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EDUCATIONAL REVIEW

Glomerular hyperfiltration: part 2—clinical significance in children

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Abstract

Glomerular hyperfiltration (GHF) is a phenomenon that can occur in various clinical conditions affecting the kidneys such as sickle cell disease, diabetes mellitus, autosomal dominant polycystic kidney disease, and solitary functioning kidney. Yet, the pathophysiological mechanisms vary from one disease to another and are not well understood. More so, it has been demonstrated that GHF may occur at the single-nephron in some clinical conditions while in others at the whole-kidney level. In this review, we explore the pathophysiological mechanisms of GHF in relation to various clinical conditions in the pediatric population. In addition, we discuss the role and mechanism of action of important factors such as gender, low birth weight, and race in the pathogenesis of GHF. Finally, in this current review, we further highlight the consequences of GHF in the progression of kidney disease.

Keywords Glomerular hyperfiltration · Pediatric population · Diabetic kidney disease · Sickle cell disease · Solitary functioning kidney · Autosomal dominant polycystic kidney disease (ADPKD) · Duchenne muscular dystrophy · Obesity-related glomerulopathy

Introduction

Glomerular hyperfiltration (GHF) is generally defined as a supraphysiologic increase of glomerular filtration rate (GFR), although a precise definition is lacking [1]. GHF is associated with progressive loss of kidney function and is considered as a significant risk factor for developing chronic kidney disease (CKD) [2, 3]. It is also associated with adverse cardiovascular outcomes and all-cause mortality [4, 5]. Despite this association, the clinical implications and long-term consequences of GHF remain poorly evaluated, especially in the pediatric population [4].

GHF can result from an increase in factors determining GFR, such as kidney plasma flow, hydraulic pressure across the glomerular filtration barrier, or ultrafiltration coefficient [6, 7]. In physiologic states, it can occur after consumption of high protein meals or during pregnancy [8]. However, in pathologic states, GHF can be due to various diseases, either congenital or acquired. The pathophysiologic mechanisms leading to GHF depend on the underlying disease and are

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incompletely understood [8]. The present review discusses the different medical conditions causing GHF, their potential mechanisms, as well as the factors associated with the development of GHF, with a particular focus on the pediatric population. This review further highlights the potential and consequential damaging effect of GHF.

Prevalence of GHF in children

GHF is regarded as one of the early markers of kidney dysfunction for some forms of CKD, and it is used to predict progressive kidney-function decline. The exact prevalence of GHF in the general pediatric population remains relatively unknown, and this might be due to the paucity of studies determining GHF in healthy children as well as the lack of consensus on the GHF definition. The exact threshold for defining GHF is not well established in pediatric population, and it ranges from 120–180 ml/min per 1.73 m^2 [9]. Regardless of these constraints, few pediatric studies have determined the prevalence of GHF in the general population. In a study to determine the metabolic risk factors in nondiabetic adolescents with GHF, Lee et al. reported that 11.8% of their study subjects had GHF when using 120 ml/min per 1.73 m^2 as the threshold. The authors further showed that GHF is associated with hypertriglyceridemia and increased insulin resistance in their cohort [10]. It is worth mentioning that in this study, GFR was estimated by using the bedside Schwartz equation, which was designed for children with CKD, and therefore may be a less adequate formula for children without any medical condition [11, 12]. Nevertheless, another study using the full age spectrum (FAS) equation and 120 ml/min per 1.73 m^2 as the threshold reported a similar prevalence (11.0%) of GHF in school-age children [13].

The pathophysiological mechanisms of GHF in relation to clinical conditions

In children, several clinical conditions are associated with increased GFR. These conditions can be classified into four groups based on the cause, namely: genetic diseases (e.g., sickle cell disease, autosomal dominant polycystic kidney disease, and Duchenne muscular dystrophy), metabolic disorders (such as diabetes mellitus), malnutrition (i.e., obesity), and solitary functioning kidney. The pathophysiological mechanisms mediating GHF differ from one disease to another. Nevertheless, it has been demonstrated that in some clinical conditions, GHF may occur at the single-nephron while in others at the whole-kidney level as illustrated in Fig. 1 [8, 14]. Regardless, it has been postulated that GHF occurs as a result of chronic arteriole vasodilation in the kidney [1], compensatory adaptation due to nephron loss, or the failure of tubuloglomerular feedback (TGF) [15].

Sickle cell disease (SCD)

This is a genetic blood disorder caused by a point mutation in the β-globin gene, and it affects approximately 1 in 300,000 newborns annually [16, 17]. This point mutation leads to vaso-occlusion and hemolytic anemia, which are the characteristic hallmarks of the disease [18]. These hallmarks have been associated with the various multi-organ dysfunctions, including the sickle cell nephropathy [19]. Sickle cell nephropathy is the term given to all the kidney abnormalities associated with SCD. These abnormalities can be grouped into three main categories, isolated hematuria, tubular dysfunction, and glomerulopathy, and if left untreated can subsequently lead to CKD and kidney failure [18].

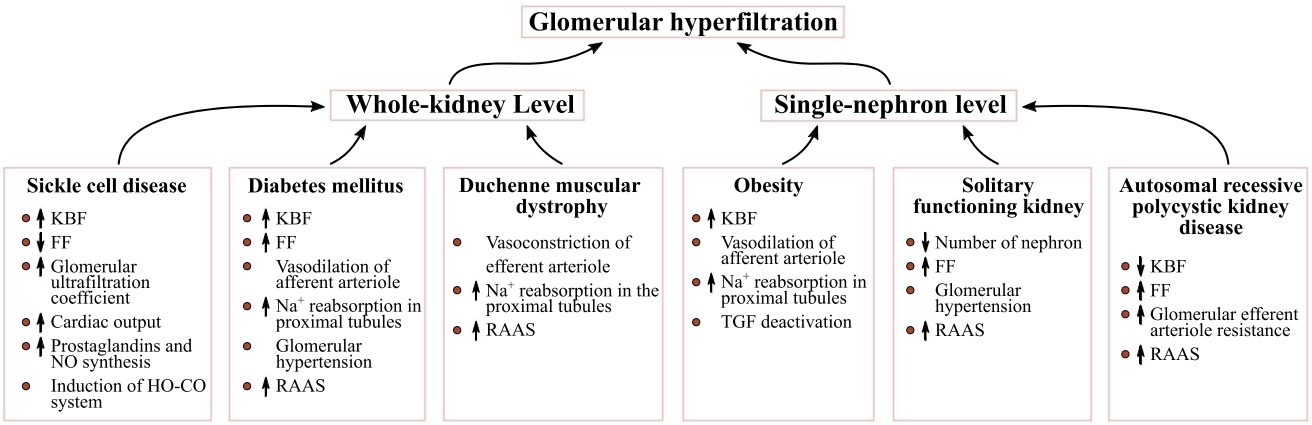

Fig. 1 Mechanisms of glomerular hyperfiltration. The pathophysiological mechanisms mediating glomerular hyperfiltration (GHF) vary from one clinical disease to another. In these diseases, GHF can either occur at the single-nephron level or at the whole-kidney level. GHF, glomerular hyperfiltration; KBF, kidney blood flow; FF, filtration fraction; NO, nitric oxide; HO-CO, heme oxygenase 1-carbon monoxide; RAAS, renin–angiotensin–aldosterone system; TGF, tubuloglomerular feedback

Glomerulopathy in children with SCD is well-described [18], with the earliest childhood clinical manifestation being GHF as demonstrated in infants (mean age = 13.7 months) recruited to the Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG) [20]. Indeed, the evolution of GFR in a population with SCD involves an initial increased GFR during early childhood, which then peaks at adolescence, before it finally begins to decline (Fig. 2a) [21, 22]. Though there is no well-established cut-off definition for GHF in the pediatric population and several methods have been used to measure or estimate GFR in SCD, the published data report the prevalence of GHF in pediatric populations ranging between 16% and 98%, as shown in Table 1 [9, 21, 23–34].

