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Obesity in Children with Kidney Disease

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Abstract

Purpose of Review We review the epidemiology, aetiology and consequences of obesity in children with chronic kidney disease (CKD).

Recent Findings CKD in children has traditionally been associated with failure to thrive. However, with increasing global childhood obesity rates, more children with CKD are now overweight than underweight. Recent large cohort studies have allowed a greater understanding of the role of obesity in cardiovascular morbidity and other adverse outcomes in children with CKD.

Summary Obesity is common in the paediatric CKD population with a multifactorial aetiology, including exposure to corticosteroids during treatment of glomerular diseases and after transplant and decreased physical activity. Obesity is associated with a number of adverse outcomes including cardiovascular disease, which is the leading cause of mortality in this group, decline in kidney function and poor graft function post-transplantation. Obesity is an important modifiable risk factor, and further research into interventions targeting obesity in children with CKD is required.

Keywords Obesity · Overweight · Chronic kidney disease (CKD) · Children · Cardiovascular disease · Body mass index (BMI) · Paediatric nephrology

Introduction

Childhood obesity is a major public health problem across the world. Children who are overweight or obese are at higher risk of cardiovascular disease, chronic kidney disease (CKD), hypertension and diabetes and are likely to remain overweight or obese into adulthood [1, 2]. Although overweight and obesity are a risk factor for all children, certain paediatric populations may be at even higher risk of experiencing significant morbidity and mortality as a consequence of obesity. Cardiovascular disease is the leading cause of morbidity and mortality in children with CKD, and obesity in this population increases this risk. Obesity may also contribute to progression of CKD and is linked to poorer outcomes after kidney transplantation [3, 4]. This review will explore the current literature on the burden and consequences of overweight and obesity in children with CKD.

Epidemiology of Childhood Obesity

The standard definition of childhood obesity is a body mass index (BMI) above the 95th percentile for children and teens of the same age and sex. Overweight is defined as a BMI at or above the 85th percentile and below the 95th percentile. In 2016, over 340 million children and adolescents were overweight and obese. The worldwide prevalence of overweight and obesity has quadrupled from 1975 to 2016, and the rapid rise has led to the coining of the term the obesity epidemic [5].

Almost 20% of children in the USA are obese, and a further 16% are overweight. Obesity is more common in Hispanic and Black children and children from low-income households [6]. This is comparable to other developed

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countries with approximately 30% of Canadian and British children and adolescents also overweight or obese [7].

Although traditionally considered a problem of higher-income countries, most overweight children live in low- and middle-income countries where obesity rates have been rising even faster than in high-income countries. These children often face the paradoxical dual threat of obesity and malnutrition [5].

Obesity in Children with CKD

Studies of children with CKD in high-income countries show high rates of overweight and obesity. The Chronic Kidney Disease in Children (CKiD) study, a prospective cohort of children and young adults with CKD in the USA and Canada, found up to a quarter of children, with mild to moderate CKD (estimated glomerular function rate; eGFR 30 to 90/min/1.73m^2), had a BMI > 90th centile, a rate significantly higher than children without CKD [8]. Increasing rates of obesity were described in a Canadian paediatric CKD population over the past 30 years reflecting the trend in the general population [9]. Of the over 500 patients, we saw in our Australian paediatric nephrology clinic in 2018, 17% were overweight and 15% were obese (S.E. Jung, A.M. McKay, S.E. Kennedy, unpublished data, 2020). The prevalence of obesity and overweight is highest in children with mild CKD and declines with increased CKD severity [8].

The aetiology of obesity in children with CKD is likely multifactorial. Certain conditions seen in the paediatric nephrology clinic are associated with a higher BMI including hypertension, nephrotic syndrome and other glomerular diseases, nephrogenic diabetes insipidus, neurogenic bladder associated with spina bifida and hypophosphatemic rickets. Obesity in these children may be associated with the underlying pathophysiology of the condition (i.e. hypertension); the consequence of treatment with corticosteroids in nephrotic syndrome and glomerulonephritis; a large intake of calorie containing fluids in children with nephrogenic diabetes insipidus or due to reduced physical activity found in the other conditions due to physical limitations [9]. Additionally, obesity is common in some genetic syndromes associated with CKD such as Bardet–Biedl syndrome. Lower household income has been consistently associated with obesity in the general population and is also a risk factor for obesity in children with CKD [3].

