FACULTY OF MEDICINE AND HEALTH SCIENCES

The effect of potassium and fiber intake on serum potassium in children with CKD

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Abstract

Background: Potassium (K^+) restricting diets are part of everyday clinical practice to reduce the risk of hyperkalemia in pediatric patients with chronic kidney disease (CKD). It is based on the assumption that dietary potassium importantly impacts serum potassium ($[K^+]s$) in these children. However, no evidence is provided in the pediatric population. Besides, potassium restriction could lead to low fiber intake. Since fiber intake has various proven health benefits, potassium restriction is increasingly questioned. Lack of research hereabout leads to questionable and vaguely described nutrition guidelines on potassium and fiber. We aimed to assess dietary K^+ and fiber intake in a pediatric CKD cohort and define their communal relationship. We intended to asses $[K^+]s$ and research the impact of a potassium binding resin on this. The ultimate aim was to define relationships between dietary K^+ intake as well as fiber intake, and $[K^+]s$.

Methods: In this two-centered, cross-sectional observational study, 52 non-dialysis pediatric patients with CKD stage 1 to 5, were included. Dietary assessment was performed through three day food diaries or 24 hours recall and $[K^+]s$ was analyzed by standard laboratory techniques. K^+ intake, fiber intake and $[K^+]s$ were compared between CKD stages. To assess the association between K^+ and fiber intake, K^+ intake was compared between three groups of patients based on fiber intake tertiles. $[K^+]s$ was compared between patients whether or not on a potassium binding resin (kayexalate), and matched for primary kidney disease and eGFR. To study the influence of dietary K^+ and fiber intake on $[K^+]s$, patients are divided in high and low intake groups. These groups are compared for each CKD stage.

Results: K^+ intake is significantly lower in CKD 4-5 (50,2[41,4;59,4] mg/kg/day) than in CKD 1-2 (76,6 [61,7;114,4] mg/kg/day) (p=0,005). Also fiber intake is significantly lower in CKD 4-5 (53,0 ± 34,6 % of dietary reference intake (%DRI)) than in CKD 1-2 (92,1 ± 37,3 %DRI) (p=0,005). A significant difference in K^+ intake is seen between groups of high and low fiber intake (p=0,017). In general $[K^+]s$ is within the normal range: 4,6 ± 0,6 mmol/L. $[K^+]s$ in patients on kayexalate was equal to or higher than $[K^+]s$ in the control patients. No significant difference of $[K^+]s$ is seen neither between high and low K^+ intake nor between high and low fiber intake, for each CKD stage, except for CKD 3. In CKD 3 an inverse relation between K^+ intake and $[K^+]s$ is found (p=0,035).

Conclusion: This study shows that fiber intake is low in pediatric CKD patients, which is more pronounced in advanced CKD. A moderate association between fiber and K^+ intake is described, which demonstrates that low fiber intake is partly caused by dietary K^+ restriction. No consistent

effect of kayexalate on [K^+] is found, which may be biased by the observational study design. No association between K^+ intake nor fiber intake and [K^+]s is seen. Further research is necessary to define efficacy and safety of dietary potassium restriction and potassium binding resins. More attention towards fiber intake is needed.

Samenvatting

Achtergrond: Een kalium (K^+) beperkend dieet maakt deel uit van de dagelijkse klinische praktijk om het risico op hyperkaliëmie bij pediatrische patiënten met chronische nierziekte (CKD) te verminderen. Het is gebaseerd op de aanname dat inname van kalium via de voeding een belangrijke invloed heeft op de serum kalium concentratie ([K^+]s) in deze pediatrische populatie. Er is echter geen klinisch bewijs gepubliceerd hieromtrent. Bovendien kan kaliumbeperking leiden tot een lage vezelinname. Wegens de verschillende gezondheidsvoordelen die met vezelinname geassocieerd zijn, wordt kaliumbeperking in toenemende mate in twijfel getrokken. Gebrek aan onderzoek op dit vlak leidt tot dubieuze, vaag beschreven nutritionele richtlijnen omtrent kalium en vezel. Het doel van deze studie was om zowel K^+ als vezelinname in een pediatrische CKD populatie na te gaan en hun onderlinge relatie te beschrijven. Daarnaast wilden we ook [K^+]s nagaan en de impact van kaliumbinders op [K^+]s onderzoeken. Het uiteindelijke doel was om zowel de relatie tussen K^+-inname en [K^+]s als die tussen vezelinname en [K^+]s te beschrijven.

Methode: In dit cross-sectioneel, observationeel onderzoek, uitgevoerd in 2 centra, werden 52 pediatrische patiënten met CKD stadium 1 tot 5 die geen nierfunctievervangende therapie volgden, geïncludeerd. Dieetevaluatie werd uitgevoerd door middel van driedaagse voedingsdagboeken of 24-uurs dieetanamnese en [K^+]s werd geanalyseerd via standaard laboratoriumtechnieken. K^+-inname, vezelinname en [K^+]s werden vergeleken tussen de CKD-stadia. Om het verband tussen K^+-en vezelinname te beoordelen, werd K^+-inname vergeleken tussen drie patiëntgroepen op basis van de vezelinname tertielen. [K^+]s werd vergeleken tussen patiënten die wel of niet een kaliumbinder (kayexalaat) kregen, en deze patiënten werden gematcht op basis van primaire nierziekte en eGFR. Om de invloed van K^+- en vezelinname op [K^+]s te bestuderen, werden patiënten verdeeld in groepen met hoge en lage inname. Deze groepen werden voor elk CKD-stadium vergeleken.

Resultaten: De K^+-inname is significant lager in CKD 4-5 (50,2 [41,4;59,4] mg/kg/dag) dan in CKD 1-2 (76,6 [61,7;114,4] mg/kg/dag) (p=0,005). Ook de vezelinname is significant lager in

CKD 4-5 (53,0 ± 34,6 %ADH) dan in CKD 1-2 (92,1 ± 37,3 %ADH) (p=0,005). Er is een significant verschil in K^+-inname tussen de groepen met hoge en lage vezelinname (p=0,017). In het algemeen ligt [K^+]s binnen de normaalwaarden: 4,6 ± 0,6 mmol/L. [K^+]s bij patiënten met kayexalaat inname was gelijk aan of hoger dan [K^+]s bij controlepatiënten. In geen enkel CKD-stadium was er een significant verschil te zien in [K^+]s noch tussen groepen met hoge en lage K^+-inname, noch tussen groepen met hoge en lage vezelinname, behalve voor CKD 3, waar er een omgekeerd verband tussen K^+-inname en [K^+]s is aangetoond (p=0,035).

Conclusie: Deze studie toont een lage vezelinname bij pediatrische patiënten met CKD, die meer uitgesproken is in gevorderde stadia. Er is een matige associatie tussen K^+-en vezelinname. Dit toont aan dat een kaliumbeperkend dieet invloed heeft op vezelinname bij deze patiënten. Er werd geen consistent effect van kayexalaat op [K^+]s gevonden, wat een vertekend beeld kan zijn wegens de observationele aard van de studie. Tussen K^+- of vezelinname en [K^+]s werd er geen verband gezien. Verder onderzoek is nodig om de doeltreffendheid en veiligheid van zowel kaliumbeperkend dieet als kaliumbinders te bepalen. Ook is er meer aandacht nodig voor vezelinname bij deze patiënten.

Introduction

1 Renal anatomy

The kidneys are paired organs that lie in the retroperitoneal cavity, on either side of the vertebral column. A kidney consists of an outer cortex and an inner medulla enclosed by a fibrous capsule. Each kidney contains about one million nephrons. A nephron is made up of a glomerulus, a proximal tubule, a loop of Henle, a distal tubule and a collecting duct. The glomeruli are located in the cortex and the tubules in the cortex and medulla (1). In the glomerulus, ultrafiltration of blood takes place with the production of primary urine as a result. The tubule is responsible for reabsorption, filtration and secretion of water and solutes. The region where the distal tubule contacts its glomerulus is called the juxtaglomerular apparatus (2). At the papilla of the renal pyramid (medulla) the collecting ducts merge into a calyx. These calices form the renal pelvis, which is the beginning of the ureter. Urine is excreted through the ureters, bladder and urethra (1, 2).