In SCD, GHF has been associated with an increased kidney blood flow, a reduced filtration fraction, and an increased glomerular ultrafiltration coefficient [35–37]. This indicates

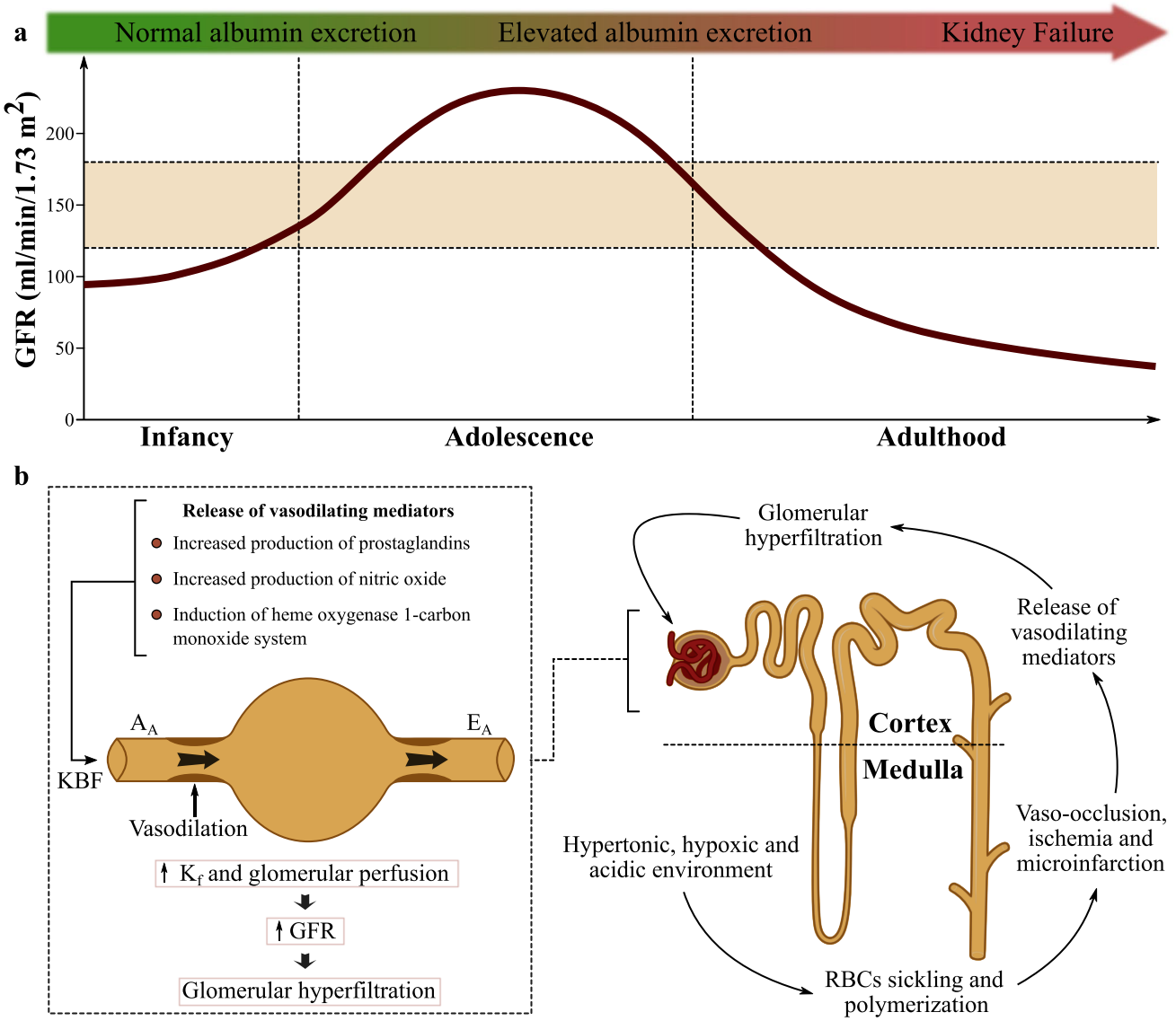

Fig. 2 Glomerular hyperfiltration in sickle cell disease. **a** The evolution of glomerular filtration rate (GFR) in sickle cell disease (SCD) involves an increased GFR which begins during early childhood and peaks at adolescence. This increased GFR is usually followed by an elevated albumin excretion and subsequent decline in GFR in adulthood due to loss of kidney function. **b** The acidic, hypoxic, and hypertonic characteristic feature of the renal medulla promotes the sickling and polymerization of red blood cells (RBCs), resulting in vaso-occlusion, ischemia, and microinfarction of the vasa recta. This destruction leads to the release of vasodilating mediators (such as prostaglandins and nitric oxide, as well as the induction of the heme oxygenase 1-carbon monoxide (HO–CO) system) which instigate an increased vasodilation of the afferent arteriole (A_A). This increased vasodilation of A_A leads to an increased kidney blood flow (KPF), which in turn results in an increased glomerular capillary ultrafiltration coefficient (K_f), thus eventually leading to glomerular hyperfiltration. GFR, glomerular filtration rate; KBF, kidney blood flow; A_A, afferent arteriole; E_A, efferent arteriole; K_f, glomerular capillary ultrafiltration co-efficient; RBCs, red blood cells

Table 1 Comparison of studies reporting the prevalence of GHF in children with sickle cell disease