While there is increasing evidence of high rates of obesity in children with mild to moderate CKD, there is still a widely held belief that children with kidney failure are at higher risk of being underweight than overweight. However, a European multicentre study of 4474 children with kidney failure (including both dialysis and transplant patients) showed 20.8% were overweight, 12.5% were obese, and just 3.5% were underweight. Even when transplanted patients, who are known to have improved growth compared to children on dialysis, were excluded, children with kidney failure were still more likely to be overweight or obese than underweight. The only exception was infants 0 to 1 year of age who were more likely to have failure to thrive [10, 11].

Decreased physical activity may contribute to the problem of overweight and obesity in children with CKD. Children with CKD are less likely to participate in 60 min of physical activity per day and are more likely to spend more than 2 h a day in front of a screen than their peers [12].

Obesity and Cardiovascular Morbidity

Cardiovascular disease is the leading cause of death in children with CKD. Almost one quarter of deaths in children and young adults with CKD are due to cardiovascular causes, and the risk of a cardiac death is 1000-fold higher compared to healthy children [13]. Children who have undergone kidney transplantation are at significantly lower risk than children on dialysis (OR 0.22), which reinforces transplant as the gold standard in treatment for children with kidney failure. However, transplanted children still have an excess cardiovascular mortality risk compared to healthy children [13]. These alarming findings have prompted many studies into cardiovascular risk factors in children with CKD.

Obesity in children with CKD is an independent risk factor for intermediate cardiovascular outcomes such as left ventricular hypertrophy [14]. This association between obesity and LVH in children with CKD was shown by a recent study involving the CKiD cohort where BMI was independently associated with greater left ventricular mass index and greater odds of LVH. Interestingly, the association between BMI and LVH is stronger in girls than boys, and it has been postulated that obesity-mediated decrease in cardio-protective oestrogen levels may be responsible.[15].

In addition to obesity, children with CKD have an excess of other cardiovascular risk factors including dyslipidaemia, hypertension and impaired glucose metabolism. The prevalence of these risk factors increases with decreasing GFR and are strongly associated with the presence of obesity [3, 8, 16]. About 50% of overweight and obese children with CKD will have at least one other cardiovascular risk factor [3]. However, children with a normal BMI and CKD also have a higher prevalence of other cardiovascular risk factors suggesting that the excess cardiovascular risk in children with CKD is not mediated through obesity alone [3, 16].

Although based on these findings interventions targeting weight reduction in children with CKD to improve cardiovascular outcomes appears logical, caution has been promoted by some clinicians due to the so-called obesity paradox. In adult studies, obesity has been associated with

a survival advantage in patients who are dialysis-dependent or have severe CKD (GFR ≤ 30 mL/min/1.73 m^2) [17]. However, this pattern has not been replicated in paediatric studies, where a U-shaped association between BMI and mortality has been found, with children at both ends of the BMI spectrum at higher risk of death. A study of nearly 2000 children with kidney failure (including both dialysis and transplant patients) in the USA showed the lowest risk of death occurred at a BMI standard deviation score (SDS) of 0.5. The risk of death increased by 6% with one standard deviation (SD), 26% with 2 SD and 67% with 3 SD above or below this point [18].

Obesity and Risk of CKD

Obesity has not only been associated with excess cardiovascular mortality but is a proven risk factor for developing de novo CKD in adults. A study of Israeli adolescents over a 25-year period showed overweight and obesity increased the risk of kidney failure (HR 3.00 and 6.89, respectively). The association was particularly strong for developing diabetic nephropathy but also significant for nondiabetic causes of kidney failure [19]. The impact of a high BMI on kidney function occurs early in the lifespan; young adults (18 to 26 years) with a BMI ≥ 35 have significantly higher rates of albuminuria, an early marker of CKD, than those with lower BMIs [20]. It has been estimated that 24% and 34% of kidney disease in US men and women, respectively, can be attributed to overweight and obesity [21].

The overall risk of CKD secondary to obesity appears to be associated with the age that a person first becomes overweight. A longitudinal study of over 5000 children in the UK found younger age (< 36 years of age) when first overweight was strongly associated with increased odds of developing CKD or nephrotic range proteinuria at age 60–64 years [22]. When we consider childhood obesity is strongly associated with overweight and obesity in adults, interventions that reduce the obesity in children might well be expected to have health benefits throughout the lifespan.

