

Childhood Obesity and Impact on the Kidney

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Keywords

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Abstract

Obesity is known to be associated with a myriad of cardiovascular and metabolic comorbidities. In children, several longitudinal studies have shown that obesity consequences start early in life and accompany the obese child into adulthood, implying a higher risk of adverse cardiovascular events. More recently, data related to the possible role of obesity in the risk of kidney disease in adults, independently of diabetes, has started to become more available. In children, the evidence is scarcer, but it has also been acknowledged that obesity acts as a risk factor for disease progression when kidney impairment already exists, thereby increasing the risk of death among children with end-stage renal disease (ESRD). Besides this, there is also evidence that otherwise healthy overweight and obese children have a significant increase in the risk of all-cause ESRD later in life. The potential mechanisms underlying this association need to be further discussed in order to allow the setting in motion of preventive strategies to halt chronic kidney disease development and progression.

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Introduction

In the last decades, overweight and obesity reached pandemic proportions and the prevalence of obesity remains historically high. The 2015 updated analysis of the Global Burden Disease Study reported a total of 107.7 million obese children and 603.7 million obese adults; since 1980, the prevalence of obesity has doubled in more than 70 countries and has continuously increased in most other countries [1]. It has been acknowledged worldwide that this continuous rise is threatening health improvements in many countries and childhood obesity has been identified as one of the most important risk factors for developing cardiovascular diseases later in life, thus undoubtedly representing a major public health concern.

In children, recent data confirmed that obesity might also contribute to an important increase of chronic kidney disease (CKD) incidence and to be associated with an increase in the risk of death among children with end-stage renal disease (ESRD).

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Obesity-Related CKD

Obesity-related glomerulopathy is a secondary form of focal segmental glomerulosclerosis, morphologically characterized by glomerulomegaly, mesangial cell proliferation, and matrix accumulation, which was first described in 1975 by Cohen [2].

Over the last decades, the obesity epidemic in the risk of kidney disease has been recognized in adults, independently of diabetes. There has been a dramatic rise in the prevalence of ESRD, which has more than doubled in the past decade, and that occurred simultaneously with the increased prevalence of obesity [3]. A 2017 systematic review and meta-analysis by Garofalo and colleagues represent to date the highest evidence available, allowing us the withdrawal of definite conclusions on the effect of body mass index (BMI) as an independent predictor of de novo CKD in the general adult population [4]. The authors reported that obesity increased the relative risk of developing low glomerular filtration rate (GFR) and albuminuria, in more than 600,000 participants enrolled in the 39 cohort studies included in the analysis, over a mean follow-up period of 6.8 years.

In CKD patients, obesity was also identified as a strong and potentially modifiable risk factor for the progression of kidney disease and more rapid loss of GFR. An association between different obesity measures and several renal outcomes has been described, including higher mortality in obese patients with ESRD [5] and kidney transplant recipients [6].

It is inarguable that the obesity problem has also been gaining more and more attention among the scientific pediatric nephrology community. Despite the fact that the body of evidence in children is somehow scarcer than the one supporting the contribution of obesity to CKD in adults, recent data seems to confirm a similar trend among children [7]. Nonetheless, it is important to notice that obesity-related nephropathy is still a virtually non-diagnosed entity in children and adolescents.

Some degree of renal impairment associated with obesity is believed to start early in childhood, long before the appearance of hypertension, diabetes, and other associated comorbidities known to contribute to renal disease [8]. In fact, it has been reported that obese children have larger kidneys and increased renal blood flow than their normal weight counterparts [9], which supports the idea that obesity triggers changes at the kidney, starting early in life. Even so, the association and the mechanisms of renal injury with obesity in children are still debated, since contradictory results continue to emerge.

Some authors reported strong positive correlations between measures of obesity and GFR, probably reflecting a hyperfiltration state, while others found lower GFR levels in overweight/obese children or no differences. These contradictory findings might result from the fact that subtle changes in the early phases of obesity-related kidney injury might be difficult to ascertain in young children.

In a Canadian tertiary pediatric nephrology clinic, an important BMI increase among patients has been reported over a period of 20 years, which might unveil a global tendency that puts a wide range of children with kidney diseases at a higher risk for developing CKD later in life [10]. In 2013, a study characterizing the European pediatric population under renal replacement therapy revealed that more than 30% of the children were overweight or obese [11], which is particularly concerning since higher BMI has been shown to be associated with an increase in the risk of death among children with ESRD [12]. Pretransplantation obesity and increased BMI after renal transplant have also been associated with decreased renal allograft survival in pediatric patients [13]. A recently published retrospective analysis of children aged 2–19 years old, beginning renal replacement therapy from 1995 to 2011 in the United States, reported that obese children were less likely to receive a living donor transplant and had a higher risk of death, and this was attenuated after adjustment for transplant in a time-dependent Cox model [14]. These results might signify that lower rates of kidney transplant may mediate a higher risk of death among obese ESRD children.

