Accepted manuscript

Carotid intima medial thickness and its association with cardiometabolic risk factors in children with overweight and obesity: A hospital based cross-sectional study

Sabitha Sasidharan Pillai [1,2,3], M.Vijayakumar[1,2], Ajitha Balakrishnan[2,4]

[1]Department of Pediatrics, Government Medical College, Kozhikode, [2]Kerala, India, [3]Center for Endocrinology, Diabetes and Metabolism, Children's Hospital Los Angeles, Los Angeles, CA, Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, CA, [4]Department of Community Medicine, Government Medical College, Thrissur,

Corresponding author: Sabitha Sasidharan Pillai, MD, Current affiliation: Department of Pediatrics, Pediatric Endocrinology Division, Children's Hospital Los Angeles, Keck school of medicine, University of Southern California, California, US, Phone: +1 860 597 1410 Email:ssasidharanpillai@chla.usc.edu

Affiliation at the time of the study: Department of Pediatrics, Institute of Maternal and Child Health, Government Medical College, Calicut, Kerala, India Email: sabithas99@gmail.com

Key words: Children; adolescents; obesity; overweight; carotid intima media thickness

Short title: Carotid intima media thickness and obesity

This peer-reviewed article has been accepted for publication but not yet copyedited or typeset, and so may be subject to change during the production process. The article is considered published and may be cited using its DOI
10.1017/S0007114525000091
The British Journal of Nutrition is published by Cambridge University Press on behalf of The Nutrition Society

Abstract:

A hospital based cross sectional study involving children aged 2-15 years attending the obesity clinic of a tertiary care hospital from January 2016 to March 2018 was carried out to study carotid intima media thickness (cIMT) and its association with cardiometabolic risk factors in children with overweight and obesity. Secondary objective was to compare children with elevated (EcIMT) and normal cIMT (NcIMT). Out of 223 patients enrolled for the study, 102 (45.7%) had elevated cIMT. Mean cIMT of the study participants was 0.41 ± 0.13 mm. Median alanine transaminase levels (27 vs. 24, p=0.006) and proportion of patients with fatty liver (63.7% vs 48.8%, p=0.025) and ≥ 3 risk factors (80.4% vs. 66.1%, p=0.003) were higher in the EcIMT group compared to NcIMT group. Proportion of patients with hypercholesterolemia (36.4% vs. 16%, p=0.024), elevated LDL-C (38.6% vs. 16%, p=0.013), low HDL-C (40.9% vs. 20%, p= 0.027) and dyslipidemia (84.1% vs. 58%, p=0.006) were higher in the pubertal EcIMT group and those with fatty liver (63.8% vs. 45.1%, p=0.034) was higher in the prepubertal EcIMT group compared to pubertal and prepubertal NcIMT groups respectively. No significant correlations were observed between cIMT and various cardiometabolic parameters. Our finding of elevated cIMT in nearly half of the study participants including young children is very concerning as these children are at increased risk of atherosclerotic cardiovascular disease in adulthood. Interventions starting at a young age are important when trajectories are likely to be more malleable and adverse cardiometabolic phenotypes and subclinical atherosclerosis are reversible.

Abbreviations: ALT(alanine transaminase); AST(aspartate transaminase); ASCVD (atherosclerotic cardiovascular disease); BP(blood pressure); BMI(body mass index); cIMT (carotid intima media thickness); DBP(diastolic blood pressure); EcIMT(elevated cIMT); FH(family history); FBG(fasting blood glucose); HbA1c(hemoglobin A1c); HDL-C(high density lipoprotein cholesterol); HOMA-IR(homeostatic model assessment of insulin resistance); IFG(impaired fasting glucose); IAP(Indian Academy of Pediatrics); IR(insulin resistance); LDL-C(low density lipoprotein cholesterol); MAFLD(metabolic dysfunction associated fatty liver disease); MS(metabolic syndrome); NcIMT(normal cIMT); SBP(systolic blood pressure); TC(total cholesterol); T2D(type 2 diabetes); VLDL-C(very low density lipoprotein cholesterol); WC(waist circumference).

Introduction:

The prevalence of Obesity among pediatric population has increased by more than eight fold over the last 4 decades and is a significant public health problem globally(1). Children with obesity are at increased risk for cardiovascular morbidity and mortality in early adulthood. Carotid intima media thickness (cIMT) is considered as an early marker of carotid arterial injury and subclinical atherosclerosis that precedes plaque formation. Subclinical atherosclerosis may start at a young age in conditions at increased risk for atherosclerotic cardiovascular disease (ASCVD) such as obesity(2). Chronic inflammation contributes to the progression of atherosclerosis and risk factors enhances the pathogenesis by hastening the underlying inflammatory process(3). Noninvasive assessment of cIMT with high resolution B-mode ultrasonography helps to identify early atherosclerosis(3). Prior studies observed that children with obesity and increased cIMT were at higher risk for ASCVD in adulthood compared with children without obesity(4). Early recognition of risk factors of vascular health in children is important as the initial lesions of atherosclerosis can be revocable with lifestyle modification(5). There have been few studies on cIMT in children with obesity from South Asia and none in children younger than 5 years of age from Asia(6–9). We aimed to study cIMT and its association with cardiometabolic risk factors in children with obesity and to compare children with elevated and normal cIMT. We hypothesized that among children with obesity metabolic abnormalities will be higher in those with elevated cIMT (EcIMT) compared to those with normal cIMT (NcIMT).

Methods:

This hospital based cross sectional study was conducted in the Department of Pediatrics, Government Medical College, Kozhikode, Kerala, India. Children whose parents had given written consent were included in the study as per the following criteria: children aged 2-15 years with overweight or obesity due to exogenous causes attending the Pediatric obesity clinic during the period from January 1st 2016 to March 31st 2018. Children < 13 years of age are admitted in the pediatric words of government hospitals in Kerala, India as per the Government policy and those ≥ 13 years are admitted and managed in the adult wards. Though both Pediatric and adult outpatient specialty clinics could see patients between13 y - 21 years of age, most patients >15 y of age preferred adult specialty clinics. Hence patients > 15y were not included in our study.

Based on a previous study [6], the mean cIMT of children with overweight and obesity was 0.5±0.1 cm. So we calculated that for similar results with a marginal error 0.02mm in mean cIMT, a sample size of 196 would be sufficient for 5% significance level and 80% power. Overweight and obesity were defined as per the Indian Academy of Pediatrics (IAP) 2015 BMI charts/age for boys and girls respectively (BMI reference curves of adult equivalent cutoff 23 and 27 were considered as overweight and obesity, respectively) for children aged 5-15 years. The 23 and 27 adult equivalent cut-offs lines are suggested by the IAP to define overweight and obesity respectively as Asians are known to have more adiposity and increased cardio-metabolic risk at a lower BMI. For children < 5 years of age, overweight and obesity were defined as per the WHO growth charts for boys and girls respectively: overweight with BMI-for-age > 1 standard deviation above the WHO Growth Reference median; obesity with BMI > 2 standard deviations above the WHO Growth Reference median(10,11). The exclusion criteria were children with genetic, endocrine and pharmacological causes of overweight/obesity or recent history of acute infectious or non-infectious inflammatory disorders.