Certain populations are at high risk of adverse renal outcomes from obesity. Obesity in Australian Aboriginal children increased the risk of albuminuria but conversely had a protective effect in non-Aboriginal children. The finding of a protective effect of increased BMI on albuminuria in non-Aboriginal children is contrary to the results of large population studies, and it has been proposed that this phenomenon represents a transient protective effect in childhood that does not persist into adulthood [23].

Obesity and other cardiovascular risk factors not only increase the risk of developing CKD but can also lead to more rapid decline in GFR in children with existing CKD. Children with multiple cardiovascular risk factors who were obese had a more rapid decline in their eGFR [3]. BMI has also been identified as an independent risk factor for developing CKD in IgA nephropathy, the risk of renal scarring with febrile urinary tract infections in children with vesicoureteric reflux and progression of early-stage autosomal dominant polycystic kidney disease [24–26]. Renal injury in obesity may be mediated via associated comorbid conditions, such as hypertension and diabetes, or via direct mechanisms [27]. While the exact pathways mediating direct renal injury are still being established, mechanisms of injury include haemodynamic changes and glomerular hyperfiltration, the action of adipocyte hormones and fat accumulation. Glomerular hyperfiltration leads to mechanical stress affecting the glomerulus and proximal tubules, increased sodium reabsorption, activation of the renin–angiotensin system and production of reactive oxygen species [28]. Alterations in adipocyte hormones including leptin, adiponectin and pro-inflammatory cytokines promote inflammation, fibrosis and podocyte injury, and intracellular lipid accumulation leads to impaired fatty acid B-oxidation, mitochondrial damage and high levels of reactive oxygen species [29].

Obesity and Kidney Transplantation

Kidney transplantation is the gold standard treatment for kidney failure in children, with improved survival, growth and quality of life compared to long-term dialysis [11, 30, 31]. Between 15 and 17% of children are overweight and 8–16% obese at the time of transplantation [4, 32]. Younger children, children with congenital anomalies of the kidney and urinary tract and history of peritoneal dialysis are more likely to be overweight or obese at the time of transplant [33].

At 6 months post-transplant, the percentage of children who are overweight can increase up to 23% and obesity to 34%. The prevalence has been shown to then remain stable for up to 2 years post-transplant, suggesting children maintain the weight they gained in the first few months post-transplant. Age between 6 and 12 years, female sex, lower BMI at transplant and black race or Hispanic ethnicity were associated with a higher risk of being overweight or obese post-transplant, and corticosteroid-free immunosuppression regimens are associated with a lower risk of obesity [32].

Obesity has also been associated with poorer graft function and an increased risk of graft failure. A US study found a linear association with the risk of graft loss increasing on average by 7% for every 1 point increase in BMI z-score [33–35]. In a study from Australia and New Zealand, children who were overweight or obese at the time of kidney transplantation had a 61% increased risk of graft failure which persisted up to 10 years post-transplant [4]. Conversely, a US study of the NAPRTCS registry did not find

an increased risk of graft failure between obese and non-obese children but a higher risk of thrombosis. Overall mortality in the North American cohort was also not different between the obese and non-obese group, but on subgroup analysis, an increased risk of death was seen in the 6–12-year age group [33]. The reason for the conflicting findings is not completely clear; however, the two studies showing increased risk of graft loss were more recent cohorts, and it is possible that with recent improvements in immunosuppression regimens, surgical techniques and other aspects of paediatric kidney transplantation, the effect of BMI on graft function has become clearer.

Interventions for Obesity in Children with CKD

Despite the fact that obesity is a potentially modifiable risk factor for many adverse outcomes in children with CKD including cardiovascular disease, rate of CKD progression and graft survival after transplantation, there are minimal published studies of interventions for obesity in this population.

Adult data shows improved GFR and reduced proteinuria with weight reduction; the most effective results were seen from bariatric surgery [36]. Bariatric surgery may also improve renal function in severely obese children. An observational study of 242 severely obese adolescents undergoing bariatric surgery found in those with baseline renal dysfunction, kidney function and albuminuria improved 6–12 months after surgery [37]. In both cohorts, the underlying cause of the renal dysfunction in many cases is either directly related to obesity or to associated diseases such as type 2 diabetes or hypertension, and whether weight loss can improve or slow the progression of renal disease in children with non-obesity-mediated renal disease is yet to be explored.

