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REVIEW

Kidney function evaluation in children and adolescents with obesity: a not-negligible need

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Abstract

The role of obesity as risk factor for chronic kidney disease (CKD) has been well-recognized. As previously demonstrated in adults, emerging data highlighted the relevant impact of obesity on renal function since childhood. As a matter of fact, obesity also affects renal health through a complex pathogenic mechanism in which insulin resistance (IR) plays a pivotal role. Worthy of note, the vicious interplay among obesity, IR, and renal hemodynamics clinically translates into a plethora of kidney function impairments potentially leading to CKD development. Therefore, renal injury needs to be added to the well-known spectrum of cardiometabolic obesity comorbidities (e.g., type 2 diabetes, IR, metabolic syndrome, cardiovascular disease). *Conclusion*: Taking this into account, a careful and timely monitoring of kidney function should not be neglected in the global assessment of children with obesity. We aimed to provide a comprehensive overview on the relevance of kidney evaluation in children with obesity by shedding lights on the intriguing relationship of obesity with renal health in this at-risk population.

What is Known:
- *Obesity has been found to be a risk factor for chronic kidney disease.*
- *Unlike adults, pediatric data supporting the association between obesity and renal function are still limited.*

What is New:
- *As observed in adults, obesity might affect renal function since childhood.*
- *Kidney function should be carefully evaluated in children with obesity.*

Keyword Kidney · Damage · Obesity · Children

Abbreviations

AGP	Alpha 1-acid glycoprotein
CKD	Chronic kidney disease
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
Gal-3	Galectin-3
GluAp	Glutamyl aminopeptidase
HOMA-IR	Homeostatic model assessment for insulin resistance
HR	Hazard ratio

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IR	Insulin resistance
KIM-1	Kidney injury molecule-1
MASLD	Metabolic-associated steatotic liver disease
NAG	N-acetylbeta-D-glucosaminidase
NGAL	Neutrophil gelatinase-associated lipocalin
ORG	Obesity-related glomerulopathy
ORKD	Obesity-related kidney disease
PCX	Podocalyxin
RAAS	Renin-angiotensin-aldosterone-system
TGF-beta	Transforming Growth Factor-beta
TNF-alpha	Tumor Necrosis Factor-alpha
T2D	Type 2 diabetes
WHtR	Waist-to-height ratio

Introduction

In addition to the well-known cardiometabolic comorbidities (e.g., type 2 diabetes (T2D), metabolic syndrome, insulin resistance (IR), and metabolic-associated steatotic liver disease (MASLD)) [1–3], emerging data found that obesity also acts as a risk factor for chronic kidney disease (CKD) [4–7]. As a matter of fact, children with obesity have been found to be at higher risk to kidney damage development (expressed as renal function decline and/or hypertension and/or albuminuria or proteinuria) [8–10]. Remarkably, cardiometabolic parameters (e.g., body mass index, waist circumference, and waist-to-height ratio (WHtR)) have been closely associated to kidney injury [4, 8–10], suggesting a close association of kidney function not only with obesity but also with its own dysmetabolic state [11, 12].

From a pathophysiological point of view, a dangerous link between IR and kidney function has been highlighted, in which chronic inflammation, oxidative stress, and adipokine dysregulation are deeply intertwined players [11]. Indeed, these shared pathogenic factors contribute to impair renal hemodynamics leading to CKD development and progression [4, 13]. More, obesity has been demonstrated as a modifiable risk factor for kidney damage in various diseases with variable kidney involvement in childhood ranging from congenital solitary functioning kidney [14], hypertension [15, 16], renal scarring [17], glomerulosclerosis [18], IgA nephropathy [19], autosomal dominant polycystic disease [20], to CKD [12, 21].

Nevertheless, CKD identification in pediatric population is challenging per se due to the wide spectrum of clinical presentations and to the intrinsically difficult assessment of kidney function in early ages [22].

To complicate matters, data regarding the impact of obesity on renal health are conflicting [10, 12, 13]. Evidence indicates that hyperfiltration could be found in the initial phase of kidney damage followed by reduced glomerular filtration rate [12, 13]. Conversely, other studies demonstrated that a reduced glomerular filtration might occur as the first sign of kidney damage in children with obesity [10, 12, 13]. This might translate into a large clinical variability from silent disease to evident kidney damage, making even more challenging the overall management of these patients [12, 22].