2 Kidney function

The kidney has three major functions. The first function is the excretion of waste products of metabolism. The second is the maintenance of a relatively constant extracellular environment. This includes pH as well as electrolyte balance. This balance is necessary for cells to function normally. The third function is the secretion of hormones that participate in the regulation of hemodynamics, red cell production and mineral metabolism (3).

2.1 Glomerular filtration rate

The function of the kidney is measured by the glomerular filtration rate (GFR). This is the rate of ultrafiltration over the glomerular capillary wall. It varies with sex, from 12 years on, and with age (1). Typical mean GFR values in children and adolescents are presented in table 1. The driving forces for GFR are the hydraulic and oncotic pressure gradients across the glomerular capillary wall. GFR is regulated by different mechanisms. One of them is the autoregulation of the glomerular capillaries. It protects the nephrons against increases of perfusion pressure. During alterations in arterial pressure, the afferent arteriole of the glomerulus contracts to prevent an increase in perfusion pressure. Another mechanism is tubuloglomerular feedback. It occurs at the juxtaglomerular apparatus. When the amount of fluid and NaCl in this part of the distal tubule increases, the glomerular filtration rate of that nephron falls. GFR is also regulated by the renin-angiotensin system and by neurohumoral influences (2, 3).

Table 1: Normal GFR in children and adolescents

Age	Mean GFR±SD (ml/min/1.73m^2)
1 week (males and females)	*41*±15
2-8 weeks (males and females)	*66*±25
>8 weeks (males and females)	*96*±22
2-12 years (males and females)	*133*±27
13-21 years (males)	*140*±30
13-21 years (females)	*126*±22

Table adapted from Jayaraman et al. (4); SD= standard deviation

Clinically, estimated glomerular filtration rate (eGFR) is used because GFR is difficult to measure. GFR can only be measured by substances that are freely filtered by the glomerulus but not secreted or reabsorbed in the tubules. In clinical settings, the most widely used biomarker to estimate GFR is creatinine. Limitations in the use of creatinine clearance as a measure of the GFR are tubular creatinine secretion, dependence on muscle mass and physical activity, and interference of drugs and physiologic substances in creatinine assays. An alternative biomarker that is widely used to estimate GFR is serum cystatin C. Cystatin C is produced by all nucleated cells and not dependent on muscle mass. Different formulas have been developed to estimate GFR in children and adults based on these biomarkers (5). The most widely used formula in children is the updated Schwartz formula based on plasma creatinine levels: *eGFR = 0,413 × L (cm)/PCr (mg/dL).* Also a Schwartz formula to estimate GFR using cystatin C is available: $eGFR=70,69\times[(cystatinC)^{-0.931}]$*(6).*

2.2 Electrolyte balance

During ultrafiltration unbound low-molecular-weight constituents of the blood are filtered. These include essential electrolytes, but also other molecules like glucose and amino acids. Most of these solutes are reabsorbed along the tubules to maintain homeostasis. Virtually all bicarbonate, glucose and amino acids are reabsorbed along the proximal tubule (1). Also sodium, phosphate, calcium and magnesium are largely reabsorbed by the kidney. Urate and potassium are both reabsorbed and secreted by the tubules (2). The more tubular secretion of a compound occurs, the less dependent its elimination is on the GFR. If the solute is more secreted than reabsorbed, the excreted amount will be higher than the filtered amount (1).

3 Potassium

Potassium (K^+) is the most abundant intracellular cation. Of total body K^+ content only 2% is located in the extracellular fluid. The high concentration of intracellular potassium is essential for maintaining cell volume, for regulating intracellular pH and controlling cell-enzyme function, for

DNA and protein synthesis and for cell growth. The low extracellular concentration of potassium is necessary for maintaining the cell membrane potential (2). The resting membrane potential is important because it is the stage from where an action potential can be provoked. This is essential for normal neural and muscular function (3).

The normal range of serum potassium in adults is 3,5 to 5,5 mmol/L. Hyperkalemia is defined as a serum potassium concentration above 5,5 mmol/L. On the other hand a serum potassium below 3,5 mmol/L is called hypokalemia. A deviation from normokalemia is associated with increased risk of major adverse cardiovascular events, hospitalization and mortality (7). Young children and infants physiologically have higher serum potassium rates. This should be taken into account when interpreting serum potassium in children. There are however no official limit values described for serum potassium in children. So in clinical practice, the same reference values are used in children as in adults (neonates excluded) (5).

The most common source of potassium load is dietary potassium. K^+ is absorbed by both the small intestine and the colon. Potassium can also originate from damaged tissue. The kidney excretes potassium based on dietary intake. The higher dietary intake, the more K^+ is secreted in the distal tubule. In addition, increased luminal flow, aldosterone and antidiuretic hormone promote K^+ excretion by the kidney. Whereas epinephrine lowers K^+ excretion (2).

Disturbances of potassium homeostasis can be of different cause. There can be a problem in the uptake of K^+ into the cell. The hormones insulin, epinephrine and aldosterone all promote transfer of K^+ into the cell. Lack of one of these hormones can thus result in hyperkalemia. Acid-base disturbances also affect internal K^+ distribution with acidosis leading to hyperkalemia. However, the primary cause of hyperkalemia is impaired renal excretion. This can be due to advanced renal failure or other abnormalities like hypoaldosteronism and distal renal tubular acidosis. Furthermore, massive breakdown of cells can lead to hyperkalemia. This is the case with intravascular hemolysis, burns, crush injuries, rhabdomyolysis, gastro-intestinal (GI) bleeding and the use of chemotherapy with leukemia or a tumor. Risk factors of developing hyperkalemia include CKD and renal impairment, type 2 diabetes mellitus, chronic heart failure, hypertension and the use of medication like renin-angiotensin-aldosteron system inhibitors (ACE inhibitors and ARB), NSAIDs and mineralocorticoid receptor antagonists. Common causes of hypokalemia are GI disturbances such as vomiting and severe diarrhea. Also an inadequate dietary intake can lead to hypokalemia (2, 7).

During hypokalemia the magnitude of the resting membrane potential increases. This reduces the excitability of the cell leading to muscle weakness. With severe hypokalemia there can be enhanced excitability of the cell due to increased intracellular sodium concentration.

With hyperkalemia the membrane excitability is increased. Persistent hyperkalemia however, is associated with decreased membrane excitability due to inactivation of sodium channels (3).

Both hypokalemia and hyperkalemia cause alterations in muscle function and cardiac arrhythmias. This is clinically important because it can lead to cardiac arrest and death. Severe hyperkalemia can also result in death by paralysis of muscles that control ventilation (8).

4 Chronic kidney disease in children

The definition of chronic kidney disease (CKD) by Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (9) is as follows: a GFR <60ml/min/1.73m^2, with or without kidney damage, during more than three months or kidney damage, with or without decreased GFR, for more than three months. Kidney damage is in this guideline defined as structural or functional abnormalities of the kidney characterized by pathologic abnormalities or kidney damage markers, which include abnormalities of blood or urine analysis or abnormal imaging. CKD is considered a chronic deterioration of renal function that may gradually progress to end-stage kidney disease (ESKD) (5). It is specified as a continuous process from mild-to-severe rather than a discrete change in renal function. It is divided into five stages (table 2) based on kidney damage and renal function. The definition of CKD as GFR below 60 ml/min/1,73m^2 is not applicable for children under the age of two because they physiologically have a low GFR, even when corrected for body surface area (table 1)(4, 5, 10).