Interventions shown to be effective in children with obesity in the general population include multicomponent lifestyle interventions (dietary and physical activity education often combined with behavioural change strategies), drugs and bariatric surgery. In a series of Cochrane reviews examining interventions for childhood obesity, lifestyle interventions were more effective in young children, emphasizing the need for early obesity intervention. Weight loss was more likely to be sustained in young children (6 and under) and adolescents than in school age children [38–40]. Several drugs including metformin (anti-diabetic medication), fluoxetine (anti-depressant), sibutramine (an appetite suppressant withdrawn from the FDA due to adverse cardiovascular outcomes) and orlistat (fat absorption inhibitor) result in small but significant reductions in BMI; however, their use needs to be weighed against potential side effects, and dose adjustment may be required in renal impairment [41].

Metformin is increasingly used for the management of obesity in children and adolescents, and a recently published meta-analysis of 24 randomized control trials of variable quality concluded that metformin has a modest effect on weight in obese children and adolescents [42, 43]. A similar beneficial effect on BMI has been seen in children and adolescents with type 1 diabetes mellitus (T1DM) [43, 44]. Additionally, when used in children and adolescents with T1DM, metformin has been shown to improve surrogate markers of cardiovascular dysfunction such as aortic wall shear stress, pulse wave velocity, carotid intima-media thickness and glyceryl trinitrate-mediated brachial artery dilatation [44, 45].

Metformin was previously linked to lactic acidosis in CKD, and it was relatively contraindicated in patients with lower GFR. However, a wealth of evidence has subsequently shown metformin to be safe and indeed beneficial in adults with mild and moderate CKD, and in 2016, the FDA revised its previous advice on metformin to now state that metformin can be initiated in patients who have an eGFR greater than 45 mL/min, and treatment can be continued in existing patients as long as the eGFR remains above 30 mL/min [46]. The 2020 Kidney Disease: Improving Global Outcomes (KDIGO) practice guideline on managing diabetes in CKD recommends treating patients with type 2 DM, CKD and an eGFR $\geq$ 30 ml/min per 1.73 m^2 with metformin [47]. We are not aware of any published trials of metformin use in children with CKD; however, given the apparent benefits of metformin in reducing BMI and improving cardiovascular health in other paediatric populations and the safety in adult CKD populations, we propose that further study of metformin in paediatric CKD is warranted.

A nutritional survey of the CKID cohort identified many children with mild to moderate CKD are consuming more than their recommended daily caloric requirements, and fast foods and snack foods were a large contributor to their overall caloric intake. The authors proposed targeting these foods to reduce energy intake. However, there are no published studies of successful interventions supporting families of children with CKD in achieving calorie reduction and weight loss, and it is recognized that adherence with nutritional advice is often poor in children with CKD [48]. Many traditional dietary modifications are challenging for the CKD population to implement, where dietary options are already limited by potassium, phosphate and fluid restrictions. Involvement of a renal dietician is essential to ensure the nutritional requirements are met in these children. We also know children with CKD are less physically active than their peers, and interventions that pair dietary modification with increased physical activity are likely to be helpful.

In the post-transplant population, corticosteroid-free immunosuppression regimens have been proposed and implemented in some centres, to address the many adverse effects from corticosteroids including obesity. Initial studies showed an unacceptably high risk of acute rejection and graft failure with these regimens [49]. More recent medium-term studies however show similar patient and graft survival despite an increased risk of rejection and improved cardiovascular risk factors including obesity, hypertension and LVH [50]. Corticosteroid-free immunosuppression strategies therefore may be an appropriate option for children at low immunological risk post-transplant.

Conclusions

Children with CKD are more likely to be overweight and obese, are less physically active and are at higher risk of cardiovascular morbidity and mortality then their healthy peers. Obese children are also at higher risk of developing CKD, progression of existing CKD and poorer graft outcomes after kidney transplantation. To date, there is little evidence exploring the efficacy, benefits and risks of weight reduction in this population. Further research into effective interventions and collaboration with paediatric obesity medicine specialists is required to achieve health throughout the life course for children with CKD.

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