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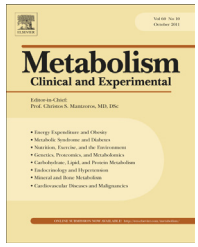

Bariatric surgery in severely obese adolescents improves major comorbidities including hyperuricemia

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ABSTRACT

Objective. Serum uric acid (sUA) is believed to contribute to the pathogenesis of metabolic comorbidities like hypertension, insulin-resistance (IR) and endothelial dysfunction (EDF) in obese children. The present pilot study investigated the association between sUA concentrations and loss of body weight following laparoscopic sleeve gastrectomy (LSG) or laparoscopic Roux-en-Y-gastric bypass (RYGB) in severely obese adolescents.

Materials/Methods. 10 severely obese adolescents underwent either LSG (n = 5) or RYGB (n = 5). 17 normal weight, healthy, age- and gender-matched adolescents served as a normal weight peer group (NWPG). Pre- and 12 months postoperatively, sUA and relevant metabolic parameters (glucose homeostasis, transaminases, lipids) were compared.

Results. Preoperatively, sUA was significantly elevated in patients with severe obesity compared to NWPG. Twelve months after LSG and RYGB, a significant decrease in sUA, BMI, CVD risk factors, hepatic transaminases, and HOMA-IR was observed. Reduction in SDS-BMI significantly correlated with changes in sUA.

Conclusions. sUA levels and metabolic comorbidities improved following bariatric surgery in severely obese adolescents. The impact of changes in sUA on long-term clinical complications of childhood obesity deserves further study.

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Abbreviations: LSG, laparoscopic sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass; BMI, body mass index; sBP, systolic blood pressure; dBP, diastolic blood pressure; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; γ-GT, γ-glutamyl transferase, HOMA-IR, homeostasis model assessment-insulin-resistance; sUA, serum uric acid; CVD, cardiovascular disease; FPG, fasting plasma glucose; FPI, fasting plasma insulin; TG, triglycerides; MRM, multiple reaction monitoring.

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1. Introduction

Metabolic dysfunction and related cardiovascular diseases in obese adults have prompted interest in studying similar conditions in obese children, to estimate the potential impact on the long term health [1]. Specifically, recent evidence suggests that serum uric acid (sUA) concentrations were strongly associated with body weight in adults [2] and obese children [3].

Hyperuricemia is believed to independently play a major role in the pathogenesis of IR and CVD [4,5] in obese individuals, because sUA enters adipocytes through a uric acid-specific transporter and plays a role in regulating the production of macrophage chemoattractant protein 1 (MCP-1). In addition, sUA may participate in the production of adiponectin [6]. Interestingly, MCP-1 is a well-known protein that modulates IR and fatty acid catabolism [7]. Moreover sUA affects various vasoactive mediators and reduces NO production in cultured pulmonary endothelial cells [8]. Increased NO metabolism is essential in the regulation of arterial hypertension, a condition that leads to CVD in the long-term [9,10].

Several long-term longitudinal studies have demonstrated that childhood obesity was associated with a cluster of risk factors for the later manifestation of CVD in adulthood, such as atherosclerosis and hypertension [11,12]. It is reasonable to assume that effective treatment of childhood obesity may reduce those risk factors including hyperuricemia [13].

Behavioral and lifestyle interventions for children and adolescents with severe obesity often fail to achieve sustainable weight loss and thus fail to reverse associated comorbidities [14]. Bariatric surgery has been increasingly suggested as an effective treatment option to achieve sustainable weight loss in severely obese adolescents [15]. The most commonly used procedures for adolescents today include LSG and RYGB. Both techniques improve metabolic and cardiovascular comorbidities such as insulin resistance (IR), an impaired glucose metabolism and CVD in this age group [16,17]. Current evidence indicates that both procedures have similar effects on body weight, food intake, and parameters of lipid and glucose homeostasis despite their surgical differences [18].

Studies focusing on the regulation of sUA in children/adolescents following weight loss therapies remain sparse. In this pilot study we have for the first time investigated the consequences of LSG and RYGB on sUA, glucose and lipid metabolism in severely obese adolescents. We hypothesized that 1) sUA levels would be more elevated in severely obese adolescents compared to lean subjects, 2) sUA levels would decrease following surgical weight loss, and 3) decreases in sUA levels would correlate with change in weight and other important clinical parameters postoperatively.

2. Methods

The study was performed in accordance with the principles of Good Clinical Practice [19] and the Declaration of Helsinki [20]. Informed consent was obtained from all subjects and/or from a legally authorized representative before initiation of any study related activities. Three cohorts were included in this multicenter study: LSG (n = 5) from the University of Leipzig, RYGB (n = 5) from Cincinnati Children's Hospital (NIH R03DK068228; protocol # 05-05-14 approved by CCHMC Institutional Review Board [IRB]). According to present guidelines for weight loss surgery [21], severely obese adolescents in both centers were identified for bariatric surgery only after failing conservative therapy. A normal weight, healthy, age- and gender-matched peer group (NWPG) from our previously described cohort (URL: http://www.clinicaltrials.gov. Identifier: NCT00176371 [22]) served as a lean comparison group. Measurements were performed at baseline and at 12-month follow-up. All subjects were characterized anthropometrically and clinically. Laboratory measurements were carried out in a blinded manner at a certified laboratory in the University of Leipzig, including the frozen specimens from Cincinnati Children's Hospital.

2.1. Cohort definitions

Children over the 90th, 97th and 99.8th BMI percentiles were considered to be overweight, obese and severely obese, respectively, according to the current national reference values [23].

2.2. Sample collection and laboratory data analysis

All blood samples were collected between 8:00 and 10:00 a.m. after an overnight fast. Fasting plasma glucose (FPG) and fasting plasma insulin (FPI) were measured by commercial kits (Glucose Assay Kit II, BioVision, CA, USA; Human Insulin ELISA Kit, Alpco Diagnostics, Salem, NH, USA). IR was evaluated applying the homeostasis model assessment (HOMA) and defined as HOMA >2.7 (HOMA-IR) [24].

Serum hepatic enzyme activities (ALAT, ASAT, γGT) were measured by colorimetric enzymatic assays (Alanine Aminotransferase Activity Assay Kit, BioVision; Aspartate Aminotransferase Activity Assay Kit, BioVision; IDTox γ-Glutamyl-Transferase Enzyme Assay Kit, IDLabs, ON, Canada).

Analysis of total cholesterol (Chol), high-density lipoprotein cholesterol (HDLc), low-density lipoprotein cholesterol (LDLc) and triglycerides (TG) was determined by the Integra 700 Analyzer (Roche Diagnostic, Hoffmann–La Roche, Ltd, Basel, Switzerland) using the standard enzymatic method from the Biochemical Laboratory instructions.

2.3. Measuring of serum uric acid

sUA sample preparation was based on a modified method by Kim et al. [25]: serum samples (10 μl) were 10-fold diluted with water which included [1,3-15 N2]-UA (Eurisotop, Saarbrücken, Germany, final concentration 50 μmol/L) and treated with 20 μl 10% TCA (w/v). The samples were vortexed for 1 min and centrifuged at 15,000 × *g* for 2 min. Supernatants were loaded into autosampler vials and analyzed by LC-MS/MS.

Analyses were carried out on an Agilent 1100 series binary HPLC system (Agilent Technologies, Waldbronn, Germany) coupled with an 4000 QTRAP™ mass spectrometer (AB Sciex, Concord, Canada) equipped with a TurboIon spray

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