Table 2: Stages of chronic kidney disease

Stage	**Description**	**GFR (ml/min/1.73m^2)**
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60-89
3a	Mild to moderate ↓ GFR	45-59
3b	Moderate to severe ↓ GFR	30-44
4	Severe ↓ GFR	15-29
5	Kidney failure	<15 (or dialyse)

Table adapted from KDOQI (11)

Children with CKD are confronted with life-long increased morbidity and mortality. It affects growth, nutrition, cognitive development and quality of life (12, 13). An observational study from

Harmer et al.(14) shows that health-related quality of life (HRQoL) is lower in children with CKD pre-dialysis than in a healthy control population. It also shows that HRQoL is associated with nutritional status in these children.

4.1 Epidemiology

Information on the epidemiology of pediatric CKD is limited because the early stages of CKD are often asymptomatic and therefore under-diagnosed and under-reported. Available data is mainly restricted to the Western world. In Europe, the incidence is about 11-12 per million of the age-related population (pmarp) for CKD stages 3-5 and 8 pmarp for stages 4-5. In Belgium, the incidence between 2001 and 2005 for children aged 0-19, was 11,9 pmarp for CKD stages 3-5 and the prevalence was 56 pmarp. Notable was the predominance of the male gender (15). Mortality rate is 30 times higher in children with CKD than in healthy children. Cardiopulmonary death was the most common cause cited in children, followed by infection. Worldwide adolescents have a higher incidence of renal replacement therapy (RRT) compared to other age groups. The youngest pediatric patients on dialysis have the worst survival after one, two and three years on RRT (13).

4.2 Etiology

In adults, common causes of CKD are diabetes mellitus, hypertension and autosomal dominant polycystic kidney disease. In contrast, the most common causes of pediatric CKD are congenital anomalies of the kidney and urinary tract (CAKUT), hereditary nephropathies and glomerulonephritis (13). CAKUT are more common in younger children, whereas older children are more likely to have glomerular disease (10). Diagnoses that are most common with pediatric ESKD include focal segmental glomerulosclerosis, renal hypoplasia or dysplasia, congenital obstructive uropathy and systemic lupus erythematosus (5). Infants born with low weight and small for gestational age have an increased risk of developing ESKD in adolescence. Also children with obesity have a higher risk of early kidney dysfunction and CKD (13).

4.3 Pathophysiology

In CKD the progressive damage of the kidney may be secondary to repeated insults to the renal parenchyma or to the adaptive hyperfiltration of the kidney (10). Initially, the kidney adapts to damage by increasing the filtration rate in the remaining nephrons. As a result, mild CKD is often associated with normal serum concentrations of creatinine, sodium, potassium, calcium and phosphorus. Also total body water remains within the normal range for patients with mild to moderate stages of CKD. This adaptive mechanism is beneficial at first, but can lead to long-term damage of the remaining nephrons. This is manifested by progressive kidney insufficiency often with proteinuria and accumulation of uremic toxins. This irreversible damage is responsible

for the development of ESKD. The prognosis depends to a large extent on the number of functioning nephrons (4, 5).

As described above, kidney damage leads to accumulation of uremic toxins. These are metabolic waste products, but they can also be produced by gut microbiota, particularly indoxyl sulfate (IS) and p-Cresyl sulfate (PCS). They have an adverse effect on biological functions. The presence of uremic toxins is called azotemia, whereas uremia refers to the clinical manifestations of azotemia (5).

The underlying etiology has a major influence on the progression of CKD. In the first years of life, renal dysplasia predominates in comparison to glomerular disease. Renal dysplasia has different causes among which primary genetic disorders, posterior urethral valves which cause lower urinary tract obstruction and teratogens (16). During fetal development severe bilateral renal dysplasia or polycystic kidney disease can lead to oligohydramnios. This can cause pulmonary hypoplasia because lung development requires factors present in amniotic fluid. Survival of these children is based on their lung development. Also, the presence of oligohydramnios is a predictor of poor renal function after birth. Glomerular diseases, on the other hand, are more likely to present later in childhood and they have a faster progression. In this case, impaired renal clearance occurs because the kidneys become affected by tubulointerstitial fibrosis and nephron loss (5).

Beside the etiology, the stage of CKD at time of diagnosis and clinical factors like hypertension, proteinuria, obesity, dyslipidemia, anemia and metabolic acidosis influence the progression of CKD. The rate of progression is also faster among African-Americans. This is documented for adults as well as children with CKD (10, 17).

4.4 Symptoms and clinical diagnosis

The clinical presentation of pediatric CKD can vary widely (Figure 1). In developed countries CAKUT are mostly detected prenatally by routine ultrasound examination. In the developing world this diagnosis may be delayed by a lack of prenatal care. If not diagnosed in early childhood, children with CAKUT may present with recurrent urinary tract infection, failure to thrive, growth impairment or concentrating defects including polyuria. It can also be diagnosed by an incidental finding of elevated serum creatinine, blood urea nitrogen or abnormal imaging. On the other hand glomerular causes of CKD present with nephritic and/or nephrotic symptoms like proteinuria, edema and elevated blood pressure (5, 10).

Children with CKD can remain asymptomatic for years, sometimes until they reach ESKD. Nevertheless, presentation of CKD with symptoms of chronic uremia, uremic pericarditis or uremic pruritis is rare in developed countries (5).

Initial symptoms are primarily associated with the underlying disease. From CKD stage 3 onwards, symptoms of impaired renal function manifest. These include hypertension, anemia, renal osteodystrophy, growth failure and significant electrolyte disturbances (10).

In the diagnosis of pediatric CKD urinalysis, blood analysis and kidney biopsy are important. They can be useful in identifying the etiology of the disease. In the later stages of CKD a biopsy is rarely useful for finding the cause. It particularly shows fibrosis and sclerosis which is common to all end stages CKD. Still it is useful to provide information on the severity of the disease and on any abnormalities which might be reversible (10).

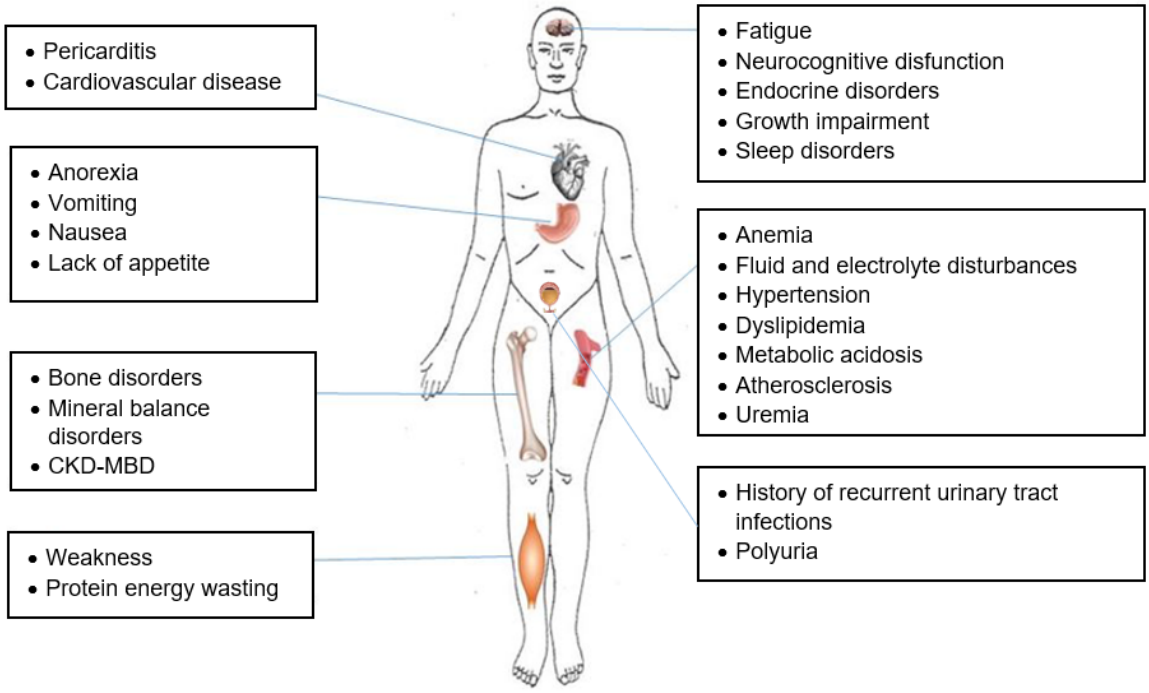

Figure 1: Symptoms of CKD in children
CKD-MBD: Chronic kidney disease - mineral and bone disorder; figure based on Wong et al. (18)

4.5 Complications

Loss of renal function can lead to a various range of complications. The most common are fluid and electrolyte disturbances, metabolic acidosis, anemia, cardiovascular complications and mineral bone disorder. In children however there are other complications like growth impairment, malnutrition and impaired cognitive development.