Preformed questionnaire was used to collect clinical and demographic data. General and systemic examination were performed in all the patients. Electronic weighing machine (Easy Care, Mumbai, Maharashtra, India) was used to measure body weight to an accuracy of 0.1 kg with the participants wearing light clothes and no foot wears. The height was taken using a stadiometer (Prestige height measuring scale, C-117, Mayapuri Industrial Area, New Delhi, India; range, 20-210 cm) to an accuracy of 0.1 cm. Waist circumference (WC) was measured midway between the lowest rib cage and the iliac crest with a non-stretchable tape, to the nearest 0.1 cm, with the subject in a standing position and no clothes covering the measuring area. Pan Indian waist circumference data that represented age and sex specific WC percentiles for Indian children aged 2-18 years were used for WC and the WC percentile > 70 percentile for age and sex was taken as the cutoff (12). Pubertal assessment was done using Tanner's sexual maturity rating: Tanner stage 1 being prepubertal and Tanner stage 2-5 pubertal(13,14). Blood pressure was measured by a trained investigator on the right upper arm with the study participant in the sitting position. Measurements were made by auscultation with a mercury-column sphygmomanometer (ELKOMETER, Anita Industries, India). The average of three consecutive

measurements was used for analysis. Blood pressure (BP) ≥ 90th percentile and > 95th percentile for age, gender and height were taken as elevated BP and hypertension respectively(15) .

Blood was collected after an overnight fast for fasting blood glucose (FBG) plasma insulin, lipid profile, alanine transaminase (ALT), aspartate transaminase (AST), uric acid, and hemoglobin A1c (HbA1c). FBG was measured by glucose oxidase-peroxidase method in HITACHI 912 autoanalyzer using colorimetric method. Fasting insulin was measured with Roche Elecsys 2010 electrochemiluminescent autoanalyzer with an immunoassay format. AST, ALT, uric acid, TC , triglyceride, HDL-C, and VLDL-C were measured with an automated analyzer and LDL-C was calculated by Friedewald equation(16). HbA1c was measured by the Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 using ion-exchange affinity chromatography method.

A diagnosis of metabolic syndrome (MS) was made in children aged 10 years and above in the presence of central adiposity(12) and any 2 of the following criteria: 1) triglycerides levels >95th percentile (0-9 years≥ 100mg/dl; 10-19 years≥ 130mg/dl), 2) high density lipoprotein cholesterol level(HDL-C) < 40mg/dl)(17), 3) systolic or diastolic BP ≥ 90th percentile for the age, gender and height(15), 4) FBG ≥ 100 mg/dl (impaired fasting glucose-IFG)(18).

Hypercholesterolemia (total cholesterol (TC) ≥200 mg/dl), hypertriglyceridemia, high low density lipoprotein cholesterol (LDL-C) (≥ 130 mg/dl) or low HDL-C was accepted as dyslipidemia(17). Hemoglobin A1c < 5.7% was taken as normal(19). Hyperuricemia was diagnosed based on the Mayo clinic laboratories reference value for boys and girls of different age groups(20). The degree of insulin resistance (IR) was determined by the homeostatic model assessment- IR (HOMA-IR) and HOMA-IR ≥ 2. 5 is taken as abnormal(21). Fasting insulin level > 15 mIU/ml in prepubertal children and > 26 mIU/mL in pubertal children was considered as hyperinsulinemia(22). Caliper database that provides a summary of age and sex-partitioned pediatric reference intervals for ALT was used to analyze ALT values(23). Fatty liver was diagnosed based on abnormal ultrasound or ALT greater than twice the upper limit of normal for the age and sex (> 50 IU/L for children < 13 years, 44 IU/L for females 13-18 years and 48 IU/L for males aged 13- 16 years)(23).

A longitudinal view of the distal common carotid artery was obtained from the suprasternal notch with a duplex scanner using a 7.5 MHz sector transducer in supine position. The cIMT

measurements were made in both carotid arteries at 2 cm before bifurcation and average was used for analysis. All B- Mode carotid measurements were done by an experienced radiologist. cIMT measurements were analyzed using the percentile curves proposed by Doyon, et al(24). EcIMT is defined as cIMT > 75th percentile for age and gender in children aged 6-15 years(25). Cut off value for normal cIMT versus increased cIMT in children below 6 years was taken as the 75th percentile cIMT value for 6 years ((0.36 mm for girls and 0.4 mm for boys). Study subjects were grouped into NcIMT) group and EcIMT group based on the cIMT values. Patients were also grouped based on their pubertal status into prepubertal and pubertal groups. Each group was assessed for the prevalence of cardiometabolic risk factors in those with EcIMT compared to those with NcIMT and the correlations between the cardiometabolic parameters and cIMT. Based on cIMT, the study population was divided into quartiles and compared to clinical and cardiometabolic factors. The study was reviewed and approved by the institutional ethical board, IEC number GMCKKD/RP 2018/IEC/191.

Statistical analysis:

Statistical analysis was done using SPSS version 18.0 for Windows. Categorical data was expressed as number (frequency) and percentage. Quantitative data was expressed as mean ± standard deviation if data is symmetric and as median with inter quartile range (IQR) if data is not symmetric. Categorical data was compared using chi square test. Quantitative data was compared using independent t test if data satisfied normality and using Mann Whitney test if data did not satisfy normality. Based on cIMT, the patients were divided into quartiles: <= 0.3, 0.31 – 0.4, 0.41 – 0.5 and > 0.5. ANOVA or Kruskal Wallis test was used to compare between these groups for normal or non-normal data respectively. Pearson's correlation was used to assess the correlation between normal variables and Spearman's rank correlation was used to assess the correlation between non-normal variables. Linear regression analysis was done to determine the predictors of cIMT. Logistic regression was used to determine the risk factors for EcIMT. Two-way ANOVA test was performed to assess the effect of pubertal stage and cIMT on various cardiometabolic parameters. All tests were two sided and a p value < 0.05 was considered as statistically significant.

