table 2)**.

Compared to the controls, obese children demonstrated elevated AST, ALT, TC fasting insulin level, HOMA-IR and homocysteine. However, no significant differences were found between the obese children and the controls in fasting glucose, TGs, HDL, LDL, Lp (a), TSH, fibrin monomers and D-dimer **(Table 3)**.

Right and left carotid artery IMT was measured in obese and non-obese children. Compared to controls, obese children showed increased left carotid IMT and mean carotid IMT values (p=0.003, p=0.002, respectively) **(Table 4)**.

Weight, height, BMI, waist/hip ratio, SBP and DBP of obese children showed non-significant correlations with the mean CIMT **(Table 5)**.

In obese children, a positive correlation was found between mean CIMT and RDW (p=0.004). Haemoglobin, MCHC and platelet count showed a significant negative correlation with the carotid CIMT (*P*=0.012; 0.002; 0.019, respectively) **(Table 6).**

In obese children serum biochemistry, lipid profile, TSH, fasting insulin, HOMA-IR, homocysteine, D-dimer showed no significant correlation with mean CIMT. However Lp (a) level showed a positive correlation (p=0.006, r:0.294) (Table 6). Fibrin monomers showed a weak negative correlation with mean CIMT in obese children (p=0.030, r=-0.233) **(Table 7).**

**Discussion:**

Obesity is associated with increased production of fibrinogen and fibrin degradation products and reduced fibrinolytic activity.[18,19]However, there is a limited number of studies investigating the relationship between obesity and D-dimer and fibrin degradation products in children. These studies reported a proinflammatory and prothrombotic state with a significantly increased fibrinogen level and increased D-dimer in childhood obesity.[20,21,22]In our study, however, we detected no statistical difference in obese children and healthy control group in terms of fibrin monomers and D-dimer, as the indicators of thrombotic events.

In our study, compared to controls, obese children showed increased mean CIMT values. CIMT was measured as 0.46 mm in obese children. An increased carotid intima-media thickness was determined in obese children compared to controls in the studies. Similar to our study, Vijayakumar et al. (0.48 mm)[23] and hacihamdioğlu et al. (0.49 mm)[24] measured CIMT in obese children. Some studies (Ozguven et al. (0.57 mm) Dabas et al. (0.54 mm)) have measured higher CIMT values.[25,26]We think that the reason for this may use the difference

procedure is measured CIMT. Also, obese children in the studies may have different conditions that affect atherosclerosis, such as metabolic risk factors. İn our study, obese children diagnosed with diabetes mellutus, hypertension and hyperlipidemia were not included. In a study, Min Zhao et al.[27] found that obese children with metabolically unhealthy had higher CIMT than those who were metabolically healthy with obese children. Hypertension, dyslipidemia, a significant degree of insulin resistance and impaired glucose tolerance are risk factors that increase atherosclerosis progression rate. Increased CIMT, which is the early indicator of atherosclerosis, was significantly associated with these risk factors in the investigations.[28,29,30,31,32]According to our study results, mean CIMT did not significantly correlated with SBP/DBP, serum lipid profile, fasting glucose, insulin levels and HOMA-IR in obese children.

In a study including 1106 subjects, 60 to 80 years old, blood viscosity and its major determinants, plasma viscosity, fibrinogen and hematocrit were all linearly related to CIMT, in men. However, no significant associations were found between any of the hemorheological factors and CIMT in women or for tissue plasminogen activator, fibrin, D-dimer, or von Willebrand factor in either sex.[33]

Lipoprotein (a) [Lp (a)] is a highly atherogenic lipoprotein that is under strong genetic control by the LPA gene locus. High concentrations of Lp (a) and genetic variants associated with high Lp (a) concentrations are both associated with cardiovascular disease.[34] Mean CIMT, the surrogate index of atherosclerosis, showed a positive correlation with Lp (a) in obese children, in our study. However, a study including 65 asymptomatic female Japanese subjects (mean age: 60 years) with low serum Lp (a) level, reported that Lp (a) was correlated independently, significantly and inversely with the CIMT.[35] In our study, Lp (a) level showed a positive correlation with CIMT.

Fibrin structure is present in the component of the early phase of atherosclerosis. Fibrin and fibrin degradation products are associated with increased risk of atherosclerosis.[36,37,38]

However, the role of fibrin and fibrin degradation products in atherosclerosis plaque has not been enlightened completely. The relation between CIMT as the early indicator of atherosclerosis and fibrin monomers were investigated in animal studies and a few postmortem human studies. Investigations indicating atherosclerosis relation between fibrin monomers and D-dimer are mostly conducted in adults. In an animal study, the effects of fibrin, fibrinogen, and fibrin degradation products to the instability of atherosclerotic plaque were investigated in rabbit aortic endothelial cells and smooth muscle cells. Matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF) are molecules playing important roles in forming and developing atherosclerosis. In this animal study, fibrinogen, fibrin and fibrin degradation products increased the expression of MMPs and VEGF. Elevated fibrinogen, fibrin, and fibrin degradation products in fibrous caps also contribute to the rupture of atherosclerotic plaques by enhancing endothelial permeability and migration of smooth muscle cells.[38] In another investigation, histological sections (n=74) of coronary arteries of males were stained immunohistochemically, who died due to sudden cardiac diseases. Fibrin structure was determined in the early phase of atherosclerosis, suggesting that fibrin may play a role in the bridge between pre-atheroma and atheroma.[39]

Although we conducted our study considering that CIMT is a sing of atherosclerosis and positive correlation with fibrin monomers, no positive correlation was found in our study. The CIMT value was found to be higher in obese patients compared to the control group. CIMT was measured as 0.46 mm in obese children. However, in the study by Vignatha Sajja et al.[40], the CIMT value of obese patients was found to be 0.50 mm, and the high CIMT value was evaluated as 0.45 mm. Since the CIMT of obese patients in our study was not very high, a

positive correlation with fibrin monomers may not be found. Another reason is that studies showing a positive relationship between atherosclerosis and fibrin monomer show that patients were examined in the acute period or postmortem period when they had complaints about the cardiovascular system. Obese patients included in our study are in the asymptomatic period, and it can be thought that there is no positive relationship with fibrin monomers.

Our study investigated the relationship between carotid intima-media changes, which play a part in the atherosclerotic process in childhood obesity, and fibrin monomers as important indicators of atherosclerotic and thrombotic events. In conclusion, in obese children, mean CIMT was determined higher, as an early indicator of atherosclerosis. We want to emphasize that obese children are at risk for cardiovascular disease and should be evaluated in terms of atherosclerosis. We could not come across a study in the literature, which investigates the relation between CIMT and fibrin monomers, in children. Finally, we would like to emphasize that more comprehensive studies are needed to investigate the relationship between mean CIMT and fibrin monomers in children.

Limitations: This study has some limitations. First, The CIMT of obese patients in our study was not very high. Second, our study was the small sample size. More extensive population-based studies are needed to confirm the results.

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