Study type	Sample size	Disease type	Age (years)	Method of GFR measurement	GHF cut-offs (ml/min/1.73 m^2)	Prevalence (%)	Reference
Prospective observational	85	Sickle cell anemia (Hb SS and Hb S/β^o-thalassemia)	1–18	^{99m}Tc-diethylenetriamine-pentaacetic acid (^{99m}Tc-DTPA)	> 1 standard deviation above the normal mean for age	76%	Aygun et al. [21]
Prospective observational	23	Sickle cell anemia (Hb SS and Hb S/β^o-thalassemia)	2.5–14	^{99m}Tc-DTPA plasma clearance	> 1 standard deviation above the normal mean for age	87%	Aygun et al. [34]
Retrospective	48	Sickle cell disease	3–17	Schwartz creatinine-based estimating formula	> 120	72.9%	Boda et al. [33]
Cross-sectional	65	Sickle cell anemia (Hb SS)	2–13	Schwartz creatinine-based estimating formula standardized to body surface area	> 140	30.8%	Aloni et al. [32]
Cross-sectional	150	Sickle cell anemia (Hb SS)	2–18	Schwartz creatinine-based estimating formula	> 140	40%	Aloni et al. [31]
Cross-sectional	112	Sickle cell anemia (Hb SS)	4–19	Schwartz (≤ 17 years of age) and the Modification of Diet in Renal Disease (MDRD) (> 17 years of age) creatinine-based estimating formula	> 140	98%	Brewin et al. [30]
Cross-sectional	413	Sickle cell anemia (Hb SS)	9–23	The MDRD, Cockcroft-Gault (CG) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-based estimating formula	> 130 (female) > 140 (male)	49.5%	Geard et al. [29]
Prospective	185	Sickle cell anemia (Hb SS and Hb S/β^o-thalassemia)	5–21	Cystatin C-based estimating formula	≥ 180 (4–10 years of age) > 140 (> 10 years of age)	43%	Lebensburger et al. [28]
Retrospective	36	Sickle cell disease	4–19	Modified Schwartz creatinine-based estimating formula	> 140	19%	Zahr et al. [27]
Cross-sectional	100	Sickle cell disease	5–21	Modified Schwartz (< 18 years of age) and the MDRD (≥ 18 years of age) creatinine-based estimating formula	> 180 (< 10 years of age) > 140 (≥ 10 years of age)	49%	Ranabothu et al. [23]
Prospective	555	Sickle cell anemia (Hb SS)	1.6–20.9	Updated pediatric Schwartz creatinine-based estimating formula	≥ 140	25.4%	Belisário et al. [26]
Cross-sectional	60	Sickle cell anemia (Hb SS)	2–18	Schwartz creatinine-based estimating formula	> 2 standard deviations above the mean eGFR obtained from the control population	16.7%	Nnaji et al. [24]
Cross-sectional	153	Sickle cell disease +	10–19	Schwartz creatinine-based estimating formula	> 140	33.3%	Inusa et al. [25]
Cross-sectional	326	Sickle cell anemia (Hb SS)	2–18	Schwartz creatinine-based estimating formula	≥ 180 (2–10 years of age) > 140 (> 10 years of age)	16%	Adebayo et al. [9]

that GHF is driven by dilatation of both afferent and efferent arterioles (with a predominant effect on the efferent arterioles due to a substantially greater increase in effective kidney blood flow compared to GFR) [38–40], increased glomerular perfusion, and glomerular enlargement (increased effective glomerular filtration surface area) [19]. To support this, the presence of abnormally distended enlarged glomeruli can be observed at the time of hyperfiltration in children with SCD as early as 7–18 months of age [41–43]. Furthermore, the rise in GFR has been suggested to be driven by increased cardiac output as a result of chronic anemia or by the localized increased release of kidney vasodilating prostaglandins (especially the high prostaglandin $E_2/F_{2\alpha}$ ratio, which may be physiologically relevant in regard to renin release [38]) and an increase in the nitric oxide (NO) synthase in response to the hypoxic condition in the renal medulla of individuals with SCD (Fig. 2b) [18, 19, 44, 45]. Although various findings support that chronic hemolysis confers risk for GHF [45, 46], the exact pathophysiological mechanisms remain unknown. Nevertheless, Nath et al. proposed that the chronic hemolysis in SCD can induce the heme oxygenase 1-carbon monoxide (HO-CO) system, which might contribute to systemic hyperperfusion and to regional hyperperfusion of the kidney and other vascular beds via CO-driven vasodilatation [47].

It should be noted that other types of chronic hemolytic anemia such as beta (β)-thalassemia [48–51] and hemolytic uremic syndrome [52] have been associated with GHF. In β-thalassemia, it has been suggested that GHF could be a consequence of chronic anemia and the iron deposition on the internal milieu within the glomeruli [49, 50].

Autosomal dominant polycystic kidney disease (ADPKD)

This is a common genetic kidney disease affecting 1 in 400 to 1 in 1000 people [53], and it is the primary genetic cause of CKD and kidney failure in the adult population [54]. ADPKD is caused by mutations in either polycystin1 or polycystin2, the proteins that regulate the morphologic configuration of epithelial cells [55]. These mutations lead to the enormously enlarged kidneys caused by the sustained expansion of large numbers of fluid-filled cysts, which are derived from abnormal proliferation of tubular epithelial cells [55, 56].

In patients with ADPKD, the kidney manifestation usually begins at birth with cystic growth and kidney enlargement [8]. These cysts can develop in a minority of medullary and cortical tubules, enlarge exponentially, and compress adjacent parenchyma. This eventually leads to apoptosis, atrophy, and fibrosis of normal functioning parenchyma and the subsequent loss of kidney function [56]. Although the kidney function in individuals with ADPKD usually remains stable until the fourth or fifth decade of life [57], it has been suggested that the preservation of the kidney in the early-stage of the disease is caused by compensatory hyperfiltration of the remnant nephrons [57], which is presented in 21–32% of the pediatric population [53, 58, 59]. Indeed, enlarged kidneys in children with ADPKD have been reported by Wong et al. [59] to be associated with a significantly elevated GFR (which may represent GHF) in comparison to age-matched controls.

Despite the fact that GHF has been considered as one of the markers of ADPKD [60], the exact mechanism by which GHF is induced in children with ADPKD still remains incompletely understood. Nevertheless, Helal et al. reported that the presence of GHF is associated with an increased rate of kidney enlargement over time [53], and this could be driven by the renin–angiotensin–aldosterone system (RAAS), which is known to be stimulated in ADPKD. Indeed, the activation of RAAS raises the angiotensin II (ANG II) level that subsequently increases the glomerular efferent arteriole resistance leading to GHF [53, 61]. In addition, ANG II can enhance cell proliferation, inflammation, oxidant injury, and fibrosis, thus contributing to the growth of the kidney cysts [61]. Furthermore, vasopressin, which is also elevated in patients with ADPKD [58], is reported to play an indirect role on the GHF by reducing sodium concentration at the macula densa, leading to the inhibition TGF control of the GFR [58, 62, 63].

Duchenne muscular dystrophy (DMD)

DMD is an X-linked recessive muscle disorder affecting approximately 1 in 3500 to 1 in 6000 newborn males [64]. This disease is caused by the absence or reduced expression of dystrophin, thereby resulting in a progressive muscle degeneration [65]. There is paucity of data regarding the involvement of the kidney in DMD. A Japanese group reported that kidney failure is a cause of death in 14% of their adult patients with DMD [66] and that 30% of the patients above the age of 30 years had increased plasma levels of cystatin C [67]. Furthermore, in the pediatric population, Braat et al. reported the presence of GHF (measured GFR > 150 mL/min/1.73 m^2) using chromium-51-labeled ethylenediamine tetraacetic acid (^{51}Cr-EDTA), in 25% of their patients with DMD [68]. The authors hypothesized that an activated RAAS may act as a possible underlying pathophysiological mechanism due to efferent arteriolar vasoconstriction, a consequence of the low kidney sodium excretion in some patients. To further support the possible role of RAAS activation, more than 50% of the patients in their cohort had elevated blood pressure (BP) and the presence of a non-dipping BP [68].

Although it is still unknown whether mutations in dystrophin protein are responsible for the GHF rather than a secondary cause for the activation of RAAS, the expression

of non-muscular isoforms of dystrophin demonstrated in the macula densa, mesangial, and endothelial cells of the kidney might support this possibility [69, 70]. Therefore, future studies should be implemented to shed more insights into the pathophysiology of the kidney damage in patients with DMD.