Results:

Among the children attending the obesity clinic of a tertiary care hospital during the study period of 2 ¼ years, 223 children aged 2-15 years were enrolled for the study. Majority of the study population were between 6 -10 years of age (n=109, 48.9%), males (n=139, 62.7%) and prepubertal (n=129, 57.8%) and had obesity (n=180, 80.7%). Mean cIMT of the study participants was 0.41 ± 0.13 mm. Elevated cIMT was seen in 102 children (45.7%).

EcIMT group was compared with NcIMT group for clinical and metabolic parameters (Table 1) and metabolic abnormalities (Table 2). Median ALT levels were significantly higher in the EcIMT group compared to NcIMT group (27 vs. 24, p=0.006). Proportion of patients with fatty liver (63.7% vs 48.8%, p=0.025) and ≥ 3 risk factors (80.4% vs. 66.1%, p=0.003) were significantly higher in the EcIMT group compared to NcIMT group. No statistically significant correlations were observed between cIMT and various clinical and cardiometabolic parameters (Table 3). No predictors for cIMT were identified on linear regression analysis. Gender or Tanner staging had no influence on cIMT. TC, triglycerides and LDL-C levels were higher in the EcIMT group compared to NcIMT group, but not statistically significant. Proportion of patients with hypertension, elevated SBP, abnormal HbA1c, hyperinsulinemia, elevated ALT levels, hypercholesterolemia, hypertriglyceridemia, elevated LDL-C, low HDL-C and dyslipidemia were higher in the EcIMT group compared to NcIMT group though not statistically significant. Out of 132 children aged ≥ 10 years, 30 had MS. Among these 30 children 16 had elevated cIMT (53.3%) compared to 41children out of 102 who did not have MS (40.2%) (p=0.287).

The prevalence of cardiometabolic risk factors was assessed separately in prepubertal and pubertal patients with normal and elevated cIMT (supplemental Tables 1). Among pubertal group (n=94), proportion of patients with hypercholesterolemia (36.4% vs. 16%, p=0.024), elevated LDL-C (38.6% vs. 16%, p=0.013), low HDL-C (40.9% vs. 20%, p= 0.027) and dyslipidemia (84.1% vs. 58%, p=0.006) were significantly higher in the EcIMT group compared to NcIMT group. Binary logistic regression with these variables was performed, but the model was not statistically significant, R^2 = 0.127, p=0.975. Among prepubertal group proportion of patients with fatty liver was significantly higher in the EcIMT group compared to NcIMT group (63.8% vs. 45.1%, p=0.034). No statistically significant correlations were noted between cIMT and

clinical and cardiometabolic parameters in both the prepubertal and pubertal groups(Supplemental Table 2).

A separate analysis was done with children below 6 years of age to assess the correlation between cIMT and clinical and cardiometabolic parameters. In this age group only age was found to be significantly correlated with cIMT (Supplemental Table 3). A linear regression model was developed with age as predictor and the model was statistically significant, R^2 = 0.206, p=0.03. The regression equation was cIMT = 0.212+0.041*age. The projected cIMT level of children below age 6 years based on this model was 0.46 mm at age 6years which was higher than the 75th percentile cIMT value for 6 years ((0.36 mm for girls and 0.4 mm for boys).

Two-way ANOVA test observed statistically significant interaction effects of the pubertal stage and cIMT on TC (p=0.035), LDL-C (p=0.003) and AST (p=0.033) levels (Supplemental file). TC and LDL-C levels were significantly higher in pubertal patients with EcIMT while AST level was significantly higher in prepubertal patients with EcIMT.

We analyzed the data to determine the predictors of cIMT using linear regression. The variables age, SBP, ALT that had statistically significant correlation coefficient with cIMT at 10% level were considered in the model. We also considered sex, BMI, presence of fatty liver and number of risk factors present in regression analysis. Since SBP was significantly correlated with age, the multi collinearity assumption could not be met. Hence in the final multivariate linear regression model we included only age, sex, BMI, presence of fatty liver, number of risk factors present and ALT as independent variables. This model was not statistically significant. R^2 = 0.032, p =0.208.

No significant differences were observed in clinical and cardiometabolic parameters across different quartiles of CIMT (supplemental tables 4 and 5).

Discussion:

Our study observed that nearly half of the children aged 2-15 years with overweight and obesity attending the obesity clinic of a tertiary care hospital during the study period of 2 ¼ years had EcIMT. Median ALT levels and proportion of patients with fatty liver were significantly higher in the EcIMT group compared to NcIMT group. When assessed separately, the proportion of patients with hypercholesterolemia and dyslipidemia were significantly higher in the pubertal

patients with EcIMT compared to their counterparts with NcIMT and the proportion of patients with fatty liver and ≥ 3 risk factors were significantly higher in the prepubertal patients with EcIMT compared to those with NcIMT. There were statistically significant interaction effects of pubertal stage and cIMT on TC, LDL-C and AST levels.

Only one other study from South Asia compared children with overweight and obesity based on cIMT like ours. This study from Chennai, India where 0.45 mm was taken as the cut off for high cIMT observed elevated cIMT in more than 3/5th of the study participants aged 10-18 years with overweight and obesity(6). Elevated cIMT places these children at increased risk of ASCVD in adulthood. Increased cIMT can compromise oxygen and nutrition diffusion to tissues through endothelial layers. This in turn gives rise to proliferation of small blood vessels supplying the large arterial walls which further increases the cIMT thickening leading to the initiation of endothelial dysfunction(26).

Present study observed higher ALT levels and percentage of patients with fatty liver in the EcIMT group compared to NcIMT. Various studies observed higher cIMT among youth with obesity who had metabolic dysfunction associated fatty liver disease (MAFLD) compared to those without(27–37). Prior studies in adults suggest that MAFLD is an independent risk factor for cardiovascular disease. Proposed pathophysiological mechanism for the MAFLD promoted atherogenesis include hepatic release of inflammatory cytokines, deranged lipoprotein metabolism, IR, decrease in adiponectin and increase in pro-coagulation factors(29). Hence it is not surprising that EcIMT group had higher median ALT levels and higher proportion of patients with fatty liver compared to NcIMT in our study.

Proportion of patients with ≥ 3 risk factors were significantly higher in the EcIMT group compared to NcIMT group. This was similar to the observation made by a multinational study involving 2427 children aged 6–17 years from population-based studies of Brazil, China and Italy. This study reported that the presence of one, two or at least three cardiovascular risk factors such as central obesity, elevated BP, triglycerides and FBG and reduced HDL-C was associated with gradually increasing odds of high cIMT as compared with none. The researchers observed that the clustering of risk factors that were used to define MS predicted high cIMT more strongly than MS among children and adolescents(38).

