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Original Articles

Total cholesterol-to-high-density lipoprotein cholesterol ratio predicts high-sensitivity C-reactive protein levels in Turkish children

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BACKGROUND: High-sensitivity C-reactive protein (hs-CRP) is a biomarker of continued long-term systemic inflammation and cardiovascular (CV) risk.

OBJECTIVE: To analyze the association of hs-CRP levels with CV risk factors in healthy school children.

METHODS: The study sample was derived from a survey on the prevalence of CV risk factors (dyslipidemia, obesity, high blood pressure, and insulin resistance in school children. Along with anthropometry, hs-CRP levels, lipids, glucose levels, and insulin levels were measured.

RESULTS: Ninety-one male (12.5 ± 3.4 years) and 77 female students (12.7 ± 3.4; $P = .624$) were included. Median (interquartile range) hs-CRP levels were similar among boys and girls (0.4 [1.2] vs 0.5 [0.7]; $P = .928$). Risk factors such as obesity (16%), high triglycerides (20%), low high-density lipoprotein cholesterol (HDL-C, 16%), and elevated blood pressure (25%) were commonly observed in study participants. Gender-stratified analysis displayed that insulin resistance (18 [19.8%] vs 3 [3.9%]; $P = .002$) and high triglycerides (26 [28.6%] vs 8 [10.4%]; $P = .003$) were more commonly observed among boys compared with girls. hs-CRP levels correlated positively with cardiometabolic risk factors such as waist circumference (boys) and total cholesterol (TC)-to-HDL-C ratio. Linear regression analysis displayed that among the covariates of age, body mass index, and glucose, TC-to-HDL-C ratio was the most significant determinant of hs-CRP levels ($P = .004$).

CONCLUSION: Cardiometabolic risk factors such as TC-to-HDL-C ratio correlate with hs-CRP levels in children and adolescents. Long-term prospective studies are needed to confirm the association between hs-CRP and cardiometabolic risk in children.

Introduction

C-reactive protein (CRP) is an acute-phase protein that increases with systemic inflammation. CRP can be measured by high-sensitive methods, and high-sensitivity CRP (hs-CRP) is associated with increased risk for vascular

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disease.[1] Several studies have confirmed the role of subclinical inflammation in the course of atherosclerosis.[2,3] hs-CRP levels associate with type 2 diabetes mellitus, dyslipidemia, upper body adiposity, insulin resistance (IR), hypertension, and increased risk for cardiovascular (CV) disease (CVD).[2,3] Prospective studies in adult populations have established hs-CRP as a novel biomarker that can predict CV events.[4,5] In fact, risk scoring systems (i.e., Reynolds Risk Score) have adopted hs-CRP in their algorithms.[6]

Metabolic syndrome (MetS) is the constellation of cardiometabolic risk factors, and numerous studies have confirmed that CRP levels are elevated in patients with MetS.[3] Clustering of cardiometabolic risk factors starts early in life.[7] Cardiometabolic risk factors in children include abdominal obesity, atherogenic dyslipidemia (high triglycerides [TG] and reduced high-density lipoprotein cholesterol [HDL-C]), impaired glucose metabolism, and elevated blood pressure.[7] Originally, MetS in children is defined as a direct consequence of endemic childhood obesity.[2] However, cardiometabolic risk factors such as high blood pressure, high TG, and reduced HDL-C are common in children even in the absence of obesity.[8] Furthermore, ethnic variations exist in the prevalence of MetS and distribution of cardiometabolic risk factors in children.[9]

In this study, we analyzed the association of hs-CRP levels with cardiometabolic risk factors in healthy school students. Our aim was to understand if the association is being driven by a single cardiometabolic risk factor vs the constellation of risk factors that are included in the definition of MetS.

Methods

The study included 168 healthy school students (ages, 10-17 years). The study sample was derived from a cross-sectional survey on the prevalence of CV risk factors in a representative sample of school children in Istanbul, Turkey. History and physical examination were performed on all study participants. For the study purposes, the definition of healthy children indicated that (1) children with acute illness including viral or bacterial infection in the last 2 to 3 weeks were excluded; (2) children with chronic health problems were excluded; and (3) children who were taking medications were excluded. Medical history was obtained from both the participants and their parents. Five different state elementary and secondary schools were selected. Students who did not want to participate in the survey were excluded (around 10% of the elementary school children and 20% of the secondary school students). The blood samples were drawn at 9 AM, and the screening took place at the schools during regular school hours. All families were informed about the purpose of the study, and written consents were obtained.

Anthropometric measurements of weight, height, and waist and hip circumference were measured by formally trained physicians. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Body circumferences were measured with the subjects in a standing position. Waist (just above the iliac crest) circumferences were measured to the nearest 0.1 cm. Using the tables provided by the waist circumference percentiles in nationally representative sample of Turkish children and adolescents, we determined subjects with increased waist circumference (>90th percentile).[10]

Biochemical analysis

Patients were considered to be fasting if they reported at least 12 hours of fasting before the blood sampling. Complete lipid profile was obtained, including total cholesterol (TC), HDL-C, and TG. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald calculation: LDL-C = TC – HDL-C – [TG/5]. TG, HDL-C, and glucose were measured by enzymatic colorimetric assay method using Cobas Integra 800 kit (Roche Diagnostic, Indianapolis, IN).

CRP (mg/L) was determined by highly sensitive method using a commercially available hs-CRP kit according to the manufacturer's recommendations (Roche Diagnostic). Insulin levels were measured by chemiluminescence immunoassay method using Modular E170 kit (Roche Diagnostic). Analyses were performed in an accredited laboratory (Centro Laboratories, which are based in Istanbul, Turkey). Measurement uncertainty of each method in use at the time of analysis was 1.5% for TC, 1.8% for TG, 2.7% for HDL-C, and 1.6% for glucose.

Definition of cardiometabolic risk factors

Age- and sex-specific cutoff points of BMI were used to assess the overweight and obesity status. These cutoff points of BMI were developed and published from the centile curves of an international reference population.[11]

As age- and sex-specific lipid percentiles were not available for the Turkish children, we used the National Heart Lung and Blood Institute Growth and Health Study as the reference population.[12] TG level ≥90th and HDL-C level ≤10th percentile were defined as high TG and low HDL-C, respectively.

Impaired fasting glucose (IFG) or IR (assessed by homeostasis model assessment-estimated IR [HOMA-IR]) was a prerequisite for MetS according to World Health Organization (WHO) definition.[13] IFG was defined as fasting plasma glucose between 100 mg/dL (5.6 mmol/L) and 125 mg/dL (6.9 mmol/L).[14] Hyperinsulinemia was arbitrarily defined as fasting value of >18 μU/mL, which is considered indicative of IR in normoglycemic subjects.[15] HOMA-IR was calculated using the formula (glucose [mmol/L] × fasting insulin [μU/ml]/22.5). HOMA-IR has been validated as a measure of IR in nondiabetic children.[16] IR was defined based on a threshold of >3.16.[17]