Diabetes mellitus (DM)

This is a chronic metabolic disease affecting both adult and pediatric populations [71], and it is one of the leading causes of kidney failure and dialysis in western countries. Kidney dysfunctions have been demonstrated to be associated with both type 1 DM (T1DM) and type 2 DM (T2DM), with the pediatric populations with T1DM or T2DM presenting markers of early diabetic kidney disease, such as moderate albuminuria and GHF. GHF is considered as a strong risk factor for progression to CKD and kidney failure and may also predict progressive diabetic kidney disease (DKD) prior to the loss of kidney function [72]. Individuals with diabetes frequently have a significantly higher GFR than nondiabetic counterparts [72, 73], with the prevalence of GHF ranging between 13–52% and 7–40% in pediatric populations with T1DM [73–77] and T2DM [78–81], respectively.

The potential mechanisms leading to the development of GHF in patients with diabetes remain incompletely unraveled. Several studies in human, particularly in the adult population, and animal models have resulted in several hypotheses. These hypotheses can be grouped into three: ultrastructural changes, vascular theory, and tubular theory [14].

GHF in diabetes has been associated with nephromegaly [82, 83]. Hypertrophy, hyperplasia of the cortical tubuli, and concomitant kidney enlargement are the earliest structural changes in diabetic kidneys. Although there is a glomerular increase in volume, most of the increase in the cortical mass may be due to the hypertrophy of the proximal tubule, which is suggested to be driven by tubular glucose reabsorption, associated with hyperglycemia, thereby leading to increased expression of growth factors such as transforming growth factor β (TGF-β), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF) [84]. In support of this proposed ultrastructural change mechanism, nonspecific and selective sodium glucose transporter-2 (SGLT-2) inhibitors have been shown to attenuate kidney hypertrophy associated with experimental diabetes [85].

Primary abnormalities in vascular control leading to kidney vasodilation and increased kidney blood flow have been observed both in human studies of early diabetes and in animal models [86–91]. Animal studies indicate that afferent glomerular arterioles dilate more than the efferent arterioles, thereby raising the GFR, intraglomerular pressure, and filtration fraction [92]. Indeed, in clinical studies, increased GFR and kidney blood flow have been reported in newly diagnosed patients with T1DM and T2DM, thus indicating afferent kidney vasodilation; moreover, patients presented glomerular hypertension as indicated by an elevated filtration fraction [86–89, 91]. Despite the fact that the mechanism leading to the afferent glomerular vasodilation still remains unclear, elevated levels of insulin, IGF-1, atrial natriuretic peptide (ANP), advanced glycation end products, and increased intrarenal NO signaling have been suggested to contribute to the afferent glomerular vasodilation [8].

Regarding the tubular theory, some investigators have suggested that impairment of the TGF mechanism is the mechanism leading to the development of GHF. Under chronic hyperglycemic conditions in experimental diabetes, the increased proximal tubular reabsorption of glucose and sodium by SGLT-2 causes the inhibition of TGF, via decreased sodium chloride delivery to the macula densa. This reduced delivery of sodium chloride to the macula densa inhibits the conversion of adenosine triphosphate to adenosine, thereby leading to a lower level of adenosine, a vasoconstrictor, and an inadequate afferent arteriolar tone, which eventually results in an increased kidney perfusion [93, 94]. This proposed mechanism has been supported by clinical studies, which showed an enhanced proximal tubule reabsorption of sodium in adult patient populations with T1DM [95] and T2DM [96]. In contrast, a study in mice deficient in the adenosine receptor A_1, which lack a TGF mechanism, demonstrated the presence of diabetes-induced GHF [97], thus suggesting that other pathways might be involved in the development of GHF. Therefore, further studies are needed to determine and validate the exact mechanisms of diabetes-induced GHF in humans, and these studies should include the pediatric population.

Malnutrition and obesity

The World Health Organization (WHO) [98] defines malnutrition as "deficiencies or excesses in nutrient intake, imbalances of essential nutrients or impaired nutrient utilization." Therefore, malnutrition can range from undernutrition, such as stunting, wasting, underweight, and micronutrient deficiencies or insufficiencies, to overweight and obesity as well as diet-related noncommunicable diseases, e.g., DM, cancer, heart disease, and stroke. Children with malnutrition are at increased risk for developing several comorbidities during adulthood, including kidney diseases [99].

Childhood obesity has become a worldwide epidemic [100]. According to the Centers for Disease Control and Prevention (CDC) website, the incidence of obesity in children and adolescents living in the United States of America (USA) is 1 in 5 [101]. The kidney is one of the main target organs for obesity-related health disease, and obesity is an independent risk factor for development of kidney disease.

A well-characterized kidney complication associated with obesity is obesity-related glomerulopathy (ORG) [102], and it results from hemodynamic changes, manifesting as glomerular hyperperfusion and GHF [103].

GHF is the earliest manifestation of ORG with a prevalence ranging from 7–31% [104–109] in childhood obesity. In these individuals, the increased body mass itself has been suggested as the main driver of GHF [103]. Obesity is associated with an increase in absolute mass of adipose tissue, which leads to the physiological maladaptation of increased cardiac output to compensate for increased blood flow to both adipose and non-adipose tissues, including the kidneys [110]. In the kidneys, this increased cardiac output causes a hemodynamic response at the single-nephron level, resulting in glomerular hypertension and increased capillary hydraulic pressure [111, 112]. Although the exact mechanisms by which obesity alters the kidney hemodynamics at the single-nephron level remain unclear, D'Agati et al. proposed 2 concepts to explain GHF in ORG [113].

In the first concept, the authors proposed that the "primary hemodynamics hypothesis", in which the primary event is vasodilation of the afferent arterioles, leads to GHF in subjects with obesity. The other proposed concept is "tubulocentric hypothesis" in which the primary event is increased proximal reabsorption of sodium and water by the proximal tubules, thereby leading to decreased solute delivery to the macula densa, TGF deactivation, preglomerular vasodilation, and consequent GHF [113].

It is worth mentioning that several studies have reported that obesity-associated GHF can improve after substantial weight loss [114–116], indicating that GHF in obesity represents a reversible physiologic adaptation. Although high-protein diets have been suggested as an effective means for rapid weight loss [117], clinical data have shown an association between GHF and high protein consumption [118]. Therefore, high-protein diets should be avoided, if possible, and plant-based proteins may be recommended for weight loss.

Solitary functioning kidney (SFK)

Individuals with only one functioning kidney have an increased risk for developing CKD in the later life. In children, SFK can either be from a primary (congenital) origin (pSFK) or secondary (acquired) after birth (sSFK) [119]. Two main abnormalities in the spectrum of congenital anomalies of the kidney and urinary tract (CAKUT) underline the pSFK: unilateral multicystic dysplastic kidney (MCDK), and unilateral kidney agenesis (UKA). MCDK, which affects 1 in 4300 newborns [120], is a condition in which the kidney parenchyma shows dysplastic and cystic differentiation with a normally atretic ureter due to abnormal early kidney development [119]. On the other hand, UKA comprises the complete absence of developing kidney tissue and a ureter in fetal life [119], and this usually affects 1 in 2000 newborns [121]. On the contrary, sSFK is acquired from uninephrectomy, performed because of kidney malignancy (e.g., Wilms' tumor) or after complete loss of kidney function due to recurrent urinary tract infection in the kidney with underlying anomalies such as dysplasia, severe vesicoureteric reflux or obstructive nephropathy, or due to a vasculopathy or trauma [119, 122].