Nevertheless, kidney damage has emerging as non-negligible obesity complication since childhood. Considering not only its tangled pathogenic interplay with dysmetabolism and adiposity [12, 23, 24] but also its relevant medical and economic burden [1, 2, 12], renal function deserves tremendous attention in these patients.

We aimed to highlight the clinical and prognostic relevance of kidney evaluation in children with obesity as a population at intrinsic greater cardiometabolic risk by discussing the most recent evidence in this intriguing research area.

Pathophysiological mechanisms of kidney damage in pediatric obesity

While the most frequent causes of CKD in the adult populations are represented by diabetic kidney disease and hypertension [12, 25, 26], childhood obesity has been found to be an important risk factor for CKD development in childhood [12, 27, 28]. Although the exact pathophysiological mechanism of kidney damage is still less defined, the negative impact of obesity and of its own dysmetabolism on renal hemodynamics has been largely documented [12, 29–31] (Fig. 1). In this context, the pivotal role of IR further contributes to kidney damage development through endothelial dysfunction and increased vascular permeability [13, 32]. Indeed, the dysmetabolic state underlying obesity affects kidney health by increasing the risk of hypertension and diabetes [29–31].

Worthy of note, the detrimental effect of a reduced nephron numbers on growth and long-term kidney function might be also considered in the development of kidney damage [33].

Obesity has been implicated directly in the impairment of kidney function via hemodynamic alterations due to a greater renal hemodynamic demand [7, 13, 21]. The association of vasodilatation of the afferent arteriole and the increased proximal tubular sodium reabsorption by upregulation of the renin-angiotensin-system (RAAS) system leads to glomerular hyperfiltration, resulting in hemoconcentration in the postglomerular circulation [7, 34]. From a clinical point of view, this translates into proteinuria and hypertension [3]. Remarkably, an intricate pathophysiological link between microalbuminuria and dyslipidemia—as another obesity feature—contributing to lipotoxicity, vascular injury, atherosclerosis, and glomerulosclerosis has been also described [7, 35]. More, angiotensin II as RAAS final effector acts as a growth factor and profibrogenic and proinflammatory cytokine, further promoting these processes [34].

Therefore, the tangled interplay among hemodynamic changes, hyperfiltration, IR, RAAS activity, proinflammatory