4.5.1 Fluid and electrolyte disturbances

Fluid and electrolyte disturbances are usually present in CKD stages 4 and 5 (10). The drop in GFR leads to water retention and impaired clearance of solutes. It is associated with volume overload, hypernatremia, hyperkalemia and hyperphosphatemia (10, 19). Volume overload and salt retention can be the cause of secondary hypertension (10). However, children with obstructive uropathies and/or dysplastic kidneys and certain genetic diseases may experience polyuria and hyponatremia due to poor urinary concentration and excessive urinary sodium loss (4, 5). Also patients on peritoneal dialysis can experience excessive sodium loss due to ultrafiltration. Chronic hyponatremia may contribute to growth impairment.

Hyperphosphatemia stimulates parathyroid gland function and has an effect on bone resorption and formation (5).

The most feared electrolyte complication of CKD is hyperkalemia. Typically, renal potassium excretion is maintained until GFR decreases to less than 10 to 15 mL/min/1.73m². When the kidney loses its ability to clear potassium, it is important to counsel children and their family to limit dietary potassium intake (8). However, there are a number of other factors that can influence hyperkalemia. These include high dietary intake, hypercatabolic state with increased tissue breakdown, metabolic acidosis, hypoaldosteronism due to ACE inhibitors or ARBs and other medication like potassium sparing diuretics, calcineurin inhibitors, NSAIDs and in some cases co-trimoxazole (4, 5, 10, 19). Of total potassium excretion 10% happens through the gastro-intestinal tract (8). With advanced CKD there is an adaptive increase in colonic potassium secretion (10). So constipation can lead to hyperkalemia in these patients (5). Unfortunately constipation is frequent in patients with CKD due to reduction of fluid intake, dietary restrictions and medications like phosphate binders or antibiotics (20). Also inadequate dialysis can be a cause of hyperkalemia(8). On the other hand hypokalemia can be seen in association with Fanconi syndrome, polyuric CKD, diuretic therapy, peritoneal dialysis and frequent hemodialysis (4, 8).

4.5.2 Metabolic acidosis

As the GFR decreases to about 50% of normal, metabolic acidosis occurs. Normally the kidney eliminates acid load by hydrogen excretion as titratable acids and through ammonium excretion. When GFR falls impaired reabsorption of bicarbonate, reduced ammonia synthesis, decreased excretion of titratable acids and decreased acidification of tubular fluid lead to metabolic acidosis (13, 19). It results in osteopenia, growth impairment, nephrolithiasis due to hypercalciuria, higher risk of secondary hyperparathyroidism and increased protein and muscle catabolism. It can also

contribute to hyperkalemia, inflammation, enhanced insulin resistance and CKD progression (5, 10, 13, 19).

4.5.3 Growth impairment and malnutrition

Growth impairment is a common complication in pediatric CKD and a major negative factor of quality of life in these patients. It is associated with a higher hospitalization and mortality rate (5). All phases of body growth are affected, starting with the infantile phase. It is thought that in this phase, impairment is largely mediated by malnutrition. Prematurity-related feeding intolerance and recurrent vomiting can be the cause. However more frequent factors of malnutrition in children with CKD include poor appetite, altered gastrointestinal motility, malabsorption, increased inflammatory status, metabolic acidosis and uremic abnormalities that influence metabolism. Malnutrition may also affect neurocognitive development (4, 5). During childhood, the most important factor is the growth hormone axis. CKD is associated with growth hormone resistance, which leads to growth disturbances. The grow spurt is limited by a reduced height velocity and duration and is associated with a more rapid decline in renal function (5, 10, 12, 13). The pubertal phase is mostly affected by the gonadotropic hormones. In children with CKD the average pubertal delay is 2.5 years. The age of onset of CKD has the biggest influence on the severity of growth retardation with the worst outcomes in younger children (10). Next to the phase related factors, there are others factors that contribute to growth impairment. These include metabolic acidosis, fluid and electrolyte abnormalities, renal osteodystrophy, anemia, infections and use of steroids (4, 5, 10, 12).

4.5.4 Anemia

Anemia is an important complication of CKD. It is linked to poor outcomes, quality of life and neurocognitive ability in patients with CKD (5, 13). In children, it is associated with growth impairment (5). Anemia presents with worsening levels of renal function starting from stage 3b on, and is more likely in stage 4 and 5 (19). The cause of anemia is a decreased red blood cell production because of an iron deficiency and because of decreased erythropoietin (EPO) production by the kidney. EPO is a hormone essential for erythropoiesis (5, 19). Iron absorption is suppressed by the hepatic hormone hepcidin, which is elevated in CKD. While EPO suppresses hepcidin production, both inflammation and iron loading stimulate it (5, 13).

4.5.5 Cardiovascular disease

The long-term survival of children with CKD is far lower than that of the healthy population. The leading cause of death in pediatric CKD is cardiovascular disease. Children with CKD have a high prevalence of cardiovascular risk factors including dyslipidemia, hypertension, left

ventricular hypertrophy, anemia, abnormal glucose metabolism, obesity, malnutrition, chronic inflammation and bone metabolism abnormalities (4, 13).

In adults, hypertension is seen as a main cause of CKD, but in children it is rather thought of as a consequence (19). The etiology of hypertension is multifactorial including factors like volume expansion, vasoconstriction because of excessive renin from the damaged kidneys and medications such as corticosteroids and calcineurin inhibitors. Also sympathetic hyperactivation, hyperparathyroidism and inflammation because of systemic inflammatory diseases like SLE may lead to hypertension (4, 10, 19). Furthermore hypertension is associated with black race, glomerular etiology, obesity, elevated serum potassium and faster GFR decline (5, 13). Because of hypertension, arterial stiffness and microvascular damage can occur in the kidneys, brain and heart. Changes in brain vasculature can lead to neurocognitive delays in children with CKD (19).

Left ventricular hypertrophy is induced by fibroblast growth factor 23 (FGF23) which increases in circulation with a decreasing GFR. It stimulates cardiac myocyte hypertrophy that contributes to ventricular hypertrophy. This leads to hypertension and cardiac morbidity. On the other hand hypertension is also a cause of left ventricular hypertrophy (19).

4.5.6 Secondary hyperparathyroidism and mineral bone disorder

Mineral bone disorder is a common feature of CKD progression. Children with CKD stage 2 do not show bone abnormalities, but may have biochemical abnormalities (4). It starts with elevation of FGF23, which prevents hyperphosphatemia in early stages by renal phosphate excretion. Besides, it inhibits activation of 25(OH) Vitamin D, which contributes to secondary hyperparathyroidism and defective bone mineralization. With decreasing renal function, FGF23 is not able to prevent hyperphosphatemia. This also contributes to secondary hyperparathyroidism (5, 10). Phosphate retention and reduction of active Vitamin D will also lead to hypocalcemia, which will also stimulate parathyroid hormone (PTH) production (4). These changes manifest as abnormalities in bone and mineral metabolism and extra-skeletal calcifications that increase the risk of cardiovascular disease (12). The bone disorder is called renal osteodystrophy and presents as low or high turnover skeletal lesions. These include growth plate architecture abnormalities, poor linear growth, epiphyseal displacement and fractures (12, 13). Clinically, this manifests as bone pain, difficulty in walking, bone deformities and spontaneous fractures (10, 12).