It is well known that reduction in the kidney mass either congenitally or acquired after unilateral nephrectomy in both pediatric and adult populations leads to compensatory kidney growth, which encompasses the hypertrophy of both the kidney tubules and the glomerulus [123]. In pSFK, especially in 24–48% of MCDK cases [120], the compensatory nephron formation which occurs during nephrogenesis may cause the remaining kidney to show hypertrophic growth in utero as early as 20 weeks of gestation [123, 124]. Although there is currently almost no technological technique in clinical settings to detect the number of nephrons in living subjects, an 80% and 56% increase in kidney weight and number of nephrons, respectively, has been reported in a single human case of pSFK compared with age-matched control [125]. Moreover, various animal models of kidney mass reduction during nephrogenesis have reported a compensatory nephron formation, with a 4–50% increase in the number of nephrons [126–128]. The underlying stimulus and mechanisms mediating kidney hypertrophy in SFK remain unclear. However, increase in the number of medullary papillae [127, 129], NO system, the renal sympathetic nerves, and the RAAS have been implicated in the compensatory nephrogenesis [123].

The other responses accompanying loss of kidney mass include an increase in single-nephron GFR (SNGFR) and in size and function of kidney tubules (increases in both the length and diameter of the proximal and distal tubules and density of the sodium transporters), thus facilitating a greater reabsorption of the increased filtered load [123, 130–132]. This increase in the filtration and function of the kidney tubules helps in compensating for the total GFR in the short term but may also drive glomerular injury and contribute to progressive loss of kidney function in the long run [123, 133]. Thus, GHF is considered as the mechanism of kidney injury in patients with an SFK. A recent meta-analysis of kidney injury after nephrectomy in childhood estimated the proportion of children with SFK who develop kidney injury, as defined by proteinuria, high blood pressure, and a decreased estimated GFR (eGFR), to be 15.3%, 14.5%, and 11.9%, respectively [134]. This clearly indicates that children undergoing a nephrectomy need a long-term follow-up. Therefore, a standardized - follow-up protocol for these children is needed, with an annual estimation of blood pressure and proteinuria, and estimation of GFR once every

5 years, except in conditions of rapid pubertal growth, pregnancy, or obesity, where it should be more frequent [133].

The mechanisms linking GHF to glomerular injury and glomerulosclerosis in SFK are still under investigation, but they implicate a role for podocyte loss in glomerular injury. GHF is influenced by various other intrarenal mechanisms, such as glomerular capillary pressure, single-nephron plasma flow, and TGF [123, 135]. The rise in the SNGFR and the increase in glomerular capillary pressure in remnant nephrons in conditions like SFK have been associated with a reduction in afferent arteriole resistance and resetting of the TGF, thereby exposing podocytes to stretch, tensile stress, and fluid flow shear stress (FFSS), which may over time cause a decrease in the integrity of the glomerular filtration barrier and result in the damage and loss of the podocytes [123].

Factors modulating the development of GHF

The factors contributing to the development of GHF in childhood are very different from those in adults, and among others, they include low birth weight (LBW), gender, ethnicity, elevated blood pressure, inflammation, age, and apolipoprotein L1 (*APOL1*) risk variants (RVs).

a. Low birth weight

LBW, defined as birth weight below 2500 g, is associated with kidney diseases in adulthood [136–138]. LBW is a result of either prematurity or intrauterine growth restriction (IUGR) [137], both of which lead to a congenital lower number of nephrons, an increase in glomerular size as a result of compensatory hypertrophy, and hyperfiltration in the remaining nephrons [136, 137, 139]. In a series of 6 patients (2 women and 4 men, mean age of 32 years), with a history of prematurity and very LBW, presenting persistent proteinuria, kidney histopathology revealed secondary focal segmental glomerulosclerosis (FSGS), without other known risk factors. This small study further reported that prematurity and LBW were associated with glomerulosclerosis and GHF, as a result of adaptive response to an increased hemodynamic stress in a setting of lower number of nephrons, leading to secondary FSGS [137, 140]. More so, Kaze et al. investigated the relationship between birth weight and eGFR in 80 children aged 5–10 years. These authors found a trend towards an increased eGFR (eGFR $\geq$ 120 mL/min/1.73 m^2), although not statistically significant, in children with LBW when compared with children with normal birth weight (NBW) [141].

Compensatory GHF is driven by changes in glomerular hemodynamics and intraglomerular pressure leading to an increase in SNGFR [138, 142, 143]. Similar changes have been demonstrated in animal models of kidney ablation and underline the "GHF theory" [138, 142, 144]. This theory suggests that either a congenital or an acquired reduction in nephron number results in increased glomerular capillary pressure and plasma flow rates causing subsequent increase in SNGFR [92, 143, 144]. Furthermore, this compensatory GHF is an important contributor to progressive kidney damage and kidney failure later in life [136, 138]. In 2 adolescents born extremely premature who developed proteinuria, Hibino et al. found kidney pathological features consistent with glomerular hypertension. The authors suggested that proteinuria seen in these patients was caused by glomerular hypertension and GHF [145]. Similar investigation by Kaze et al. reported significant proteinuria in children with LBW in comparison with those with NBW and related this finding to GHF theory [141].

b. Gender

Gender differences have been reported as a risk factor for GHF in some specific diseases, particularly SCD and DM. In SCD, previous studies in humans as well as in animals have reported an association between male gender and the onset of GHF [29, 146, 147]. In a cohort of 326 children with sickle cell anemia (SCA) living in the Democratic Republic of the Congo (DRC), the authors observed an association between male gender and GHF [9]. This finding is similar to that observed in an adolescent SCD cohort living in Cameroon [29]. Intriguingly, Derebail et al. found that male gender was associated with lower odds of baseline GHF in a cohort of 292 adult patients with SCD [148].

An association between male gender and GHF has been further studied in animal models of SCD. In a humanized sickle cell mice model, Kasztan et al. observed a rapid onset of GHF as well as a strong association between the magnitude of GHF and the degree of long-term kidney injury in male SCA mice [146]. The mechanisms by which gender influences the development of GHF in SCD have not been fully elucidated. However, Kasztan and colleagues postulated, using humanized sickle cell mice, that a greater degree of hypoxia and testosterone level in males, lower hemolysis markers, and a higher fetal hemoglobin level in females might contribute to the gender differences associated with GHF. Indeed, testosterone has been found to increase susceptibility to hemolysis, aggravate ischemia–reperfusion injury, and inhibit NO production, which subsequently could exacerbate the development of kidney injury in males, including GHF [146, 147]. The authors further suggested that these gender differences can be driven by an elevation in endothelin-1 (ET-1) expression leading to changes in the filtration barrier components, which results in GHF [147]. This elevation in ET-1 was significantly greater in male mice when compared

with female. In fact, sex hormones have been suggested to modulate the expression of ET-1 [149, 150]. Ovarian hormones, particularly estrogen agonists, have been shown to produce similar effects to those of endothelin-1 type A receptor (ET-A) antagonists, explaining the relative protective advantage in females [146, 147]. Moreover, testosterone may promote kidney injury by upregulating ET-1 production [151].