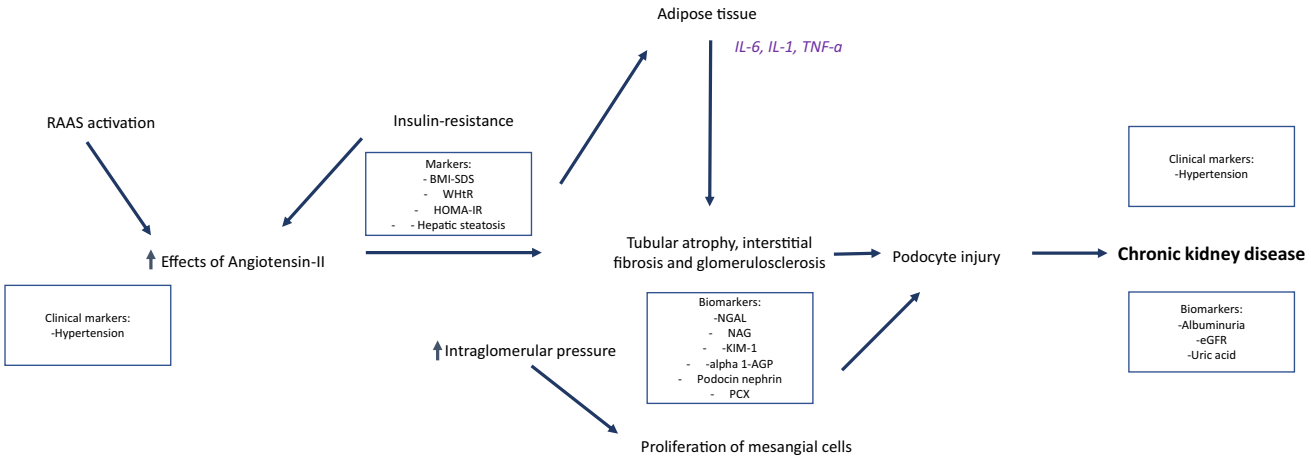

Fig. 1 Pathophysiological mechanisms of kidney damage in pediatric obesity

pathways, and mitochondrial damage [12, 34] has been found to be responsible for kidney damage development including glomerular damage, podocyte injury (as the histopathological hallmark of ORG), and tubulointerstitial inflammation [12, 13, 27, 36]. Furthermore, other processes indirectly contribute to kidney damage including persistent low-grade inflammation mediated by the endogenous production of nephrotoxic adipose derived cytokines and mediators (e.g., tumor necrosis factor, leptin, interleukin 6 (IL-6)) and oxidative stress due to lipid deposition in the kidney of patients with obesity [7, 35]. Secretion of adipokines, cytokines, and specific angiogenic factors play a crucial pathophysiological role in fat perivascular depot as renal sinus fat and contributes to kidney damage progression through endothelial dysfunction and increased vascular permeability [35].

To complicate matters further, focal segmental glomerulosclerosis and glomerulomegaly [27, 37] development has been pathogenically linked to dyslipidemia in patients with obesity through a complex interaction among RAAS system, oxidative stress, profibrotic growth factors (e.g., platelet-derived growth factors, Transforming Growth Factor-beta (TGF-beta), Tumor Necrosis Factor-alpha (TNF-alpha), macrophage activation, and inflammation [13, 34, 35]. Of note, RAAS activation promotes inflammatory adipokine expression, in turn leading to worsening in glucose metabolism by affecting glucose transporter Typ 4 (GLUT4) translocation and insulin receptors phosphorylation [34].

Definition of kidney damage in children with obesity

Kidney damage has recently emerged as a serious obesity-related consequence in the context of pediatric obesity [12, 27]. Indeed, the obesity-related kidney disease (ORKD) [12, 38], also known as obesity-related glomerulopathy (ORG) [13], represents a condition with significant clinical and prognostic implications [10, 39].

As its initially subclinical course [10] without detectable changes in conventional markers of abnormal kidney function (e.g., serum creatinine, glomerular filtration rate, blood urea, and urinary albumin creatinine ratio) [40, 41], early kidney damage identification in childhood through a careful anthropometric, biochemical, and urinary assessment (Fig. 1) represents a challenge for clinicians. Indeed, if untreated or misdiagnosed, kidney damage might evolve to CKD. Taken into account not only the potential disease course but also its relevant cardiometabolic burden, prevention of kidney damage progression into adulthood is also of paramount importance [40–42].

CKD is a condition defined by the Kidney Disease Improving Global Outcomes (KDIGO) as abnormalities of kidney structure or function for at least 3 months determining impaired estimated glomerular filtration rate (eGFR) (< 90 mL/min/1.73 mq) and/or albuminuria [12, 25, 26, 43, 44]. However, its definition in childhood is challenging since the physiological age-related modification of GFR in the first years of life and the wide clinical presentation variability [16, 22].

CKD global prevalence is increasing at an alarming rate in both adults and children [25, 37, 43]. In particular, its prevalence rates are increasing in parallel with the spread of pediatric obesity [25, 43]. In line to adult data reporting that at least 10% of the general adult population is affected by CKD [45], similar pediatric trends are becoming available [22, 46, 47]. Although still limited as the intrinsic challenge of CKD definition in childhood [22], epidemiological data indicated a prevalence ranged from 15 to 74.7 cases per million of the age-related population [46, 48].

Reassuming, kidney damage in children with obesity can be defined by the presence of reduced eGFR and/or albuminuria [49] after a confirmation over a 3-month period of time [26]. In turn, reduced eGFR was defined by eGFR < 90 mL/min/1.73 m^2 while albuminuria by an albumin-to-creatinine ratio (ACR) was ≥ 30 mg/g [5, 14]. Moreover, the presence of hypertension defined according to Flynn et al. [50] is also important for the clinical management of children with obesity.

Risk factors for kidney damage in children with obesity

Obesity and kidney damage share certain pathophysiological factors including IR, inflammation, and oxidative stress [27, 28, 40, 41].

In light of the tangled interplay among IR, inflammation, and renal hemodynamics, both conditions present with a progressive course potentially affecting not only quality of life but also life expectancy [12, 43]. To complicate matters, early-onset obesity has been associated with persistence of obesity in adulthood and a subsequent greater cardiometabolic risk profile later in life [12, 40, 46, 51, 52]. Conversely, obesity has been found to be responsible for 24–33% of all kidney diseases in adulthood [53], with a remarkable impact also in childhood [41, 43, 44, 51, 54]. A large prospective study demonstrated that adolescents with overweight showed a hazard ratio (HR) of 3.00 (95% CI, 2.50–3.60) and obesity of 6.89 (95% CI, 5.52–8.59) for all-cause treated of kidney failure during a 25-year follow-up period [55]. In line with these findings, a recent systematic review demonstrated an association between overweight (HR, 2.17 (95% CI, 1.71–2.74)) and obesity (HR, 3.41 (95% CI, 2.42–4.79)) in adolescence with non-diabetic kidney failure [56]. More, a prevalence of 12–15% of obesity in the pediatric CKD and end-stage renal disease (ESRD) population has been reported [16, 56].