4.5.7 Neurodevelopment and cognition

Pediatric CKD may be associated with limitations of neurocognitive ability. However, the limitations are mild and have improved because of adequate therapy (4, 10). Children with mild-

to-moderate CKD fall within normative ranges for IQ, academic achievement and executive functioning (13). On the other hand, there is a trend toward lower IQ for more severe renal failure, while higher GFR predicts improved academic achievement (12, 13).

4.6 Management

The management of CKD consists of several steps which are needed with the progression of the disease. The first step is identifying the underlying etiology and management of reversible causes. This means evaluating patients for fluid depletion, nephrotoxic drug intake, infection, inflammation and congestive heart failure. The second step is slowing the progression of renal dysfunction. Hypertension associated with proteinuria is a risk factor of CKD progression. Therefore strict blood pressure control is important in slowing the disease progression. This can be realized by pharmacologic treatment with an ACE inhibitor or ARB. In addition to blood pressure control, anti-proteinuric effects of this treatment, may promote kidney survival. However, children with renal failure and proteinuria often do not tolerate these medications because the reduction in blood pressure leads to a reduction in perfusion pressure of the kidneys and thus a reduction in GFR. Therefore it is recommended to measure renal function within a few weeks after starting the medication. In adults restriction of protein has shown to be effective. However, this is not recommended in pediatric patients because of the danger of malnutrition. The third step involves treatment of complications which appear in CKD stage 3. In stage 4 the last step takes place: adequate preparation for renal replacement therapy (RRT) (4, 10).

4.7 Renal replacement therapy

When the patient reaches stage 4 of CKD, preparation for RRT should be started. The therapy of choice in children with ESKD is preemptive transplantation (i.e. before dialysis is started). If this is not an option, a decision is made between hemodialysis and peritoneal dialysis. This decision is based on personal circumstances, family preference, medical and social constraints. Later on, a transplantation can still take place (4, 10).

4.7.1 Transplant

When children reach CKD stage 5, RRT is usually initiated. Transplantation conveys a four times higher survival rate than dialysis. Preemptive transplantation has shown better graft survival and reduced mortality compared to transplantation following dialysis. Other advantages of preemptive transplantation are better growth and development and avoidance of the morbidity of dialysis (4, 13). It must be taken into account that the minimum weight for kidney transplantation in children is around 10 kg. Children with a weight below 10 kg will be treated with dialysis until they reach the minimum weight. Transplants can come from the cadaveric transplant waiting list

or from a living related donor (LRD). Parents or other close loved ones can become an LRD for the child. This provides shorter waiting times and improved graft survival. If possible, this is the best treatment option for pediatric CKD patients (4, 10).

4.7.2 Dialysis

Despite the benefits of preemptive transplantation, there are situations where dialysis is necessary. The KDOQI guidelines recommend considering dialysis at an eGFR <15 ml/min/1.73m^2. European guidelines recommend a threshold of 6 ml/min/1.73m^2. Absolute indicators to start dialysis include anuria, severe electrolyte disturbances like hyperkalemia, neurologic consequences, pericarditis, bleeding diathesis, refractory nausea and hypertension. Side effects of uremia are considered relative indicators (13).

The preferred option of dialysis for younger children is peritoneal dialysis. The advantage is that it can be performed at home. The best option is continuous automated peritoneal dialysis during the night, such that it does not disturb school attendance or other day activities. This kind of therapy can put a lot of pressure on families. Together with other factors like infections, ultra-filtration failure and technical problems, this may lead to a switch to hemodialysis (4).

Hemodialysis is performed within a pediatric nephrology center. This has a major impact on daily activities of the child as it takes place three to four times a week for 3-4 hours. Vascular access is traditionally through a large central venous catheter or arteriovenous fistula. Arteriovenous fistulas provide access with less risk of infection but are technically difficult in small children due to small vessel size. They are preferred in children weighing more than 20kg. Despite, central venous lines are often used in practice (4).

4.8 Potassium management

Requirements for potassium in healthy children vary among age. According to WHO guidelines (21) the recommended potassium intake of at least 90 mmol/day in adults should be adjusted downward for children, based on the energy requirement of children relative to those of adults. In this guideline children include all individuals between 2 and 15 years of age. European Food Safety Authority (EFSA) (22) and the High Health Council of Belgium (HGR) (23) express specific recommendations based on age (table 3).

Table 3: Recommendations of daily potassium intake in healthy children

EFSA		HGR	
Age	**Potassium (mg/day)**	**Age**	**Potassium (mg/day)**
7 - 11 months	750	0 - 12 months	39 – 78[a]
1 - 3 years	800	1 - 3 years	800 - 1,000
4 - 6 years	1,100	4 - 6 years	1,100 - 1,400
7 - 10 years	1,800	7 - 10 years	1,600 - 2,000
11 - 14 years	2,700	11 - 14 years	2,000 - 3,100
15 - 17 years	3,500	15 - 18 years	2,500 - 5,000

a: per kg of body weight
EFSA: European Food Safety Authority; HGR: High Health Council of Belgium; table based on EFSA (22) and HGR (23)

Recommendations for potassium intake in children with CKD are scarce and based on research in adults. The KDOQI guidelines (8) recommend limiting potassium intake for children with CKD stages 2 to 5 and 5D who have or are at risk of hyperkalemia. However no data are available on the degree of potassium restriction in children with CKD and hyperkalemia. In adults with CKD, potassium intake is limited to less than 2,000 to 3,000 mg daily, which corresponds to 30 to 40 mg/kg/day for a 70-kg standard adult. Based on this, recommendations for infants and young children with CKD are 40 to 120 mg/kg/day.

4.8.1 Diet

Potassium intake can be lowered by restricting intake of high potassium foods. Foods containing less than 100 mg or less than 3% daily value (DV) are considered low in potassium. These include apples, grapes, berries, white rice, onions, eggplant, zucchini, cucumber and pineapple. Foods containing 200 to 250 mg or greater than 6% DV are considered high in potassium. These include bananas, oranges and orange juice, potatoes, avocados, potato chips, mangoes, papayas, dried fruits, tomato products, pumpkin, legumes and lentils, nuts and seeds, yoghurt and chocolate. Also potassium-containing salt substitutes must be avoided in patients at risk for hyperkalemia (5, 8, 19, 24). Potassium is infrequently listed on food labels and cannot be tasted, which makes it difficult for patients to restrict high potassium foods (24). Meats are often absent from high-potassium food lists, despite containing more potassium than recommended. They can be enhanced with potassium-based food additives, which greatly increases potassium content. An analysis found that enhanced boneless loin strip steak contained 930mg of potassium per 100g. This is almost three times more than a similar unenhanced product. Thus meats often contain as much or even more potassium than many high potassium fruits and vegetables (25).

Potassium content can also be lowered by different cooking techniques. Potassium-rich vegetables can be peeled, diced and presoaked in water to lower potassium content. The water should be discarded before preparing the vegetables. Presoaking root vegetables can lower their potassium content by 50% to 75% (5, 8, 24). Other recommended cooking techniques are boiling in water and blanching. Also using frozen or canned foods plus washing can lower potassium intake. Furthermore, serving sizes should be reviewed; a high serving of low potassium foods can also lead to high potassium intake (20, 24, 26). Dietary restriction can be challenging in infants with CKD. This usually involves low potassium diet in mothers who are breastfeeding their infant (19).

Potassium restriction thus often includes restriction of many plant-based foods and fibers (figure 2). Plant-based foods have potential health benefits which are related to their alkalinizing effects. A study in adults has shown that the intake of plant-based foods leads to reduction of metabolic acidosis and kidney disease progression in acidic, non-diabetic patients with CKD stage 4. Serum potassium in this population was not increased by diets containing potassium-rich foods despite relatively low potassium intake at baseline (27). Furthermore the bioavailability of potassium in high-fiber foods is lower compared to other potassium foods (28). Potassium derived from plants may promote intracellular potassium distribution by stimulating alkaline and insulin. In addition, natural fiber intake promotes fecal excretion of potassium. These effects are currently only described in adults (29). Contradictory, no studies have shown a difference in serum potassium levels between patients mostly consuming plant-derived potassium sources and patients mostly consuming omnivore-derived potassium sources (26). With decreased intake of plants and fibers, dysbiosis of intestinal microbiota occurs. This leads to increased production of uremic toxins as IS and PCS, which can lead to accelerated progression of kidney disease (30). Fiber supplementation has shown to lower plasma PCS by 20% to 37% in adult CKD patients with elevated compliance (20).