Contrary to nondiabetic kidney disease, female patients with DM have a greater risk to develop GHF [152]. In a study on adolescents with T2DM aged 12–17 years, girls had a higher baseline eGFR and a greater risk to develop GHF over 5 years compared with boys [79, 153]. Similar findings were observed in a cohort of 98 adolescents with T1DM [74]. Despite these findings, the mechanisms responsible for this gender difference have not been well established [152, 153]. In T1DM, higher efferent arteriolar resistance has been found in women who developed GHF and has been suggested to explain this gender difference in GHF, by increasing intraglomerular pressure [152, 153].

In SFK, gender has been implicated to be associated with the clinical manifestations of GHF. The role of gender is yet to be confirmed in the human population, but animal models of SFK have reported that male animals show a higher degree of GHF [154], a higher blood pressure [132], and a higher glomerular pressure and have more glomerular hypertrophy [155] than their female counterparts. This gender difference has been further explained to be driven by testosterone [155, 156]. Therefore, future studies should confirm this gender association in humans, especially in adolescents and young adults, since the differences between genders only starts to appear from puberty [124].

c. Race/ethnicity

Prior studies in the USA in adolescents and young adults have found an association between race and GHF [10, 105]. Indeed, among nondiabetic adolescents aged 12–17 years in the USA, a variation in the prevalence of GHF according to race has been reported. Hispanic adolescents presented a significantly higher prevalence of GHF compared with other ethnic groups (non-Hispanic Whites and Blacks) [10]. Similarly, Turer et al. observed a racial difference in the prevalence of GHF among US adolescents and young adults with overweight and obesity. Non-Hispanic White adolescents had lower odds to present GHF compared with other ethnic groups (Hispanics, non-Hispanic Blacks, other non-Hispanics [105]). There are a few possible explanations for this racial discrepancy. Socio-economic, behavioral, and genetic risk factors may contribute to the residual confounding unaccounted for. For example, sickle cell trait and RVs in *APOL1* gene, which are highly prevalent in African ancestry, have been implicated to contribute to racial discrepancy associated with kidney disease in the African population [10, 157].

d. Apolipoprotein L1 risk variants

APOL1 is a 14.5-kb gene with seven exons encoding APOL1, a 398 amino acid protein. Two main RVs have been identified: G1 (rs73885319, p. serine 342 glycine and rs60910145, p. isoleucine 384 methionine) and G2 (rs71785313, asparagine 388, and tyrosine 389 deletion). These RVs are exclusively found in people of African origin, providing innate protection against human African trypanosomiasis (HAT), the deadliest form of African sleeping sickness. On the other hand, these RVs increase the risk of developing various progressive CKD in people of African ancestry [157]. In children, especially those affected by SCD, human immunodeficiency virus (HIV), or various glomerular diseases, *APOL1* RVs have been associated with the development of hypertension, albuminuria, and more rapid decline of kidney function [158, 159]. Studies investigating the association between A*POL1* RVs and the occurrence of GHF are limited. However, a recent study in 326 children with SCA from the DRC reported a strong association between *APOL1* RVs and GHF in these children. Indeed, the presence of A*POL1* RVs was associated with sevenfold increased odds of GHF (adjusted p-value = 0.001) [9].

Although the exact involvement of *APOL1* in GHF is still yet to be elucidated, the expression of *APOL1* G1 transgene in nephrocytes has been reported to enhance nephrocyte function, causing hypertrophy [160]. Likewise, overexpression of *APOL1* in podocyte models has been reported to lead to podocyte detachment, with podocyte expressing *APOL1* G2/G2 genotype exhibiting significantly reduced and disorganized actin filaments, and fewer adhesion sites leading to higher permeability to albumin [161]. More so, low nephron endowment is reported to be related to *APOL1* RVs, thereby suggesting that GHF might serve as a compensatory adaptation in individuals with *APOL1* RVs, as in the case of SFK [6, 162]. Regardless, further studies are still needed to better elucidate the potential role of *APOL1* in the development of GHF in children.

e. Elevated blood pressure (hypertension)

In the pediatric population, the presence of elevated blood pressure or hypertension is relatively low, with a prevalence ranging from 2–4% [163, 164]. However, hypertension is not infrequent in children with diseases such as SCD [33, 165], DM [79, 166] and SFK [119, 167], where it has been suggested to play a role in progression of kidney damage.

Nearly three decades ago, GHF was described in patients with essential hypertension and emerged as an early marker of hypertensive nephropathy [168]. In this study, the authors

suggested that GHF is driven by increases in intraglomerular pressure as a result of increased efferent arteriolar resistance [169]. In pediatric patients with SCD, GHF has been demonstrated to be associated with elevated blood pressure [21]. Here, the authors reported a positive correlation between GFR and systolic blood pressure, even after adjusting for age, gender, and height. However, it remains unknown whether hypertension is a trigger of GHF or whether hypertension is a consequence of GHF in this disease. Thus, further longitudinal studies should be established to understand this causal relationship in various clinical conditions associated with GHF.

f. Age

Age has been reported as a factor modulating GHF in several clinical conditions. In SCD, age has been reported to have an inverse association with GHF or eGFR [29, 148]. Previous studies have demonstrated an increase in GFR in infancy, which plateaus during adolescence and finally begins to decline thereafter [21, 22]. This decline in GFR after adolescence might represent the actual loss of kidney function [148], as illustrated by an increased prevalence of albuminuria with increasing age in individuals with SCD [29].

Age has also been reported to be an important factor in the clinical manifestation of GFR in SFK. The age at which kidney mass reduction occurs may strongly influence compensatory nephron formation and GFR, with data suggesting that the compensation is more robust when the kidney mass is reduced congenitally or during a young age compared with adults [170]. Indeed, following uninephrectomy in adults, GFR recovers to approximately 70% of pre-uninephrectomy values [171, 172], whereas in children with either congenital or early-sSFK, GFR is preserved at a normal two-kidney level [173]. An explanation for this difference between pSFK and sSFK acquired later in life is that compensatory nephron formation begins earlier in fetal life and continues to progress throughout childhood, while uninephrectomy later in life initiates the remnant nephrons to undergo compensatory changes, by increasing their size (but not their number) in order to mitigate the substantial loss in the filtration surface area [173].

g. Inflammation

The role of inflammation has been generally described in the development of kidney disease. In the pediatric population, inflammatory markers have been implicated to be associated with the development of GHF, particularly in DKD and ORG.

The pathophysiological implications of inflammation in DKD have been described at various levels [174]. A study of adolescents with T1DM showed that GHF was associated with increased excretion of urinary cytokines and chemokines [75]. Indeed, high serum levels of tumor necrosis factor α (TNFα) have been demonstrated to be important in the development of kidney hypertrophy and GHF [175]. To support the role of TNFα in kidney hypertrophy and GHF, urinary TNFα has been reported to be associated with increased sodium retention [176], and this in turn can induce the expression of TGFα and the development of kidney hypertrophy [177].

Emerging evidence from various studies suggest that obesity is a chronic pro-inflammatory disease, with an increasing number of investigations implicating the role of inflammation in the pathogenesis of ORG, including GHF [113, 178]. In a Portuguese cohort of children with overweight and obesity, the authors reported a positive correlation between GFR and myeloperoxidase (MPO) activity [179]. Although the mechanism by which MPO is directly involved in GHF is unknown, the ex vivo perfusion of glomeruli with MPO and hydrogen peroxide has been demonstrated to induce epithelial cell foot process effacement [180] and the local MPO activity has been reported to contribute to glomerular damage [181]. It is worth noting that correlation does not necessarily have to reflect causality, therefore, future studies should shed more insights on such associations.