Proportion of patients with EcIMT were similar among prepubertal and pubertal children in the present study. Chennai study from India on children aged 10-18 years observed no differences in the mean cIMT according to pubertal status (6). Among the pubertal patients, the proportion of patients with hypercholesterolemia, elevated LDL-C, low HDL-C and dyslipidemia were significantly higher in the EcIMT group compared to NcIMT group in our study. While the prevalence of fatty liver was higher in those with EcIMT compared to NcIMT group among the prepubertal patients, no such difference was noted between the EcIMT and NcIMT groups among the pubertal patients. Statistically significant interaction effects of cIMT and pubertal stage were noted on TC, LDL-C and AST levels: TC and LDL-C levels were significantly higher in pubertal patients with EcIMT and AST level was significantly higher in prepubertal patients with EcIMT. On our meticulous search we did not come across other studies that analyzed cIMT among prepubertal patients and pubertal patients separately. More studies exploring cardiometabolic abnormalities in children with obesity, especially cIMT and the impact of pubertal stage are warranted.

Current study did not find any difference between the EcIMT and NcIMT groups regarding blood pressure, lipid levels, hypertension, dyslipidemia, dysglycemia, hyperinsulinemia, HOMA-IR and MS, similar to the observations made by the Chennai study on 50 children aged 10-18 years with overweight and obesity(6). In contrast to our findings, a study from Germany on 81 children aged 6-16 years with overweight and obesity observed higher weight, BMI, BMI-SDS, SBP, DBP and uric acid levels in children with cIMT $\geq$ 0.45 mm compared to those with cIMT < 0.45 mm(39). The conflicting reports could be due to the differences in sample size and characteristics, cut -offs for cIMT used, and racial and/or ethnic characteristics between the studies.

Present study observed no statistically significant correlations between cIMT and BMI, lipid levels, liver enzymes, uric acid, glucose, HbA1c, fasting insulin and HOMA-IR in contrast to several other studies majority of which had included children with both normal and abnormal BMI(3,7,8,39–55). While our findings were similar to that reported by few other studies(48,53,56). Studies from Egypt and Mexico on children and adolescents with obesity reported no significant correlations between cIMT and LDL-C and HDL-C and glucose and cholesterol levels respectively(48,53). Another study from Turkey on children with obesity and

age and gender matched controls reported no correlation between cIMT and lipid levels(56). A systematic review on cIMT and adiposity measures such as BMI, weight status, body fat percentage and WC, in children and adolescents reported that adiposity did not seem to be associated with cIMT in preadolescents (mean age < 12 years) based on studies mostly from Western Europe and United States. Out of 19 studies on adolescents (mean age ≥ 12 years of age), 13 observed positive associations between cIMT and adiposity measures(57). The different conclusions may be explained by the non-homogenous populations studied.

Mean cIMT of the study population was 0.41 ± 0.13 mm similar to that was reported by studies from Columbia and Egypt(43,45). Compared to our observation, higher cIMT was reported by several studies on children with overweight and obesity(2,3,6–8,26,39–42,44,46,47,49–51,55,58–70) while lower cIMT was reported by another study from Pune, India on 139 children aged 6-17 years with obesity and overweight(9). The differences in study population including age and racial and/or ethnic characteristics, exposure duration to obesity, sample size and the variety of ultrasound methods used for cIMT measurements may explain the difference noted between the various studies. The difference may also be due to the measurement of cIMT in various parts of the common carotid artery in these studies.

Prior studies reported reduction in cIMT with weight loss and exercise suggesting the reversibility of early atherosclerosis and hence improvement in cardiovascular risk(59,71). Wunsch, et al. reported decrease in cIMT following considerable weight loss through one year of outpatient obesity intervention program in 56 prepubertal children with obesity(59). A meta-analysis of randomized controlled trials on effects of exercise on cIMT in children with obesity observed significant reduction in cIMT with exercise(71). Pollock, et al. observed that cardiovascular risk, as denoted by altered cIMT can be dynamic moving between high and low cardiovascular risks over the life course of an individual. Children who betted their relative cardiovascular risk over the life course gained good midlife cardiovascular health despite having a poor metabolic health during adulthood while those who continued to have a high cardiovascular risk throughout the life course had the worst cardiovascular risk outcome as adults(72). The findings of these studies underscore the importance of efforts to change modifiable cardiovascular risk factors early in life.

Our study has several limitations, including lack of a control group, its cross-sectional study design, which does not allow causal or temporal inferences and being a single institution study. Accuracy of cIMT measurement in young children may be limited by the relatively short neck compared to the length of the US transducer and the poor compliance. Also, cut off value for normal cIMT versus increased cIMT in children below 6 years was taken as the 75th percentile cIMT value for 6 years as there were no normative data available for children younger than 6 years of age(73). However, the projected cIMT level of children below age 6 years based on the linear regression model developed was 0.46 mm at age 6years which was higher than the 75th percentile cIMT value for 6 years ((0.36 mm for girls and 0.4 mm for boys).There have been very few studies from South Asia assessing cIMT in children with obesity and overweight(6–9) and ours is the first study from Asia assessing cIMT in children below 5 years of age with obesity and overweight.

Conclusions:

Our finding of elevated cIMT in nearly half of the study participants including young children is very concerning as these children are at increased risk of atherosclerotic cardiovascular disease in adulthood. Public health efforts are needed in early childhood to mitigate overweight and obesity to avoid associated cardiometabolic risks that are already emerging in childhood. Early interventions are important when trajectories are likely to be more malleable and adverse cardiometabolic phenotypes and subclinical atherosclerosis are reversible.

Disclosure statements:

Acknowledgements: None

Financial Support: No funding was secured for this study.

Conflict of Interest: All the authors have no conflicts of interest to disclose. **Authorship:** SSP conceptualized and designed the study, designed the data protocol, collected data, carried out the initial analyses, drafted the initial manuscript, and critically reviewed and revised the manuscript. AB performed descriptive statistics and critically reviewed and edited the manuscript. MV conceptualized the study, coordinated, and critically reviewed and revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data availability statement: Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Reference:

1. Ling J, Chen S, Zahry NR, Kao TSA. Economic burden of childhood overweight and obesity: A systematic review and meta-analysis. Vol. 24, Obes Rev. John Wiley and Sons Inc; 2023. p. e13535.

2. Kim SA, Park KH, Woo S, Kim YM, Lim HJ, Park WJ. Vascular Alterations Preceding Arterial Wall Thickening in Overweight and Obese Children. J Clin Med. 2022;11(12):3520.

3. Nalbantoğlu A, Kızılca Ö, Güzel S, Emeksiz HC, Nalbantoğlu B. Increased Carotid Intima–Media Thickness and Endothelial Cell-Specific Molecule-1 (Endocan) Levels in Obese Children. Angiology. 2021;72(7):633–9.