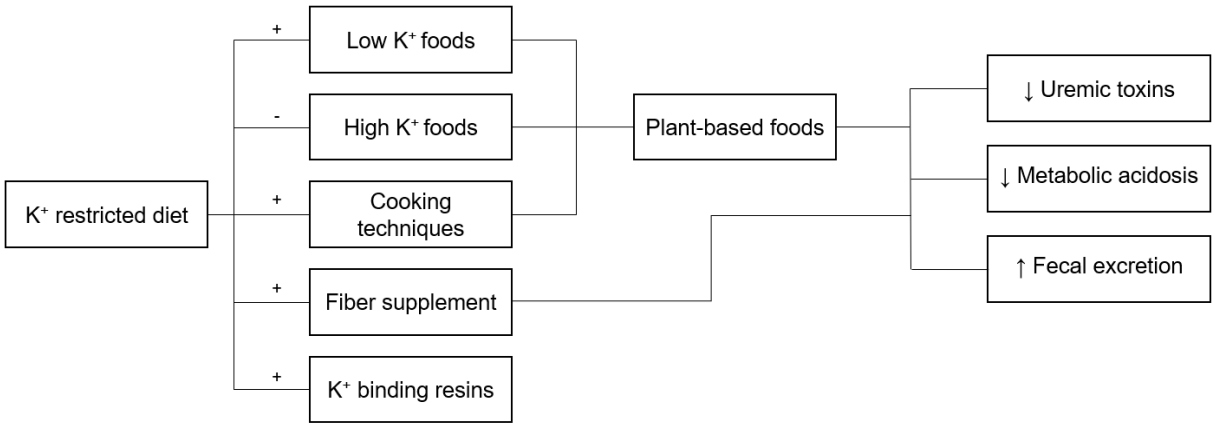

Figure 2: Mind map potassium restricted diet

Increasing intake of dietary fiber in adults with CKD leads to reduction of metabolic acidosis, reduction of intestinal dysbiosis, reduction of uremia and inflammation, reduction of serum urea and creatinine and increase of intestinal transit. This can be achieved by fiber intake through low potassium fruits and vegetables or fiber supplements without added potassium (figure 2) (28, 30, 31). Furthermore, intake of dietary fiber lowers cardiovascular disease in healthy adults (32-36). Despite all these positive effects, KDOQI guidelines do not describe recommendations for dietary fiber intake in pediatric CKD. Instead, they refer to fiber intake recommendations for healthy children (8). The age-based recommendations on fiber intake for healthy children from the High Health Council of Belgium (23) are given in table 4. As might be expected, children with CKD have difficulty meeting this recommendation due to dietary potassium restriction (37).

Table 4: Recommendations of daily fiber intake in healthy children

Age	**Dietary fiber (g/day)**
< 1 year	No recommendation
1-3 years	10
4-6 years	14
7-10 years	16
11-14 years	19
15-17 years	21

Table adapted from HGR, 2016 (23)

High potassium intake in adults with CKD is associated with hyperphosphatemia and uremic neuropathy. In contrast, low potassium intake is associated with hypertension and renal fibrosis (38). Dietary potassium restriction is based on the assumption that dietary potassium intake is

an important determinant of serum potassium. Despite, two studies have shown only a weak association between dietary potassium intake and pre-dialysis serum potassium in adult hemodialysis patients (25, 39). A meta-analysis of Morris et al. (40) does show a reduction of serum potassium with dietary potassium restriction in adult CKD patients with normokalemia. Also, in these patients potassium restriction was associated with reduced mortality but, it was not significantly associated with disease progression. However, these statements are supported by very-low-quality evidence.

Hyperkalemia can also be present in combination with metabolic acidosis. To reduce hyperkalemia it may be necessary to manage metabolic acidosis. This can be accomplished by a diet rich in vegetables as mentioned above or by oral bicarbonate (30).

4.8.2 Potassium binders

If dietary restrictions alone are not sufficient, potassium-binding resins can be prescribed. Sodium polystyrene sulfonate is a potassium binder which can be administered orally or rectally. It contains sodium and thus can lead to volume expansion. It is not a fast-acting medication and should not be used as a sole therapy in acute hyperkalemia. The use of polystyrene sulfonate can cause diarrhea and fluid replacement may be necessary. A rare side effect is colonic necrosis which limits its use in neonates (5, 24). Potassium binders can also be used to pretreat formulas to lower the potassium content par example in formulas for infants or enteral feedings. Pre-treatment with potassium binders lowers the potassium content by 12% to 78% based on the dose, and is associated with an increase or reduction of other nutrients like sodium, calcium and magnesium (8, 24). Patiromer and zirconium cyclosilicate are novel emergent oral agents for the treatment of chronic hyperkalemia. However, there is currently no information available on its use in children (5).

4.8.3 Loop diuretics and renal replacement therapy

When hyperkalemia cannot be controlled by low potassium diet and potassium binders, loop diuretics can be given. Furosemide therapy given 1-2 times a day ensures an increase in potassium excretion (19). If hyperkalemia is not controlled by conservative management, initiation of dialysis is required (10).

4.8.4 Hypokalemia

Unlike hyperkalemia, also hypokalemia can develop in children with CKD. Especially in those on peritoneal dialysis or frequent hemodialysis therapy. Hypokalemia is treated with a high potassium diet, KCl supplements or addition of potassium to the dialysate (8).

Objective

The existing KDOQI guidelines (8) regarding dietary potassium limitation in children with CKD are vaguely described and little substantiated. This is because of unavailable data on potassium in children with CKD, on intake as well as on serum values. Furthermore, there is little evidence of a correlation between potassium intake and serum potassium in both adult and pediatric CKD patients. In adult hemodialysis patients two studies (25, 39) described only a weak association between dietary potassium intake and pre-dialysis serum potassium. A recent meta-analysis did show associations between potassium restriction and reduction of serum potassium as well as a reduction of mortality in adult CKD patients, but this study is based on very-low-quality evidence (40). Nevertheless, many clinicians nowadays still assume that dietary potassium restriction beneficially influences serum potassium in adult as well as pediatric CKD patients. To our knowledge, no studies have examined this in children. But care should be taken when potassium restrictions are prescribed, since they may lead to lower fiber intake. As described in the introduction, fiber intake has a lot of positive effects in adult CKD patients like reduction of uremia, inflammation and intestinal dysbiosis. On top of that, it also improves cardiovascular disease in healthy adults (32-36). So the question arises whether dietary potassium restriction is really beneficial in children with CKD.

Besides, many patients are bothered by dietary restrictions as well as pharmacologic treatment (41-43). This may contribute to reduced quality of live (QoL) in children with CKD (44-46). So the question is asked whether dietary restrictions and potassium binding resins are effective and necessary.

The objective of this study is to describe serum potassium concentrations, and potassium and fiber intake in children with different stages of CKD through cross-sectional analysis. Potassium intake will be compared to the norms of the KDOQI guidelines (8), fiber intake to the recommendation of the High Health Council of Belgium (23) and serum potassium concentration to the conventional reference values. The association between dietary potassium intake and dietary fiber intake will be examined and the impact of potassium binding resins on serum potassium concentrations will be assessed. Furthermore, associations will be evaluated between dietary potassium intake as well as dietary fiber intake and serum potassium concentrations.