Also, the adipose tissue can act as an endocrine organ for the secretion of angiogenic and inflammatory adipokines, which might have distant effects in the kidney [113, 182], such as the alteration of the glomerular cell size and hypertrophy in glomerular mesangial cells, thereby leading to GHF [183].

An overview of the factors modulating the development of GHF in the pediatric population is presented in Table 2.

Glomerular hyperfiltration: when is it damaging?

GHF has been associated with progressive kidney injury and loss of kidney function leading to kidney failure [184]. However, the exact mechanisms by which GHF induces this kidney injury are not fully elucidated.

Previous studies have implicated RAAS in the development of GHF-mediated injury via inducing alterations in kidney hemodynamics [184, 185]. This finding justified the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) to treat patients with GHF. These drugs have effectively delayed the progression of GHF-mediated injury in some but not all kidney diseases, such as SCD, ADPKD, and CAKUT [184, 185].

Another recently proposed mechanism for GHF-mediated injury is the effect of hyperfiltration-related mechanical forces, namely tensile stress and FFSS on the filtration

Table 2 Summary of factors modulating the development of GHF and their potential mechanisms of action

S/N	Factors	Mechanisms of action	References
a	Low birth weight	It causes a congenital low number of nephrons and an increased glomerular size, thus leading to an increased hemodynamic stress in the remnant nephrons and GHF	[136, 137, 139, 140]
b	Gender	Male individuals with SCD and SFK are more prone to GHF because of the high level of testosterone which causes a significant elevation of ET-1 in male individuals Female subjects with DM have a greater risk to develop GHF due to higher efferent arteriolar resistance seen in women	[9, 29, 146, 147, 152–156]
c	Race/ethnicity	Socio-economic, behavioral, and genetic risk factors (e.g. sickle cell trait and *APOL1* RVs which are predominantly found in African population) can promote kidney damage	[10, 157]
d	*APOL1* RVs	*APOL1* RVs are associated with low nephron endowment and podocyte detachment thereby causing hypertrophy	[6, 160–162]
e	Elevated blood pressure	Elevated blood pressure leads to an increased efferent arteriolar resistance	[168, 169]
f	Age	Increasing age causes an increased loss of kidney function in SCD, with patients experiencing an increased GFR until adolescence In SFK, the age at which the kidney mass is reduced influences GHF. Therefore, individuals with congenital SFK are more prone to GHF since the kidneys can still undergo compensatory nephron formation, which entails the hypertrophy of the kidney tubules and the glomeruli	[21, 22, 148, 170, 173]
g	Inflammation	In DKD, high serum levels of TNFα cause increased sodium retention which leads to an induction of TGFβ and subsequent development of kidney hypertrophy In obesity, secreted angiogenic and inflammatory adipokines cause alteration of the glomerular cell size and hypertrophy in the glomerular mesangial cells Also, MPO which is elevated in obese subjects can induce epithelial cell foot process effacement leading to GHF and eventually glomerular damage	[75, 113, 175–177, 179–183]

barrier [186], as illustrated in Fig. 3. Tensile stress results from an increase in glomerular capillary pressure on capillary wall structures (Fig. 3a), leading to podocyte damage through the activation of the RAAS. On the other hand, FFSS results from a high ultrafiltrate flow in the Bowman's space (Fig. 3a), causing podocyte and tubular damage by activating the cyclooxygenase 2–prostaglandin E_2–E-prostanoid 2 receptor ($COX2–PGE_2–EP_2$) pathway. Indeed, FFSS upregulates COX2, which subsequently activates arachidonic acid metabolism, resulting in increased synthesis of prostaglandins, especially PGE_2, a ligand of EP_2 receptor [185]. Elevated PGE_2 levels act as a mediator of GHF-mediated injury in podocytes and tubules [184].

In podocyte, these biochemical forces cause damage to podocyte structure and function, leading to an increased glomerular basement membrane length and surface. As a result, a mismatch develops between the glomerular surface area and the podocyte foot process coverage. Podocyte reacts via cellular hypertrophy to cover this increased glomerular surface. Thus, the podocyte's body becomes stretched and thinned with foot processes deformed [184, 186]. All these changes might result in podocyte detachment, increased glomerular protein permeability, and glomerulosclerosis [184].

Interestingly, the effects of podocyte hypertrophic stress in the development and progression of CKD have been studied in diabetic and nondiabetic rat models subjected to high nutrient intake [187, 188]. In these studies, an increased release of growth factors and exposure to abundant nutrients was reported to trigger podocyte hypertrophic stress via glomerular volume enlargement and activation of the mammalian target of rapamycin complex 1 (mTORC1) pathway. In turn, these led to accelerated podocyte detachment, reduced podocyte density, albuminuria, glomerulosclerosis, and ultimately progression to kidney failure. Moreover, the authors demonstrated potential renoprotective effects of nutritional reduction in ameliorating kidney injury induced by podocyte hypertrophic stress [187, 188]. As previously mentioned, this approach has been shown to be effective in the management of GHF in obesity.

Likewise, these forces induce tubular damage characterized by dilatation of tubular urinary spaces, epithelial cell hypertrophy, and increased proximal tubular sodium reabsorption, thereby resulting in tubulointerstitial inflammation, hypoxia, and fibrosis [184, 186] (Fig. 3b). Therefore, the $COX2–PGE_2–EP_2$ pathway may be a potential target for developing novel therapies against GHF-mediated injury [185].

Despite these findings, studies investigating the long-term outcomes of GHF in children are lacking. In a humanized sickle cell mice model, Kasztan et al. found that early GHF was a determinant and a predictor of subsequent progression to CKD, only in the male mice [146]. Indeed, in these