4. McPhee PG, Singh S, Morrison KM. Childhood Obesity and Cardiovascular Disease Risk: Working Toward Solutions. Vol. 36, Can J Cardiol. 2020. p. 1352–61.

5. Licenziati MR, Iannuzzo G, Morlino D, Campana G, Renis M, Iannuzzi A, et al. Fat mass and vascular health in overweight/obese children. Nutr Metab Cardiovasc Dis. 2021;31(4):1317–23.

6. Sajja V, Jeevarathnam D, James S, Rathinasamy J. A study on carotid artery intima–media thickness and metabolic risk factors in overweight and obese Indian children. Diabetol Int 2019;11(2):142-149. 2019;11(2):142–9.

7. Vijayakumar M, Sabitha S, Princy K, Rajendran V, Gopalan A. IMPORTANCE OF CAROTID INTIMA MEDIA THICKNESS IN CHILDHOOD OBESITY. J Evol Med Dent Sci . 2017;6:586–91.

8. Dabas A, Thomas T, Gahlot M, Gupta N, Devasenathipathy K, Khadgawat R. Carotid intima-medial thickness and glucose homeostasis in Indian obese children and adolescents. Indian J Endocrinol Metab. 2017;21(6):859–63.

9. Pandit D, Kinare A, Chiplonkar S, Khadilkar A, Khadilkar V. Carotid arterial stiffness in overweight and obese Indian children. J Pediatr Endocrinol Metab. 2011;24(1–2):97–102.

10. Khadilkar V V., Khadilkar A V. Revised Indian Academy of Pediatrics 2015 growth charts for height, weight and body mass index for 5-18-year-old Indian children. Vol. 19, Indian J Endocr Metab. 2015. p. 470–6.

11. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards based on length/height, weight and age. Acta Paediatr Suppl. 2006;450:76–85.

12. Khadilkar A, Ekbote V, Chiplonkar S, Khadilkar V, Kajale N, Kulkarni S, et al. Waist circumference percentiles in 2-18 year old indian children. J Pediatr. 2014;164(6):1358-62. e2.

13. Marshall WA, Tanner JM. Variations in Pattern of Pubertal Changes in Girls. Arch Dis Child. 1969;44(235):291–303.

14. Marshall WA, Tanner JM. Variations in the Pattern of Pubertal Changes in Boys. Arch Dis Child. 1970;45(239):13–23.

15. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents [Internet]. Vol. 140, Pediatrics. 2017. Available from: http://publications.aap.org/pediatrics/article-pdf/140/3/e20171904/1104403/peds_20171904.pdf

16. Knopfholz J, Disserol CCD, Pierin AJ, Schirr FL, Streisky L, Takito LL, et al. Validation of the friedewald formula in patients with metabolic syndrome. Cholesterol . 2014;2014:261878.

17. Stewart J, Mccallin T, Martinez J, Chacko S, Yusuf S. Hyperlipidemia. Pediatr rev [Internet]. 2020;41(8):393–402. Available from:

http://publications.aap.org/pediatricsinreview/article-pdf/41/8/393/1279230/pedsinreview_20190053.pdf?casa_token=NdihqqyjVJYAAAAA:9AlAQ7yxfckgW8UNGZXPeiIq6vBoCeHZWushOpRsynlZsS9BN

18. Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome - A new world-wide definition. A consensus statement from the International Diabetes Federation. Vol. 23, Diabetic Medicine. 2006. p. 469–80.

19. Elsayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 14. Children and Adolescents: Standards of Care in Diabetes—2023. Diabetes Care. 2023;46.

20. Uric Acid, Serum - Mayo Clinic Laboratories, Pediatric Catalog [Internet]. Available from: https://pediatric.testcatalog.org/show/URIC

21. Gutch M, Kumar S, Razi SM, Gupta K, Gupta A. Assessment of insulin sensitivity/resistance. Indian J Endocrinol Metab. 2015;19(1):160–4.

22. Kendall D, Vail A, Amin R, Barrett T, Dimitri P, Ivison F, et al. Metformin in obese children and adolescents: The MOCA trial. J Clin Endocrinol Metab. 2013;98(1):322–9.

23. Adeli K, Higgins V, Trajcevski K, White-Al Habeeb N. The Canadian laboratory initiative on pediatric reference intervals: A CALIPER white paper. Vol. 54, Critical Reviews in Clinical Laboratory Sciences. Taylor and Francis Ltd; 2017. p. 358–413.

24. Doyon A, Kracht D, Bayazit A, Deveci M, Duzova A, Krmar R, et al. Carotid Artery Intima-Media Thickness and Distensibility in Children and Adolescents: Reference Values and Role of Body Dimensions. Hypertension. 2013;62(3):550–6.

25. Dalla Pozza R, Ehringer-Schetitska D, Fritsch P, Jokinen E, Petropoulos A, Oberhoffer R. Intima media thickness measurement in children: A statement from the Association for European Paediatric Cardiology (AEPC) Working Group on Cardiovascular Prevention endorsed by the Association for European Paediatric Cardiology. Vol. 238, Atherosclerosis. Elsevier Ireland Ltd; 2015. p. 380–7.

26. Garibay-Nieto N, Hernández-Morán BA, Villanueva-Ortega E, Garcés-Hernández MJ, Pedraza-Escudero K, Arroyo-Valerio A, et al. Comparison of Carotid Intima-Media

Thickness in Children and Adults With and Without Obesity: A Hysteresis Model. Endocr Pract. 2022;28(3):315–20.

27. Sasidharan Pillai S, Madhava V, Balakrishnan A. Non-Alcoholic Fatty Liver Disease in Children with Overweight and Obesity. Indian J Pediatr [Internet]. 2024 [cited 2024 Mar 6]; Available from: 10.1007/s12098-024-05058-5

28. Schiel R, Heinrichs M, Stein G, Bambauer R, Steveling A. Non-Alcoholic Fatty Liver Disease (NAFLD) in overweight and obese children and adolescents. Archives of Clinical Gastroenterology. 2020;082–7.

29. Koot BGP, De Groot E, Van Der Baan-Slootweg OH, Bohte AE, Nederveen AJ, Jansen PLM, et al. Nonalcoholic fatty liver disease and cardiovascular risk in children with obesity. Obesity. 2015;23(6).

30. Sert A, Pirgon O, Aypar E, Yilmaz H, Odabas D. Relationship between left ventricular mass and carotid intima media thickness in obese adolescents with non-alcoholic fatty liver disease. Journal of Pediatric Endocrinology and Metabolism. 2012;25(9–10):927–34.