Methods

1. Study design

This study is a two-center cross-sectional analysis of serum potassium concentrations, potassium and fiber intake in 52 children with CKD. Information was assembled from the departments of pediatric nephrology of the Ghent University Hospital (UZ Gent) and the University Hospital of Antwerp (UZA). Data was collected between September 2015 and January 2017.

2. Patient inclusion and clinical assessment

In this prospective, observational study, children with CKD stages 1 to 5, who were not on renal replacement therapy, were included. Children who consulted the outpatient clinic or who were hospitalized in the pediatric nephrology departments of both centers and who met the inclusion criteria, were asked to participate in this study. Inclusion criteria for this study involved: dated and signed informed consent, age ≤18 years, and diagnosed with CKD stage 1-5 according to KDOQI guidelines (9) (table 2). Informed consent was signed by the parents and if the child was 12 years or older, it was signed by the child as well. Patients on dialysis were excluded as well as children with unstable disease states like active inflammatory diseases or malignancies.

During the consultation, information on demographics such as age and sex, was obtained. Also information on etiology of primary kidney disease, history of kidney transplant and diet (see below), was collected. Information on treatment with medication was obtained from the patient's history. Length and weight of the patients was measured and blood samples were taken. Length, weight and body mass index (BMI) were standardized for age by a standard deviation score (SDS).

3. Dietary assessment

Dietary potassium and fiber intake were estimated through diet investigations in two different manners. The first manner was a three day food diary. The patients and/or parents were asked to fill in a printed diary with different food categories. The diary had to contain everything the patient ate and drank during the three days preceding the outpatient clinic visit. Quantities were expressed in tablespoons, glasses, grams, slices, pieces… The second manner was a 24 hours recall. Ambulatory, the patient and/or parents were asked by a skilled dietician in a structured way, what the child had eaten and drunk the 24h before consultation. Quantities were estimated by the portion size book (Valetudo Consulting, third edition, March 2014) such that the patients could indicate the quantities of their portions by pointing out the corresponding photo.

The written quantities were calculated to grams with help of the instruction manual 'Weights and measures' of the High Health Council of Belgium (47). If the product was not described in this manual, measures were used of the software package for dieticians, Evry-Diëtist 6.7.7.0 (Evry BV, Alphen aan den Rijn, The Netherlands). If Evry did not contain this information, it was searched for on the internet.

Dietary potassium and fiber were calculated through Evry by entering all foods and quantities. For the three day food diaries a mean value for 24 hours was obtained. A coding method was used for the input of this information. For every food a matching code in Evry was noted. This made it possible to insert the information quickly. The products that were not available in Evry, were searched for in the brand name database 'Internubel' (Nubel vzw) or in the Dutch nutrient database (Nevo, 4^{th} edition). If not available there, it was searched for on sites of stores and nutritional brands themselves. The product was then newly entered in Evry and included in the coding method. When no amount was mentioned during the diet investigation, a list was used, which expresses an average weight for each food in the coding method.

Because of the convention from the KDOQI guidelines (8), daily potassium intake was divided by weight to get a more standardized measure for K^+ intake in mg/kg/day. Fiber was corrected for body surface area (BSA), calculated by the Haycock formula ($=0{,}024265*(length^{0{,}3964})*(weight^{0{,}5378})m^2$) (48). If a patient was on laxatives, this was taken into account and fiber content was added to the daily fiber intake of the patient. Further, fiber was also standardized by the percentage dietary reference intake (%DRI) for fiber. This measure expresses total dietary fiber intake of a patient as a percentage of the age-dependent DRI for fiber, according to the Belgian nutrition recommendation (table 4) (23).

4. Laboratory analyses

Blood samples were centrifuged (2095g, 10min, 4°C) and preserved at a temperature of -80°C until analysis of the sample. For the small water soluble molecules (creatinine), the protein albumin and electrolytes (Na^+, K^+), concentration was analyzed by the laboratories of clinical biology of UZ Gent and UZA, through standard laboratory techniques.

The updated Schwartz formula (see above) was used to calculate eGFR. For definition of the CKD stages reference is made to table 2.

5. Statistics

Statistical analysis are performed using SPSS version 26. Study population as well as potassium intake, fiber intake and serum potassium per stage of CKD are described through a cross-sectional analysis. Normality is checked for by the Shapiro-Wilk test. If data are normally

distributed, it is presented as mean ± standard deviation (SD). If data are skewed, it is expressed as median [25th;75th percentile]. For categorical data, frequencies and percentages are given.

Height SDS, weight SDS and BMI SDS are compared between the CKD stages by a one-way ANOVA test. For age and eGFR, a Kruskal-Wallis test is used. Further, fiber intake and serum K^+ concentrations ([K^+]s) are compared between the CKD stages by a one-way ANOVA test with post hoc Tukey comparison. To compare K^+ intake between CKD stages, a Kruskal-Wallis test with post hoc Dunn's analysis and Bonferroni correction is used.

To study the association between fiber and K^+ intake, %DRI fiber is divided into three groups based on tertiles. These three groups are compared by the Kruskal-Wallis test with Dunn's post hoc comparison and Bonferroni correction.

To research the effect of potassium binding resins on [K^+]s, a comparison is made between patients who are on kayexalate and patients who are not. They are matched based on primary kidney disease and eGFR. Between these matched pairs, K^+ intake and [K^+]s are compared.

For the association of K^+ intake and [K^+]s, the cohort is divided in two groups based on the median K^+ intake. Each group is further divided into three, based on CKD stage. An independent T-test is used to compare [K^+]s between high and low K^+ intake, for each stage of CKD. To compare [K^+]s between the CKD stages, for either high or low K^+ intake, an ANOVA test with post hoc Tukey analysis is performed. If the assumption of homogeneity of variances is not met, a Welch test with post hoc Games-Howell comparison is performed instead.

The same method is used to research the association between [K^+]s and fiber intake. Except for CKD stage 1-2, a Mann-Whitney U test is used instead of an independent T-test due to skewed data.

Statistical significance is set at a 2-tailed probability level of <0,05.

Results

1. Demographics

There were 52 participants in this study (table 5). Patients assessed were between 11 months and 17 years of age with a median of 8,6 [4,4;14,2] years. Of the 52 participants, 14 were female (26,9%). Average height standard deviation score (SDS), weight SDS and BMI SDS were -1,23 ± 1,17; -0,99 ± 1,36 and -0,32 ± 1,22, respectively. Distribution of the patients among the CKD stages was 18,17 and 17 patients for CKD 1-2, 3 and 4-5 respectively, with a median eGFR of 48,5 [25,2;68,2] ml/min/1.73m². No difference in age, height SDS, weight SDS and BMI SDS was seen between the CKD stages. Of the 52 included patients, 7 already underwent a kidney transplantation. The most frequent cause of primary kidney disease was hypoplasia or dysplasia of the kidneys (32,7%). To estimate dietary intake of potassium and fiber, 20 out of 52 patients kept a three day food diary and the remaining 32 patients made use of the 24 hours recall. Seven out of 52 patients were on a potassium binding resin (kayexalate), of which 4 were in CKD stage 4-5 while the remaining 3 were in CKD stage 3.