In addition to the well-documented negative role of reduced eGFR and hypertension in the context of cardiometabolic risk in pediatric obesity [4, 12], similar evidence has also emerged for albuminuria, uric acid, and steatotic liver [6, 23, 57]. Nonetheless, the negative role of low birth weight, family history for cardiometabolic diseases, and anthropometric parameter such as waist circumference and WHtR has been also demonstrated [4, 46, 47]. Likewise, convincing studies demonstrated that congenital reduced nephron endowment represents a CKD risk factor [33].

In line with adult evidence [58, 59], albuminuria has been highlighted as a marker of kidney damage in children with obesity, since its pathogenic link with IR [23]. Growing data also indicated uric acid as an effective cardiometabolic risk factor in these young patients [60, 61]. Remarkably, its role in identifying kidney damage has been also demonstrated in the context of metabolically healthy obesity [5].

Over the last years, robust evidence has also supported an intimate link between steatotic liver and kidney damage since childhood [62, 63]. Various shared pathogenic factors have been implied in this association, but a crucial role for IR, inflammation, and oxidative stress has been reported [62].

Interestingly, following the recent renaming of fatty liver definition as MASLD, emerging data confirmed a close relationship of steatotic liver with kidney damage in children and adolescents with obesity [6, 62].

Kidney damage in children with obesity: from evidence to clinical implications

Unlike adults [3, 7, 38, 41], data evaluating the impact of kidney damage in children are still limited [56, 64–66]. Of note, a wide clinical phenotypic variability (ranging from albuminuria, proteinuria, hypertension, reduced eGFR, hyperfiltration to CKD) might be clinically indicative of kidney damage [12, 13, 23].

As a result of glomerulomegaly and focal segmental glomerulosclerosis [13, 67, 68], persistent proteinuria in subnephrotic range (defined as 3.5 g/die) has been largely recognized as the most common feature of ORG [12, 13] with a slower progression overtime [43, 69]. Of note, recent evidence supported the role of proteinuria as a sign of early-stage ORG even with a preserved renal function [43].

As a CKD marker, the role of microalbuminuria has been also investigated [10, 12, 40] (Fig. 1). A study conducted on 142 adolescents with obesity in absence of a history of CKD or hypertension or genetic obesity highlighted the role of microalbuminuria in the context of kidney damage [10]. All the enrolled patients performed 24-h arterial blood pressure monitoring and electrolytes, uric acid, triglycerides, cholesterol, and serum creatinine as laboratory tests and also they collected 24 h urine for albumin. Patients were divided into three groups such as "elevated GFR," "normal GFR," and "decreased GFR." This latter group showed higher urine concentration of neutrophil gelatinase-associated lipocalin (NGAL) and daily megalin excretion. Compared to controls ($n = 62$), albuminuria levels significantly increased from the "elevated GFR" to "normal GFR" and "decreased GFR" group (17.2 ± 8.3; 13.2 ± 7.2; 19.2 ± 2.2, respectively). Patients belonging to the "normal" and "decreased GFR" group also reported increased serum uric acid levels. Of note, triglycerides, cholesterol, and NGAL levels were significantly higher in the "normal GFR" group than others [10]. Therefore, authors suggested a potential role for

all these parameters as CKD predictors in adolescents with obesity [10].

As a matter of fact, an annual screening with a urine microalbumin/creatinine ratio has been recommended in children with obesity aged ≥ 10 years or at pubertal onset [40] followed by an annual screening of eGFR in case of clinical symptoms of kidney damage [12, 70]. Therapeutic options in this context have been also proposed in childhood, in line with adult evidence [71–73]. In particular, there is evidence demonstrating that an adequate treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers in patients with obesity and proteinuria had an antiproteinuric effect by reducing the incidence of CKD [10, 13, 72, 73].