Moreover, besides the impact of obesity as a risk factor for disease progression when kidney impairment already exists, 2 recent cohort studies showed that otherwise healthy overweight and obese children have a significant increase in the risk of all-cause ESRD later in life [15, 16].

At this point it is important to underline that some early life determinants might impact the way obesity affects the kidney. Children with reduced nephron mass, for example, those who are born small for gestational age or preterm [17], besides having an increased risk of becoming obese due to prenatal programming, are also more prone to a faster renal deterioration, since excessive weight gain will increase the metabolic and hemodynamic load on each individual nephron, whose number was fixed at birth [18]. The main factors that seem to predispose to reduced renal development seem to be protein and calorie malnutrition, placental malfunction, and ma-

ternal hyperglycemia [19]. In these settings of adverse prenatal conditions, the discussion of the importance of obesity as an additive factor detrimental for renal survival assumes particular importance. If besides obesity, the children or adolescent already accumulates obesity-associated comorbidities, such as hypertension, dyslipidemia, or insulin resistance, all known to contribute to renal impairment, then the risk of later ESRD is even higher. In fact, a study on a large sample of European children showed that about half of the children already present adverse CV risk factors before or at the onset of puberty, and that the clustering of 2 or more risk factors was present in about 11% of the children [20].

Mechanisms of Kidney Injury

Obesity-related kidney damage is thought to be initiated by a hyperfiltration phase, which initially functions as a physiological adaptation of the kidney to the increased body mass [21]. The chronic state of hyperfiltration later potentiates progressive renal damage, with increased loss of proteins and a last phase of glomerulomegaly, cellular remodeling, and fibrotic scarring [22].

Obesity is a well-recognized low-grade inflammatory state – adipose tissue (especially visceral) is a major source of endocrine bioactive proinflammatory compounds, while the systemic levels of anti-inflammatory adipokines are reduced. There is increasing evidence that this proinflammatory state along with increased levels of oxidative stress and an overactivated renin-angiotensin-aldosterone system might be among the underlying mechanisms determining the association between obesity and altered metabolic states, vascular dysfunction, cardiovascular disease, and also kidney changes. These potential mechanisms between obesity and kidney disease need to be further investigated, especially in children, in order to allow the setting in motion of preventive strategies to halt CKD development and progression.

Implications for Practice

The evaluation of childhood obesity trends, across time and in different populations, poses several challenges. It is important to have well-defined classification criteria that one can apply to population-based data over time, but actually several definitions exist for pediatric obesity. However, several definitions for pediatric obesity

have been used overtime which limits comparability between studies.

The adjustment or scaling of GFR is another important practical point to be considered. The findings of adult studies show that alternative indexing methods and body size variables need to be further evaluated and tested and, to our knowledge, only a recent study of our group addressed this problematic in children [23]. We found that, compared to normal weight children, the mean absolute GFR was higher in the overweight and obese children, whereas BSA-adjusted GFR was lower. In the interpretation of these findings, it became evident that the important inconsistencies introduced by GFR adjustment for body size in overweight and obese children probably result from the fact that normalization to conventional BSA, a body size descriptor dependent on weight, systematically yields lower GFR estimates in these children than in normal weight children.

Nonetheless, acknowledging that GFR varies with weight and height, GFR must include some adjustment for body size. But, although varying with weight and height, the kidney size and the number of functioning nephrons will not increase if an individual of a certain height and weight gains additional fat mass and becomes obese at some point of the life course. So, at any undetermined moment of weight gain, when adjusting for real BSA, we will start over adjusting. Thus, it is crucial to consider that the method of adjustment for body size might be a major confounder of GFR determination in individuals with abnormal body habitus.

While assessment of absolute GFR without any indexing may represent an appropriate approach in cohorts with substantial variation of fat mass and is suitable for intra-individual longitudinal analyses, it does not allow comparisons with reference values and with children across the pediatric age range. Normalization of GFR to BSA calculated from ideal body weight rather than actual weight might be a promising option that deserves further investigation.

Conclusions

The recognition of obesity as a major detrimental determinant for the cardiovascular health and renal function in young children, should make clinicians aware of the importance of implementing early strategies to prevent and fight childhood obesity. It has become more and more evident that global and public health strategies need

to be identified and set in motion with the objective of counteracting the obesity-associated CKD epidemic, at a population level, and the accelerated progression towards kidney failure, at an individual level, observed in the last decades.

Lifestyle recommendations, including diet and physical exercise, in obese patients at risk of CKD, appear to be justified even considering the paucity of long-term stud-

ies in the pediatric population, particularly if other comorbidities, such as hypertension and insulin resistance are already present.

Disclosure Statement

The authors have no conflicts of interest to declare.

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