31. Manco M, Bedogni G, Monti L, Morino G, Natali G, Nobili V. Intima-media thickness and liver histology in obese children and adolescents with non-alcoholic fatty liver disease. Atherosclerosis. 2010;209(2):463–8.

32. Akin L, Kurtoglu S, Yililmaz A, Kendirci M, Elmali F, Mazicioglu M. Fatty liver is a good indicator of subclinical atherosclerosis risk in obese children and adolescents regardless of liver enzyme elevation - PubMed. Acta Paediatr. 2013;102(3):e107–13.

33. Fatih Demirciog Ã, Koçyig A, Arslan N, Hızlı amil, Tuncel Sedat A. Intima-Media Thickness of Carotid Artery and Susceptibility to Atherosclerosis in Obese Children With Nonalcoholic Fatty Liver Disease. J Pediatr Gastroenterol Nutr [Internet]. 2008;47(1):68–75. Available from: http://journals.lww.com/jpgn

34. Pacifico L, Anania C, Martino F, Cantisani V, Pascone R, Marcantonio A, et al. Functional and morphological vascular changes in pediatric nonalcoholic fatty liver disease. Hepatology. 2010;52(5).

35. Pacifico L, Cantisani V, Ricci P, Osborn JF, Schiavo E, Anania C, et al. Nonalcoholic Fatty Liver Disease and Carotid Atherosclerosis in Children. Pediatr Res. 2008;63(4):423–7.

36. Gökçe S, Atbinici Z, Aycan Z, Çinar HG, Zorlu P. The relationship between pediatric nonalcoholic fatty liver disease and cardiovascular risk factors and increased risk of atherosclerosis in obese children. Pediatric Cardiol. 2013;34(2):308–15.

37. Torun E, Aydın S, Gökçe S, Özgen İT, Donmez T, Cesur Y. Carotid intima-media thickness and flow-mediated dilation in obese children with non-alcoholic fatty liver disease. Turk J Gastroenterol. 2014;25.

38. Zhao M, Caserta CA, Medeiros CCM, Lopez-Bermejo A, Kollias A, Zhang Q, et al. Metabolic syndrome, clustering of cardiovascular risk factors and high carotid intima-media thickness in children and adolescents. J Hypertens. 2020;38(4):618–24.

39. Schiel R, Beltschikow W, Radon S, Krammer G, Perenthaler T, Stein G. Increased Carotid Intima- Media Thickness And Associations With Cardiovascular Risk Factors in Obese And Overweight Children And Adolescents. Eur J Med Res. 2007;12(10):503–8.

40. Simsek E, Balta H, Balta Z, Dallar Y. Childhood obesity related cardiovascular risk factors and carotid intima-media thickness. Turk J Pediatr. 2010;52(6):602–11.

41. Elkiran O, Yilmaz E, Koc M, Kamanli A, Ustundag B, Ilhan N. The association between intima media thickness, central obesity and diastolic blood pressure in obese and owerweight children: A cross-sectional school-based study. Int J Cardiol. 2013;165(3):528–32.

42. Hacihamdioğlu B, Okutan V, Yozgat Y, Yildirim D, Kocaoğlu M, Lenk MK, et al. Abdominal obesity is an independent risk factor for increased carotid intima- media thickness in obese children. Turk J Pediatr. 2011;53(1):48–54.

43. Borda WA, Badillo FL, Suarez JCM, Rey JJ. Carotid intima media thickness in obese children. Rev Colomb Radiol. 2015;26(2):4185–91.

44. Fang J, Zhang JP, Luo CX, Yu XM, Lv LQ. Carotid Intima-media thickness in childhood and adolescent obesity relations to abdominal obesity, high triglyceride level and insulin

resistance [Internet]. Vol. 7, Int. J. Med. Sci. 2010. Available from: http://www.medsci.org278

45. Fouad HM, Shalaby SA, Kamal M, Thabet MM, Shalaby SA, Khalifa I, et al. Carotid Intima-Media Thickness in Children with Overweight/Obesity: A Single-center Study. Int J Pediatr [Internet]. 2022;10(5):15945–56. Available from: http://ijp.mums.ac.ir

46. Mahfouz AA, Massoud MN, Omar OM, Abou–Gabal AM. Carotid intima-media thickness and cardiovascular risk factors in childhood and adolescent obesity. Int J Community Med Public Health. 2018;5(11):4643–50.

47. Stabouli S, Kotsis V, Karagianni C, Zakopoulos N, Konstantopoulos A. Blood Pressure and Carotid Artery Intima-Media Thickness in Children and Adolescents: The Role of Obesity. Hellenic J Cardiol. 2012;53:41–7.

48. Al-Drawny Z, Hamdy S, Saleh A, Abdel A, El-Sammak A, Attia HM. Carotid Intima Media Thickness in Obese Egyptian Children and Adolescent. The Egyptian Journal of Hospital Medicine [Internet]. 2020;80(1):672–7. Available from: http://creativecommons.org/licenses/by/4.0/

49. Căşăriu ED, Virgolici B, Greabu M, Totan A, Daniela M, Mitrea N, et al. Associations between carotid intimamedia thickness and cardiovascular risk markers in obese children. Farmacia. 2011;59(4):471–82.

50. Leite A, Santos A, Monteiro M, Gomes L, Veloso M, Costa M. Impact of overweight and obesity in carotid intima-media thickness of portuguese adolescents. Acta Paediatr. 2012;101(3):e115–21.

51. Al-Shorman A, Al-Domi H, Al-Atoum M. The associations of body composition and anthropometric measures with carotid intima-media thickness in obese and non-obese schoolchildren: A possible predictor for cardiovascular diseases. Vascular. 2018;26(3):285–90.

52. Özkan EA, Khosroshahi HE, Serin Hİ, Özdemir ZT, Kılıç M, Ekim M, et al. The evaluation of carotid intima-media thickness and mean platelet volume values and

correlation with cardiac functions in obese children. Int J Clin Exp Med [Internet]. 2015;8(12):22557–63. Available from: www.ijcem.com/

53. Alba-Rojas EL, Rodríguez-de-Ita J, Yañez-Sánchez JM, Salán-Gómez M, Acosta-Sandoval MA, Estrada-Mendizábal RJ, et al. Carotid intima-media thickness and its correlation with anthropometric and clinical variables in pediatric patients with obesity: An exploratory study. Medicina Universitaria. 2019;21(3):100–4.

54. Mihuta MS, Paul C, Borlea A, Roi CM, Velea-Barta OA, Mozos I, et al. Unveiling the Silent Danger of Childhood Obesity: Non-Invasive Biomarkers Such as Carotid Intima-Media Thickness, Arterial Stiffness Surrogate Markers, and Blood Pressure Are Useful in Detecting Early Vascular Alterations in Obese Children. Biomedicines . 2023;11(7):1841.