Hypertension has been considered as further result of obesity-related renal impairment [12, 74]. An Israeli study examined a representative cohort of healthy adolescents aged 16 to 20 years since 1975, excluding those with kidney disease, increased albuminuria, and hypertension [74]. Adolescents were divided into two groups based on high BMI (≥ 85 percentile) or lean BMI and further clustered in four groups according to blood pressure risk class [74] such as group A (< 120/ < 80 mmHg; reference group), group B (120/ < 80–129/ < 80 mmHg), group C (130/80–139/89 mmHg), and group D (≥ 140/90 mmHg) [50, 74]. According to BMI status, an increased HR for early kidney impairment was reported in group C depending on BMI status and also in group D in the third decade [74]. Therefore, both BMI and of higher levels of blood pressure (≥ 130/80 mmHg) in adolescence were found to act as key factors for early kidney damage development in young adulthood [74].

Given that, ambulatory screening for hypertension and its management is crucial since childhood [43, 50, 75, 76]. Remarkably, evidence suggested that kidney damage might benefit from ACE-inhibitor treatment in CKD pediatric population with hypertension [40, 71, 77]. More, dyslipidemia and IR (as common features of pediatric obesity) have been found to exacerbate hypertension [43, 78–81], potentially leading to cardiovascular disease (CVD) [43]. In particular, high-density lipoprotein cholesterol has been identified as the main CVD risk predictor [43].

Impairments in renal function such as reduced [5, 12, 13, 82] or high [4, 12, 24, 83, 84] eGFR represent another robust marker of kidney damage. A large Italian study examined the relationship of eGFR with certain clinical and metabolic parameters in 2957 children with obesity [4]. Patients were stratified according to tertiles for BMI *Z*-score, WHtR, blood pressure, HOMA-IR, and duration of obesity. A statistically significant positive correlation of eGFR levels with BMI *Z*-score and a negative association with HOMA-IR, systolic blood pressure, pubertal stage, and obesity duration across tertiles was reported [4]. Particularly, obesity duration was found to be the most significant parameter associated to eGFR levels [4].

Similarly, a significant association between high eGFR and cardiometabolic dysfunction in 360 children with obesity was also reported [16]. An overall worse cardiometabolic profile including increased systolic blood pressure, transaminase, HOMA-IR, glucose, and insulin during OGTT; lower insulin sensitivity levels; and a higher percentage of microalbuminuria was found in subjects with an eGFR > 1 SD [24]. More, these patients also showed a higher percentage of hyperuricemia, in turn linked to an unfavorable cardiometabolic profile [24].

More, mildly reduced estimated glomerular filtration rate (MRGFR) (defined as eGFR > 60 and < 90 mL/min/1.73 m^2) has been linked to an unfavorable cardiometabolic risk profile including thyroid dysfunction [78], higher BMI-SDS, non-high-density lipoprotein cholesterol, and uric acid levels in children and adolescents with overweight/obesity [79]. A significant association of MRGFR with reduced indices of central sensitivity to thyroid hormones in a large cohort of 788 Italian pediatric patients with overweight/obesity was described [78].

In a multicenter study involving 3118 children with overweight/obesity, the association of eGFR (calculated through bedside Schwartz equation (eGFRBSE) and full age spectrum equation (eGFRFAS)) with a specific cluster of cardiometabolic risk factor was investigated [79]. MRGFR by eGFRFAS was found to be closely linked to higher BP, BMI *Z*-score, and uric acid levels [79].

Additional evidence supported the intriguing relationship of kidney damage (expressed as reduced eGFR (< 90 mL/min/1.73 m^2) and/or albuminuria) with metabolic features such as HOMA-IR, BMI *Z*-score, uric acid, hepatic steatosis, and inflammation markers in children with metabolically unhealthy (MUO) obesity and metabolically healthy (MHO) phenotypes [5]. Patients with obesity and in particular with MUO phenotype showed an increased risk of kidney damage. Both phenotypes showed a significant association of HOMA-IR with kidney damage. Worthy of note, uric acid was found to be a strong predictor of kidney damage in MHO children [5].

Based on these findings, eGFR monitoring plays a central role in kidney damage evaluation in children with obesity [21, 47].