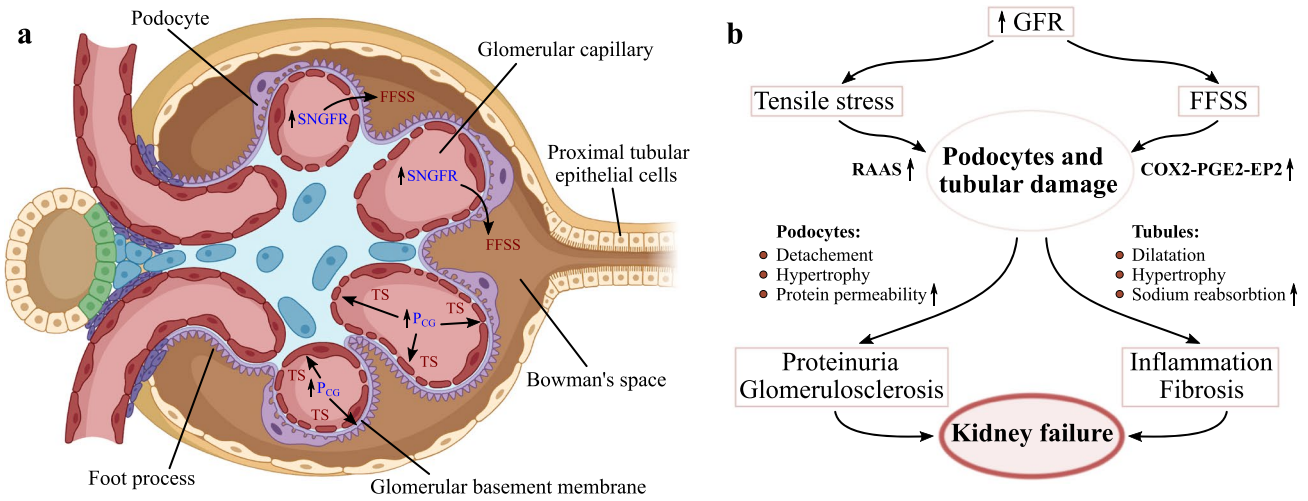

Fig. 3 Proposed mechanism of glomerular hyperfiltration-related kidney damage. Glomerular hyperfiltration is associated with two mechanical forces in the filtration barrier, namely tensile stress (TS) and fluid flow shear stress (FFSS). **a** Increased glomerular capillary pressure (P_{CG}) causes TS on the capillary wall structure and podocyte, while increased single-nephron glomerular filtration rate (SNGFR) leads to high ultrafiltrate flow in Bowman's space, exerting a fluid flow shear stress (FFSS) on the podocyte. **b** These two mechanical forces can cause damage to kidney cells through different pathways. TS activates the renin–angiotensin–aldosterone system (RAAS), whereas FFSS activates the cyclooxygenase 2–prostaglandin E_2–E-prostanoid 2 receptor ($COX2–PGE_2–EP_2$) axis. Subsequently, these forces cause podocyte and tubular damage, resulting in proteinuria, glomerulosclerosis, tubulointerstitial inflammation, and fibrosis. All these detrimental factors can induce progressive kidney injury and loss of kidney function leading to kidney failure. SNGFR, single-nephron glomerular filtration rate; GFR, glomerular filtration rate; FFSS, fluid flow shear stress; TS, tensile stress; P_{CG}, glomerular capillary pressure; RAAS, renin–angiotensin–aldosterone system; $COX2–PGE_2–EP_2$, cyclooxygenase 2–prostaglandin E_2–E-prostanoid 2 receptor

male mice, GHF developed at 12 weeks of age and was significantly correlated with kidney damage (manifesting as proteinuria, albuminuria, decline of GFR, and elevated plasma creatinine) at 32 weeks. In addition, these investigators found that the magnitude of GHF was associated with the degree of subsequent kidney damage [146]. In a cohort of a pediatric population with SCA, Lebensburger et al. conducted a prospective cohort study to determine the relationship between GHF and the development of albuminuria [28]. These investigators found that children who presented GHF during early childhood were more likely to develop persistent albuminuria at an earlier age than those without GHF. These data suggested that GHF precedes the development of persistent albuminuria in children with SCA. Nevertheless, more prospective studies are needed to better evaluate the long-term consequences of GHF in patients with SCD.

In patients with DM, data regarding the association of GHF and adverse kidney outcomes are controversial. Prior studies suggested that GHF was associated with an increased risk of developing adverse kidney outcomes in patients with T1DM and T2DM [189, 190]. On the contrary, in a cohort study of 446 participants with T1DM who underwent measurement of GFR using 125I-iothalamate clearance, 106 (24%) presented GHF at baseline. Over a median follow-up of 28 years, 53 (12%) participants presented decreased eGFR (< 60 ml/min per 1.73 m^2). However, the investigators did not find an association between early GHF and the risk of developing decreased eGFR or severely increased albuminuria (albuminuria excretion rate ≥ 300 mg/24 h) in the multivariable-adjusted Cox proportional hazards model, suggesting that GHF is not a marker of adverse kidney outcomes in patients with T1DM [191]. It is notable that this study provided robust data on the long-term outcomes of GHF in T1DM patients, with a longer follow-up duration and a gold standard measurement of GFR, offering an optimal classification of GHF at baseline [1].

Future perspectives and closing remarks

A supraphysiological elevation of GFR might occur in the pediatric population, especially in those with clinical conditions, such as SCD, DM, ADPKD, obesity, and DMD. In children with reduced numbers of functioning nephrons, elevated GFR remains the main compensatory mechanism. Nevertheless, GHF displays different etiologies and may cause CKD in people. It is therefore important to unravel the molecular mechanisms responsible for these features in order to find new targets for future therapy which can be used to identify and monitor the disease progression and outcome in high-risk individuals. For this purpose, research in identification of novel prognostic indicators (biomarkers)

of disease progression is needed to detect those individuals who would benefit from early-life treatment before the onset of kidney injury. Thus, large cohort studies in the pediatric population are required to help identify these possible prognostic biomarkers. Several interventions like NO bioavailability, SGLT-2 inhibitors, and RAAS blockade are associated with ameliorating GHF in some clinical conditions. The potential benefit of these candidate treatments in other diseases associated with GHF should be tested in available disease-specific model systems, as well as in clinical trials.

Key summary points

- GHF is generally defined as a supraphysiologic increase of GFR that can occur from an increase in factors determining GFR, such as kidney plasma flow, hydraulic pressure across the kidney membrane, or an ultrafiltration coefficient.
- The exact threshold for defining GHF is not well established in pediatric population, and it ranges from 120–180 ml/min per 1.73 m^2.
- GHF can occur in either physiologic or pathologic states. In physiologic state, it can occur after consumption of high protein meals or during pregnancy. In pathologic states, GHF can be due to various diseases which are either congenital or acquired. These pathological conditions include SCD, ADPK, DMD, DM, obesity, and SFK.
- The pathophysiological mechanisms mediating GHF vary between different clinical conditions, occurring either at the single-nephron level or in the whole-kidney.
- The development of GHF in children can be mediated via multiple factors that differ from those seen in the adult population.
- GHF can induce progressive kidney injury and loss of kidney function leading to kidney failure through the activation of RAAS and the direct effect of hyperfiltration-related mechanical forces.

Multiple-choice questions

1. Which factor determines GFR?

   a) Permeability of glomerular basement membrane
   b) Hydraulic pressure
   c) Fluid flow shear stress
   d) Tensile stress
   e) COX2–PGE_2–EP_2 pathway

2. Which of the following statements is FALSE?

   a) The exact threshold for defining GHF can range from 120–180 ml/min per 1.73 m^2
   b) GHF can occur at both the single-nephron and the whole-kidney levels
   c) The mechanisms mediating GHF are similar in all clinical conditions
   d) In SFK, GHF is considered as the main mechanism of kidney injury
   e) The etiology of GHF can be multifactorial

3. Which one of these clinical conditions is not linked with GHF in the pediatric population?

   a) Sickle cell disease
   b) Renal agenesis/aplasia
   c) Enuresis
   d) Obesity
   e) Diabetes mellitus

4. Which clinical condition is associated with single-nephron GHF?

   a) Duchenne muscular dystrophy
   b) Autosomal dominant polycystic kidney disease
   c) Sickle cell disease
   d) Enuresis
   e) Cancer

5. Which of the following hormones plays a role in the association between gender and GHF?

   a) Gastrin
   b) Insulin
   c) Cortisol
   d) Progesterone
   e) Testosterone

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Declarations

Conflict of interest The authors declare no competing interests.

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Answers 1. b; 2. c; 3. c; 4. b; 5. e