55. Garcia J, Saab Benedeti ACG, Caixe SH, Filho FM, Nogueira-De-Almeida CA. Ultrasonographic evaluation of the common carotid intima-media complex in healthy and overweight/obese children. J Vasc Bras. 2019;18:e20190003.

56. Onal Z, Soydan L, Ozturk H, Sag C, Gurbuz T, Nuhoglu C, et al. Carotid intima media thickness in obese children: is there an association with hyperlipidemia? J Pediatr Endocrinol Metab [Internet]. 2016;29(2):157–62. Available from: https://www.degruyter.com/document/doi/10.1515/jpem-2015-0221/html?lang=en

57. Park MH, Skow Á, De Matteis S, Kessel AS, Saxena S, Viner RM, et al. Adiposity and carotid-intima media thickness in children and adolescents: A systematic review. BMC Pediatr. 2015;15:161.

58. Ozguven I, Ersoy B, Ozguven A, Ozkol M, Onur E. Factors affecting carotid intima media thickness predicts early atherosclerosis in overweight and obese adolescents. Obes Res Clin Pract. 2010;4(1):e1–82.

59. Wunsch R, De Sousa G, Toschke AM, Reinehr T. Intima-media thickness in obese children before and after weight loss. Pediatrics . 2006;118(6):2334–40.

60. Farello G, Iapadre G, Lizzi M, Centile C, Altobelli E, Ciocca F, et al. Carotid intima media-thickness is increased in obese children metabolically healthy, metabolically

unhealthy, and with metabolic syndrome, compared to the non-obese controls. Eur Rev Med Pharmacol Sci . 2021;25(1):241–9.

61. Iannuzzi A, Licenziati MR, Acampora C, Salvatore V, Auriemma L, Romano ML, et al. Increased carotid intima-media thickness and stiffness in obese children. Diabetes Care . 2004;27(10):2506–8.

62. Ozcetin M, Celikyay Z, Celik A, Yilmaz R, Yerli Y, Erkorkmmaz U. The importance of carotid artery stiffness and increased intima-media thickness in obese children. S Afr Med J . 2012;102(5):295–9.

63. Woo KS, Chook P, Yu CW, Sung RYT, Qiao M, Leung SSF, et al. Overweight in children is associated with arterial endothelial dysfunction and intima-media thickening. Int J Obes Relat Metab Disord. 2004;28(7):852–7.

64. Zhu W, Huang X, He J, Li M, Neubauer H. Arterial intima-media thickening and endothelial dysfunction in obese Chinese children. Eur J Pediatr. 2005;164(6):337–44.

65. Rumińska M, Witkowska-Sędek E, Majcher A, Brzewski M, Czerwonogrodzka-Senczyna A, Demkow U, et al. Carotid intima-media thickness and metabolic syndrome components in obese children and adolescents. In: Advances in Experimental Medicine and Biology. Springer New York LLC; 2017. p. 63–72.

66. Elshorbagy HH, Fouda ER, Kamal NM, Bassiouny MM, Fathi WM. Evaluation of epicardial fat and carotid intima-media thickness in obese children. Iran J Pediatr. 2016;26(1):e2968.

67. Genoni G, Menegon V, Secco GG, Sonzini M, Martelli M, Castagno M, et al. Insulin resistance, serum uric acid and metabolic syndrome are linked to cardiovascular dysfunction in pediatric obesity. Int J Cardiol. 2017;249:366–71.

68. Corica D, Oreto L, Pepe G, Calabrò MP, Longobardo L, Morabito L, et al. Precocious Preclinical Cardiovascular Sonographic Markers in Metabolically Healthy and Unhealthy Childhood Obesity. Front Endocrinol (Lausanne) . 2020;11:56.

69. Kozakova M, Morizzo C, Bianchi V, Marchetti S, Federico G, Palombo C. Hemodynamic overload and intra-abdominal adiposity in obese children: Relationships with cardiovascular structure and function. Nutr Metab Cardiovasc Dis. 2016;26(1):60–6.

70. Pires A, Martins P, Pereira AM, Silva PV, Marinho J, Marques M, et al. Insulin Resistance, Dyslipidemia and Cardiovascular Changes in a Group of Obese Children. Arq bras cardiol . 2015;104(4):266–73.

71. García-Hermoso A, González-Ruiz K, Triana-Reina HR, Olloquequi J, Ramírez-Vélez R. Effects of exercise on carotid arterial wall thickness in obese pediatric populations: A meta-analysis of randomized controlled trials. Child Obes. 2017;13(2):138–45.

72. Pollock BD, Stuchlik P, Harville EW, Mills KT, Tang W, Chen W, et al. Life course trajectories of cardiovascular risk: Impact on atherosclerotic and metabolic indicators. Atherosclerosis. 2019;280:21–7.

73. Skrzypczyk P, Pańczyk-Tomaszewska M. Methods to evaluate arterial structure and function in children – State-of-the art knowledge. Adv Med Sci. 2017;62(2):280–94.

Table 1: Clinical and demographic data of study participants

Patient characteristics	Total (n= 223)	Participants with normal cIMT (n=121)	Participants with elevated cIMT (n=102)	p value
Age, years	10.5 (3.8)	10.6 (4.3)	10.4 (3.5)	0.651 (0.107)
2- 5 years (n (%)) 6-10 years 11- 15 years	23 (10.3%) 109 (48.9%) 91(40.8%)	13 (10.7%) 60 (49.6%) 48 (39.7%)	10 (9.8%) 49 (48%) 43 (42.2%)	0.924
Female (n (%)) Male	84 (37.3%) 139 (62.7%)	44 (36.4%) 77 (63.6%)	40 (39.2%) 62 (60.8%)	0.661 (0.95)
Patients with obesity (n (%)) overweight	 180 (80.7%) 43 (19.3%)	 98 (81%) 23 (19%)	 82 (80.4%) 20 (19.6%)	0.91
BMI ($kg/m^{2)}$ (mean ± SD)	24.1 ± 3.3	24.0 ± 3.3	24.3 ± 3.3	0.431 (0.997)
Birthweight, kg (mean ± SD)	3.0± 0.77	3.0 ± 0.68	2.95 ± 0.55	0.515
FH of hypertension (n (%))	141 (63.2%)	82 (67.8%)	59 (57.8%)	0.126
FH of dyslipidemia(n (%))	118 (52.9%)	67 (55.4%)	51 (50%)	0.423
FH of T2D (n(%))	160 (71.7%)	84 (69.4%)	76 (74.5%)	0.4
FH of heart attack (n(%))	87 (39%)	50 (41.3%)	37 (36.3%)	0.441
WC, cm (mean ± SD)	84 ± 12	83.8 ± 9.5	84.2 ± 9.5	0.789
SBP, mm Hg	100 (20)	100 (20)	100 (16)	0.193
DBP, mm Hg	62 (10)	62 (10)	62 (10)	0.889
Prepubertal (n) Pubertal (n)	129 (57.8%) 94 (42.2%)	71 (58.7%) 50 (41.3%)	58 (56.9%) 44 (43.1%)	0.785
AST IU/L	26 (12)	25 (11)	26 (14.1)	0.294

