CLINICAL BRIEF

Anthropometric and Biochemical Determinants of Estimated Glomerular Filtration Rate in a Large Cohort of Obese Children

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Objective: We aimed to investigate which clinical and metabolic factors could influence the estimated glomerular filtration rate (eGFR) levels, evaluating a large population of obese children without suspect of primary kidney disease.

Design: Retrospective, cross-sectional study.

Setting: Pediatric university department.

Subjects: We enrolled 2,957 obese children and adolescents consecutively attending our department between January 2000 and 2017. Inclusion criteria were body mass index (BMI) > 95th percentile and eGFR > 90 mL/min/1.73 m^2. Exclusion criteria were secondary forms of obesity, eGFR < 90 mL/min/1.73 m^2, proteinuria/hematuria at urine dipstick, or consumption of any medication.

Interventions: Weight, waist circumference, height, waist to height ratio (W/Hr), BMI-standard deviation score (SDS), pubertal stage, systolic blood pressure (SBP) and diastolic blood pressure (DBP), duration of obesity, insulin, eGFR, and homeostasis model assessment (HOMA-IR) were obtained. A general linear model was performed for a multiple variable analysis.

Main Outcome Measure: The population was divided in tertiles for BMI-SDS, W/Hr, SBP- and DBP-SDS, HOMA-IR, and duration of obesity. We compared eGFR levels among these tertiles.

Results: The eGFR levels significantly increased across both BMI-SDS and W/Hr tertiles. Conversely the eGFR levels significantly decreased across SBP-SDS, HOMA-IR, and duration of obesity tertiles. No significant differences in eGFR levels across DBP-SDS tertiles were detected. Pubertal patients presented significantly lower eGFR values compared with prepubertal patients. A general linear model for eGFR variance including as covariates W/Hr, HOMA-IR, duration of obesity, pubertal stage, BMI-SDS, and SBP-SDS (model R^2 39.7%; model $P < .00001$) was performed. It confirmed a direct association of eGFR values with BMI-SDS and an indirect association with HOMA-IR, duration of obesity, pubertal stage, and SBP-SDS.

Conclusions: We showed a positive correlation of eGFR with both BMI-SDS and a negative one with SBP-SDS, HOMA-IR, pubertal stage, and duration of obesity. The duration of obesity was the variable most significantly associated to eGFR levels.

Introduction

DURING THE LAST 2 decades, the prevalence of chronic kidney disease (CKD) has more than doubled and one of the causing factors could be the epidemic increase of obesity.[1,2] Understanding the pathophysiology of estimated glomerular filtration rate (eGFR) in childhood obesity would allow us to identify subjects from a pediatric age exposed to factors potentially influencing eGFR; and thus, the potential of needing specific and intensive clinical management. We aimed to investigate which clinical and metabolic factors could influence the eGFR levels, evaluating a large population of obese children without suspect of primary kidney disease.

Methods

We retrospectively enrolled 2,957 obese children and adolescents (1,485 girls; age range 3-18 years) consecutively attending our department between January 2000 and January 2017. Inclusion criteria were body mass index (BMI) > 95th percentile according to reference values[3] and eGFR > 90 mL/min/1.73 m^2. Exclusion criteria were secondary forms of obesity, eGFR < 90 mL/min/1.73 m^2, presence

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of proteinuria or hematuria at urine dipstick, or consumption of any medication. Subjects with reduced eGFR and positive urine dipstick were excluded as they could present a possible underlining primary kidney disease potentially affecting our analysis. The ethical committee of our university approved the study. Written informed consent was obtained before any procedure. Weight, waist circumference, height, waist to height ratio (W/Hr), BMI-standard deviation score (SDS), and pubertal stage were obtained in the same manner as the 2016 study by Grandone et al.,[4] and as the 2017 study from Marzuillo et al. for blood pressure measures.[5] When provided by the patients' pediatricians, we calculated the duration of obesity evaluating patient's growth charts. These data were available in 1,007 patients.

