White blood cell count may identify abnormal cardiometabolic phenotype and preclinical organ damage in overweight/obese children

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Abstract *Background and Aims:* Subclinical inflammation is a central component of cardiometabolic disease risk in obese subjects. The aim of the study was to evaluate whether the white blood cell count (WBCc) may help to identify an abnormal cardiometabolic phenotype in overweight (Ow) or obese (Ob) children.

Methods and Results: A cross-sectional sample of 2835 Ow/Ob children and adolescents (age 6−18 years) was recruited from 10 Italian centers for the care of obesity. Anthropometric and biochemical variables were assessed in the overall sample. Waist to height ratio (WhtR), alanine aminotransferase (ALT), lipids, 2 h post-load plasma glucose (2hPG), left ventricular (LV) geometry and carotid intima-media thickness (cIMT) were assessed in 2128, 2300, 1834, 535 and 315 children, respectively. Insulin resistance and whole body insulin sensitivity index (WBISI) were analyzed using homeostatic model assessment (HOMA-IR) and Matsuda's test. Groups divided in quartiles of WBCc significantly differed for body mass index, WhtR, 2hPG, HOMA-IR, WBISI, lipids, ALT, cIMT, LV mass and relative wall thickness. Children with high WBCc (≥8700 cell/mm^3) showed a 1.3−2.5 fold increased probability of having high normal 2hPG, high ALT, high cIMT, or LV remodeling/concentric LV hypertrophy, after adjustment for age, gender, pubertal status, BMI and centers.

Conclusions: This study shows that WBCc is associated with early derangements of glucose metabolism and preclinical signs of liver, vascular and cardiac damage. The WBCc may be an effective

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and low-cost tool for identifying Ow and Ob children at the greatest risk of potential complications.

Introduction

Several studies have previously demonstrated that systemic inflammation is associated with insulin resistance, altered glucose metabolism, high risk of progression towards diabetes, and cardiovascular events [1–3]. These associations reflect a meaningful pathophysiological process, since inflammation is detrimental for many tissues, i.e. pancreatic islets, liver, cardiac and vascular tissues [3].

It is also well known that obesity is associated with systemic inflammation [2], therefore the sum of these two conditions may accelerate the progression toward cardiometabolic diseases. This burden is particularly significant in pediatric obesity, considering the worldwide epidemic spreading of this condition. In other words, identifying subclinical inflammation in subjects at high risk of cardiometabolic diseases, such as obese children, might contribute to the implementation of more stringent strategies to prevent morbidity.

As observed in adults [4–6], white blood cell count (WBCc) represents a marker of systemic inflammation also in children. In fact, several epidemiological studies have demonstrated a positive relationship between WBCc and overweight [7,8] or components of metabolic syndrome [9]. However, the comprehensive relationship between high WBCc, glucose metabolism, and preclinical signs of organ damage remains less explored in children. Thus, the aim of our study was to analyze whether high WBCc is associated with an abnormal cardiometabolic phenotype or preclinical signs of organ damage in a large population of Italian overweight (Ow) or obese (Ob) children and adolescents.

Methods

Subjects

In this retrospective cross-sectional study, clinical data of 2835 Ow/Ob children and adolescents included into the "CARdiometabolic risk factors (CMRFs) in Ow and Ob children in ITALY (CARITALY) Study" were reviewed. Briefly, the study was endorsed by the Childhood Obesity Group of the Italian Society of Pediatric Endocrinology and Diabetology, and designed to investigate the prevalence of the major CMRFs in Italian outpatient children and adolescents [10,11]. Each center provided medical records of all children and adolescents with overweight or obesity consecutively referred by general practitioners for the evaluation of their health status and advice about weight loss. Exclusion criteria were: recent history of acute infection and acute non-infectious inflammatory disorders, diabetes mellitus, secondary obesity, chronic diseases, malformations and chronic use of drugs leading to metabolic disturbances.

Measurements

Each center adopted a standardized procedure for the evaluation of anthropometric, clinical and biochemical variables. Weight and height were measured in all participant centers by the same investigator, who was specifically trained in anthropometry. Weight was determined to the nearest 0.1 Kg on a medical scale, height was measured to the nearest 0.1 cm with a wall-mounted stadiometer. Waist circumference (WC) was measured in standing position, midway between the lowest rib and the superior border of the iliac crest using a non-extensible steel tape in 2128 participants. Waist-to-height ratio (WHtR) was calculated as an estimate of the relative amount of abdominal fat independent of age and gender. Children's sexual maturity was evaluated by Tanner staging (I–V). Blood pressure (BP) was measured using aneroid sphygmomanometers with cuffs of appropriate size, according to standard procedures. Briefly, blood pressure was measured at the right arm in sitting position after 5-min resting using the auscultatory method; K1 was used for systolic blood pressure (SBP) and K5 for diastolic blood pressure (DBP) as recommended by the European Society of Hypertension [12]. After 12 h of fasting, blood samples were drawn for analysis of WBCc, total cholesterol, triglycerides (Tg), high-density lipoprotein-cholesterol (HDL-C), glucose and insulin in the whole population. WBCc was measured using an automated analyzer in each center. Alanine aminotransferase (ALT) measurement was available in 2300 participants. Oral glucose tolerance test (OGTT) with 1.75 g/kg up to a maximum of 75 g was performed in 1834 participants. Insulin-resistance (IR) was calculated by the homeostatic model assessment (HOMA-IR) using the following formula: fasting plasma glucose (FPG) x fasting plasma insulin (FPI)/22.5. Insulin sensitivity was calculated by whole body insulin sensitivity index (WBISI) with reduced time points with the following formula: $10,000/\sqrt{(FPG \times FPI \times 2hPG \times 2hPI)}$, where FPG and 2hPG represent the value of plasma glucose at time $0'$ and $120'$, and FPI and 2hPI represent the value of serum insulin at time $0'$ and $120'$ [13]. All biochemical and hormonal data were analyzed in the centralized laboratory of each center, as described elsewhere [11]. Although analyses were performed in different laboratories, all laboratories belong to the Italian National Health System and are certified