ALT IU/L	25.6 (21)	24 (16)	27 (26)	0.006 (0.134)
Uric acid mg/dl	4.3 (1.3)	4.3 (1.2)	4.3 (1.5)	0.814
FBG mg/dl (mean ± SD)	86.1 ± 13.0	86.5± 11.3	85.4 ± 8.9	0.397
Fasting insulin mIU/L	13.4 (10.6)	13.3 (9.1)	13.6 (11.4)	0.544
HOMA-IR	2.8 (2.3)	2.77 (2.03)	2.79 (2.65)	0.835
HbA1c %	5.4 (0.6)	5.3 (0.6)	5.4 (0.65)	0.75
TC, mg/dl (mean ± SD)	178 ± 33.1	175.9 ± 32.9	180.6 ± 33.3	0.297
Triglycerides, mg/dl	106.9 (67)	104 (62)	112 (79.5)	0.242
LDL-C, mg/dl (mean ± SD)	111.9 ± 29.8	110.2 ± 30.7	114.1 ± 28.8	0.328
VLDL-C, mg/dl	21 (12.8)	20 (12)	22 (15)	0.18
HDL-C, mg/dl (mean ± SD)	42.6 ± 8.3	42.9 ± 7.8	42.3 ± 8.9	0.567

ALT- alanine transaminase; AST-aspartate transaminase; BMI- body mass index; cIMT-carotid intima media thickness; DBP-diastolic blood pressure; FH- family history; FBG – fasting blood glucose; HbA1c- hemoglobin A1c; HDL-C – high density lipoprotein cholesterol; HOMA-IR- homeostatic model assessment of insulin resistance; IFG- impaired fasting glucose; LDL-C- low density lipoprotein cholesterol; SBP- systolic blood pressure; TC- total cholesterol; T2D- type 2 diabetes; VLDL-C – very low density lipoprotein cholesterol; WC- waist circumference.

All values are expressed as median (IQR) unless otherwise specified. Adjusted p value is given in bracket.

Table 2. Cardiometabolic abnormalities in patients with elevated cIMT vs. patients with normal cIMT

Cardiometabolic abnormalities	Total patients (n=223)	Patients with normal cIMT (n=121)	Patients with elevated cIMT (n=102)	p value
Central adiposity (n (%))	213 (95.5 %)	117 (96.7%)	96 (94.1%)	0.518
Hypertension (n (%))	35 (15.7%)	18 (14.9%)	17 (16.7%)	0.714
Elevated SBP (n(%))	17 (7.6%)	7 (5.8%)	10 (9.8%)	0.259
Elevated DBP (n(%))	27 (12.1 %)	14 (11.6%)	13 (12.7%)	0.789
IFG (n (%))	21 (9.4%)	13 (10.7%)	8 (7.8%)	0.46
HbA1c ≥ 5.7% (n (%))	64 (28.7%)	33 (27.3%)	31 (30.4%)	0.608
HOMA-IR ≥ 2.5 (n (%))	131 (58.7%)	75 (62%)	56 (54.9%)	0.285
Hyperinsulinism (n (%)	54 (24.2%)	25 (20.7%)	29 (28.4%)	0.177
Elevated ALT (n (%))	111 (49.8%)	56 (46.3%)	55 (53.9%)	0.256
Hyperuricemia (n (%))	6 (2.7%)	3 (2.5%)	3 (2.9%)	1.0
Hypercholesterolemia (n (%))	57 (25.6%)	27 (22.3%)	30 (29.4%)	0.226

Hypertriglyceridemia (n (%))	100 (44.8%)	50 (41.3%)	50 (49.0%)	0.25
Elevated LDL-C (n (%))	57 (25.6%)	29 (23.9%)	28 (27.5%)	0.552
Low HDL-C (n (%))	73 (32.7%)	34 (28.1%)	39 (38.6%)	0.108
Dyslipidemia (n (%))	151 (67.7%)	79 (65.3%)	72 (70.6%)	0.399
Fatty liver (n (%))	124 (55.6%)	59 (48.8%)	65 (63.7%)	0.025* (0.18)
1 risk factor present 2 risk factors present >= 3 risk factors present	20 (9%) 42 (18.4%) 162 (72.6%)	9 (7.4%) 32 (26.4%) 80 (66.1%)	11 (10.8%) 9 (8.8%) 82 (80.4%)	0.003 (0.485)

ALT- alanine transaminase; DBP-diastolic blood pressure; HbA1c- hemoglobin A1c; HDL-C – high density lipoprotein cholesterol; HOMA-IR- homeostatic model assessment of insulin resistance; IFG- impaired fasting glucose; LDL-C- low density lipoprotein cholesterol; SBP-systolic blood pressure.*Statistically significant at 5% level. Adjusted p value is given in bracket.

Table 3. Correlation between cIMT and clinical and cardiometabolic parameters

Clinical and cardiometabolic parameter	Correlation coefficient (r)	p value
Age	0.12*	0.08
BMI	0.06	0.40
Birth weight	0.02	0.75
WC	0.05	0.44
SBP	0.12*	0.09
DBP	0.03*	0.80
AST	-0.07*	0.82
ALT	0.13*	0.05
Uric acid	0.02*	0.79
FBG	-0.04	0.53
HOMA-IR	0.06*	0.34
Fasting insulin	0.06*	0.36
HbA1c	0.07*	0.33
TC	0.02	0.82
Triglycerides	0.09*	0.17
LDL-C	-0.01	0.89
VLDL-C	0.08*	0.22
HDL-C	0.00	1.00

ALT- alanine transaminase; AST-aspartate transaminase; BMI- body mass index; cIMT-carotid intima media thickness; DBP-diastolic blood pressure; FBG- fasting blood glucose; HbA1c-hemoglobin A1c; HDL-C – high density lipoprotein cholesterol; HOMA-IR- homeostatic model assessment of insulin resistance; LDL-C- low density lipoprotein cholesterol; SBP- systolic blood pressure; TC- total cholesterol; VLDL-C – very low density lipoprotein cholesterol; WC-waist circumference.

*Spearman's correlation coefficient, others Pearson correlation coefficient