Serum alanine transaminase, aspartate transaminase, insulin, triglycerides, total cholesterol, high-density lipoprotein cholesterol, and glucose were assayed, and homeostasis model assessment (HOMA-IR) was calculated. The HOMA is an index of insulin resistance, and it is calculated with the following formula: (glucose [mg/dL] × insulin [μU/mL])/405.[6] Serum creatinine (mg/dL) was always measured with Jaffè method, and the eGFR was calculated by using the Schwartz equation.[7] According to the Schwartz equation, we used the following formula to calculate eGFR: k × patient's length (cm)/serum creatinine (mg/dL).[7] The value of k was 0.55 for children and adolescent girls, whereas it was 0.7 for adolescent males.[7] We normalized the eGFR to the ideal body weight–derived body surface area with the methods indicated in the article by Correira-Costa et al.[8]

The population was divided in tertiles for BMI-SDS, W/Hr, systolic blood pressure (SBP)- and diastolic blood pressure (DBP)-SDS, HOMA-IR, and duration of obesity (ranges for these tertiles are shown in the Supplementary Table 1). The patients were considered "pubertal" if they presented a pubertal stage ≥2 according with the Turner classification of puberty, otherwise the patients were considered "prepubertal".[9] We compared eGFR levels between male and females, prepubertal and pubertal patients, and among the different tertiles of BMI-SDS, W/Hr, SBP- and DBP-SDS, HOMA-IR, and duration of obesity. The Kruskal-Wallis test was used, as all variables were not normally distributed. A general linear model was performed for a multiple variable analysis, including W/Hr, HOMA-IR, duration of obesity, pubertal stage, BMI-SDS, and SBP-SDS as covariates and eGFR as dependent variable. P values $< .05$ were considered statistically significant. The Stat-Graph XVII software for Windows was used for all statistical analyses.

Results

Clinical and laboratory characteristics of enrolled patients are shown in Supplementary Table 2. The population mean age was 10.3 ± 2.94 year; the mean BMI-SDS was 2.9 ± 0.86. Nine hundred ninety-nine of 2,957 (33.78%) patients were pubertal.

Males and females showed similar eGFR values (Fig. 1A).

The eGFR levels significantly increased across both BMI-SDS and W/Hr tertiles (Fig. 1B and C). Conversely, the eGFR levels significantly decreased across SBP-SDS, HOMA-IR, and duration of obesity tertiles (Fig. 1D, F and H). Pubertal patients presented significantly lower eGFR values compared with prepubertal patients (Fig. 1G). No significant differences in eGFR levels across DBP-SDS tertiles were detected (Fig. 1E).

A general linear model for eGFR variance, including W/Hr, HOMA-IR, duration of obesity, pubertal stage, BMI-SDS, and SBP-SDS (model R^2 39.7%; model $P < .00001$) as covariates, was performed (Table 1). It confirmed a direct association of eGFR values with BMI-SDS and an indirect association with HOMA-IR, duration of obesity, pubertal stage, and SBP-SDS. The most significantly associated variable was the duration of obesity.

Discussion

In childhood, contrasting data about the relationship between obesity and eGFR values exist. Some authors found a positive correlation between BMI and eGFR,[10,11] whereas other studies did not find any difference in eGFR levels comparing obese children with lean controls.[12–14] This contrasting data are probably derived from a nonlinear correlation between eGFR and obesity. In fact, the eGFR in obesity-related nephropathy can present an evolution characterized first by a gradual increase ("hyperfiltration") and second by a gradual decrease of its levels.[15,16] Our results showed contrasting data about the association of BMI-SDS (direct) and HOMA-IR (indirect) with eGFR levels. A possible explanation could be similar to the obesity-related nephropathy evolution, in that childhood obesity is first characterized with an increase of eGFR levels and second by an eGFR levels reduction, when HOMA-IR increases its effect over the time (duration of obesity). Evidence exists that obesity during adolescence predicts onset of CKD in the general adult population,[17] and moreover, there is a positive relationship between duration of pediatric overweight/obesity and comorbidities later in life.[18] In contrast, no evidence about the effect of duration of obesity on eGFR levels in childhood is available. Interestingly, we identified a correlation of the duration of obesity on the reduction of eGFR levels in children, although the eGFR remains within the normal range. This is in line with the findings of Vivante et al.,[17] who show in their cohort of patients, 17 years of age and older, a significantly higher cumulative incidence of treated end-stage renal disease in obese adults compared with