Example of clinical practice management of kidney damage in children with obesity

In our clinical practice, a baseline kidney damage assessment in all children with obesity was used to classify the patients into one of the risk class categories (Table 1)

Table 1 Risk class categories for kidney damage

Low risk	Intermediate risk	High risk
No family history for cardiometabolic diseases No steatotic liver No metabolic dysfunction	Family history for cardiometabolic diseases Steatotic liver OR Metabolic dysfunction*	Family history for cardiometabolic diseases Steatotic liver Metabolic dysfunction

*Metabolic dysfunction was defined as the presence of at least one of the following metabolic abnormalities among waist circumference > 95° percentile, prediabetes, high blood pressure (BP) (< 13 years, BP ≥ 95° percentile; ≥ 13 years, BP > 130/85 mmHg), high plasma triglycerides (TG) (< 10 years, ≥ 100 mg/dL; ≥ 10 years, ≥ 150 mg/dL), or low high-density lipoprotein cholesterol (HDL-c) (≤ 40 mg/dL) [2]

(Fig. 2). Patients are classified as "low," "intermediate," and "high" risk based on family history for cardiometabolic diseases and of the presence of steatotic liver and/or metabolic dysfunction, as described elsewhere [6].

At first evaluation, all patients undergo blood pressure measurement, as described elsewhere [5]. Biochemical and urinary assessments include creatinine, eGFR, uric acid, and albuminuria. An abdomen ultrasound has to be also conducted to rule out kidney and urinary tract anomalies and to evaluate the presence of hepatic steatosis. In case of presence of kidney damage, the patient should be referred to a pediatric nephrologist. On the other hand, risk class category should be considered to schedule follow-up of children without kidney damage (Fig. 2).

Future perspectives

Given its clinical and prognostic relevance, both diagnostic and therapeutic strategies for early kidney damage detection need to be improved.

While in adults the renoprotective effect of certain anti-obesity drugs such as GLP-1 agonists has been tested [85], their use in childhood is not yet authorized. Therefore, lifestyle interventions including diet and physical activity remain the cornerstone of the treatment [1]. However, bariatric surgery represents an emerging treatment option in adolescents with severe obesity [86]. Besides robust evidence supporting its beneficial effect on glucose metabolism, IR, and central adiposity, preliminary but promising data also

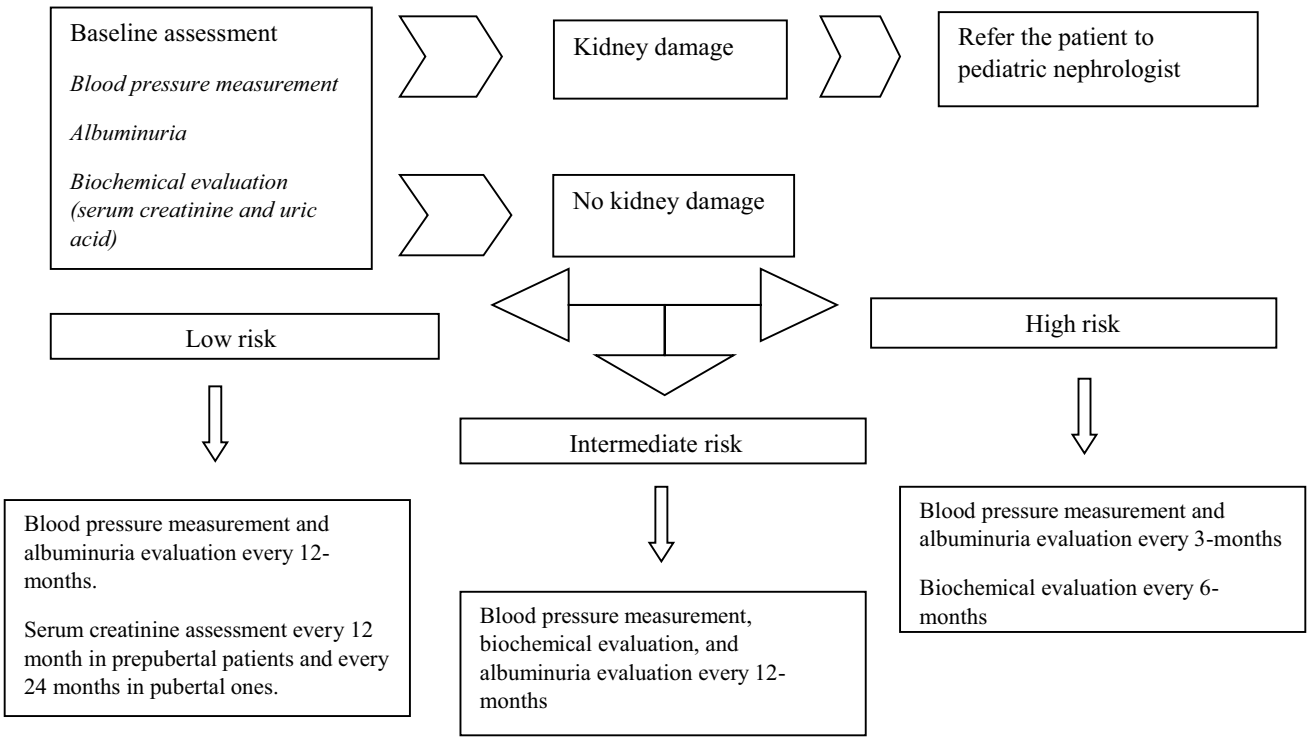

Fig. 2 Internal protocol for kidney damage assessment in children with obesity

suggested a significant improvement in kidney damage features in these young patients [86, 87].

On the other hand, identification of biomarkers for early kidney damage represents a challenging research area [16, 88].

Recent evidence suggested an association of kidney function with certain urinary biomarkers such as kidney injury molecule (KIM-1), NGAL, galectin-3 (Gal-3), and alpha 1-acid glycoprotein (AGP), urinary glutamyl aminopeptidase (GluAp), urinary podocalyxin (PCX), podocin, nephrin, and urinary N-acetylbeta-D-glucosaminidase (NAG) [10, 12, 16, 88], although results are still contrasting [10, 40, 89, 90] (Fig. 1). Among these promising molecules, alpha 1-AGP, an acute-phase protein, NAG, and NGAL have been recently recognized as a potential marker of early tubular damage in children with obesity [16, 88, 89].

A recent Italian study conducted in 40 prepubertal children with obesity found significantly higher urinary NGAL and KIM-1 values in these patients compared to controls [88]. Of interest, a significant association of these kidney injury biomarkers with certain metabolic parameters (e.g., adiposity indices and IR) was demonstrated, suggesting a role for obesity in kidney impairments development [88].

AGP has been also recognized as a promising biomarker of early glomerular damage in children with obesity [16, 89]. Medyńska et al. observed a higher urinary α1-AGP excretion in children with obesity compared to non-obese before the onset of albuminuria [89], suggesting that it might serve as an early glomerular injury biomarker in children with obesity [89]. Additionally, podocin, nephrin, and PCX, a main surface antigen of podocytes, have been also found to be associated with glomerular injury in the context of obesity [88, 90].

Further insights into renal injury have been provided by more innovative technologies such as proteomics and metabolomics through the identification of certain plasma and urinary polypeptides and metabolites as potential biomarkers, but evidence in the field is still limited [16, 88].

In view of the relevant impact of childhood obesity on renal function, more scientific efforts in the field are required for a deeper understanding of pathophysiological mechanisms of kidney damage in children with obesity. On this ground, identification of novel biomarkers might improve the overall management of kidney damage in these patients, as their potential usefulness in prevention, diagnostic, and therapeutic strategies.

In addition to significant clinical improvements in the overall management of obesity comorbidities, this might also pave the way for insightful strategies of personalized medicine for children with obesity as subjects at greater intrinsic cardiometabolic risk.

Conclusions

Given the emerging role of kidney damage as serious obesity consequence, a careful evaluation of kidney health and a conservative management of a potential CKD (treatment of hyperuricemia, hypertension, acidosis, etc.) are mandatory in children and adolescents with obesity.

Albeit insightful data on potential therapeutic options are becoming available, healthy lifestyle promotion still remains a cornerstone in the treatment of pediatric obesity with a further relevance if signs of kidney damage have been already developed.

In the challenging fight against childhood obesity, more efforts are needed to counteract the overall negative effect of obesity also on kidney function overtime.

Authors' contributions Barlabà A and Di Sessa A wrote the manuscript; Marzuillo P, Miraglia del Giudice E, and Di Sessa A conceived the manuscript. Miraglia del Giudice E, Marzuillo P, and Di Sessa A supervised the manuscript drafting. Grella C, Tammaro G, Petrone D, and Guarino S reviewed the literature data. Each author contributed important intellectual content during manuscript drafting or revision.

Data availability No datasets were generated or analyzed during the current study.

Declarations

Ethical approval Not applicable.

Consent to participate Not applicable.

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Conflict of interest The authors have no conflicts of interest relevant to this manuscript to disclose.

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