Table 5: Baseline characteristics

	CKD stages			Total	*p-value*
	Stage I-II (n=18)	Stage III (n=17)	Stage IV-V (n=17)	(n=52)	
Age (yr)	6,0 [4,9;9,2]	11,9 [7,3;14,7]	7,8 [3,0;13,8]	8,6 [4,4;14,2]	*0,174*
Height SDS	-1,20 ± 1,16	-1,09 ± 1,43	-1,39 ± 0,93	-1,23 ± 1,17	*0,767*
Weight SDS	-0,91 ± 1,20	-1,17 ± 1,79	-0,89 ± 1,03	-0,99 ± 1,36	*0,800*
BMI SDS	-1,78 ± 0,90	-0,68 ± 1,48	-0,11 ± 1,22	-0,32 ± 1,22	*0,337*
Male sex	11 (61,1)	14 (82,4)	13 (76,5)	38 (73,1)	
eGFR (ml/min/1.73m²)	73,4 [65,9;100,2]	45,9 [36,2;54,4]	18,5 [13,7;25,5]	48,5 [25,2;68,2]	*<0,001*
Primary kidney disease category					
Glomerular	4 (22,2)	3 (17,6)	1 (5,9)	8 (15,4)	
Obstructive	1 (5,6)	3 (17,6)	4 (23,6)	8 (15,4)	
Hypoplasia/Dysplasia	4 (22,2)	5 (29,4)	8 (47,0)	17 (32,7)	
Other non-glomerular	8 (44,4)	4 (23,6)	3 (17,6)	15 (28,8)	
Cystic disease	1 (5,6)	2 (11,8)	1 (5,9)	4 (7,7)	
Transplant patients	5 (27,8)	2 (11,8)	0 (0)	7 (13,5)	
3 day food diary	9 (50,0)	7 (41,2)	4 (23,6)	20 (38,5)	
Kayexalate	0 (0)	3 (17,6)	4 (23,6)	7 (13,5)	

Results are presented as n (%), mean ± SD or median [25th; 75th percentile]; SDS= standard deviation score

2. K^+ and fiber intake

Table 6 shows an overall K^+ intake of 1711 ± 812 mg/day, which (if corrected for weight) results in a median of 61,8 [43,5; 81,4] mg/kg/day. This lies within the recommendation of 40-120 mg/kg/day according to the KDOQI guidelines (8). There are, however, 15 patients who do not meet the recommendation of K^+ intake (figure 3A). Nine patients have a K^+ intake below 40

mg/kg/day and six patients have an intake above 120 mg/kg/day. Noticeable is that 4 out of 6 patients with K^+ intake higher than the guideline, are in CKD stage 1-2 and none are in CKD 4-5. Boxplots of K^+ intake by CKD stage, are given in figure 4A. Notice that the distribution of K^+ intake is not the same between CKD stages (p=0,006). However, K^+ intake is only significantly lower in CKD stage 4-5 than in CKD stage 1-2 (p=0,005). In the group of CKD stage 1-2, there are two outliers, 241,2 and 253,3 mg/kg/day specifically.

Table 6: K^+ intake, K^+ serum concentration ([K^+]s) and fiber intake overall and by CKD stage

	CKD stages			Total
	Stage I-II (n=18)	Stage III (n=17)	Stage IV-V (n=17)	(n=52)
K+ intake (mg)	1918 ± 809	1936 ± 814	1266 ± 656	1711 ± 812
K+ intake/weight (mg/kg)	76,6 [61,7;114,4]	67,9 [38,0;83,0]	50,2 [41,4;59,4]	61,8 [43,5;81,4]
[K+]s (mmol/L)	4,4 ± 0,5	4,8 ± 0,6	4,7 ± 0,5	4,6 ± 0,6
Fiber diet (g)	13,4 ± 6,0	13,5 ± 6,1	8,7 ± 6,2	11,9 ± 6,4
Fiber/BSA (g/m²)	16,0 [12,4;20,4]	10,1 [7,7;13,3]	8,8 [4,0;12,0]	11,1 [7,8;16,1]
%DRI fiber	92,1 ± 37,3	79,3 ± 33,8	53,0 ± 34,6	75,2 ± 38,3

Results are presented as mean ± SD or median [25th; 75th percentile]; BSA= Body surface area; %DRI = % of daily recommended intake

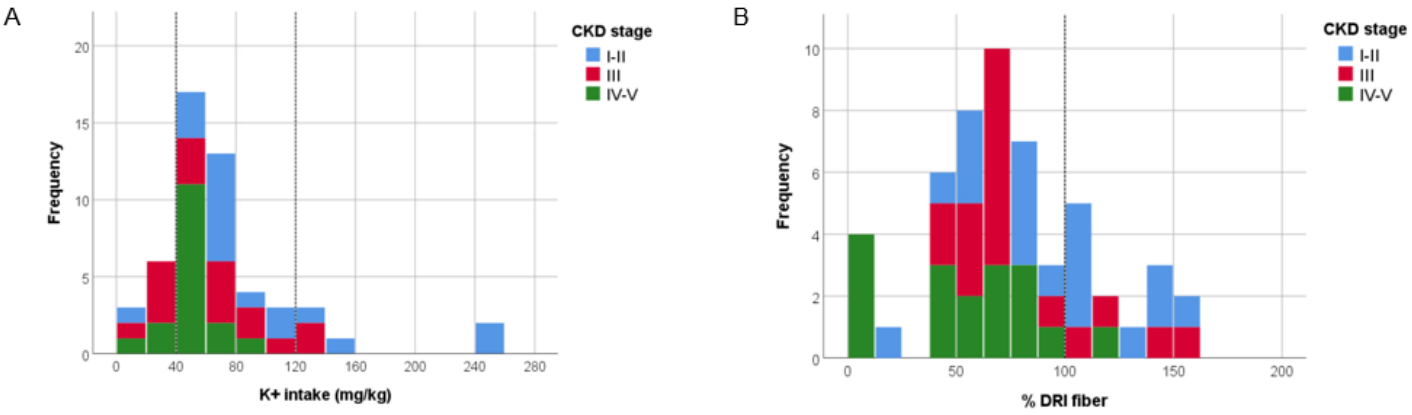

Figure 3: Stacked histogram of A: K+ intake (mg/kg) by CKD stage; reference lines of 40 mg/kg and 120 mg/kg are given according to the KDOQI guidelines (8); B: %DRI fiber by CKD stage; reference line of 100% is given

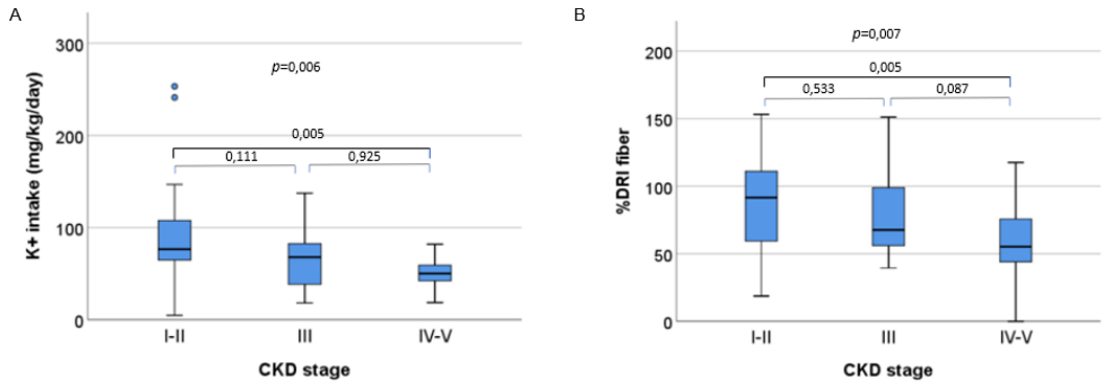

Figure 4: Boxplots of A: K⁺ intake (mg/kg/day) by CKD stage; B: %DRI fiber by CKD stage

Daily fiber intake was estimated as 11,9 ± 6,4 g. If adjusted for BSA, this provides an overall fiber intake of 11,1 [7,8;16,1] g/m²/day. When expressed as %DRI fiber, this results in 75,2 ± 38,3 %. As this outcome does not approach 100%, it indicates that the majority of the patients fail to reach the age-dependent fiber recommendations of the High Health Council of Belgium (23). Only 13 out of 52 patients meet recommended fiber intake (figure 3B). Most of them are in CKD stage 1-2. Solely one patient is in CKD stage 4-5. In figure 4B, boxplots of %DRI fiber by CKD stage are given. The same tendency can be seen as for potassium intake (figure 4A). The distribution of %DRI fiber is not the same between CKD stages (p=0,007), but a decline can only be seen between CKD stage 1-2 and 4-5 (p=0,005).

To study the association between K+ and fiber intake, the population was divided in three groups based on %DRI fiber. Figure 5 shows that K⁺ intake rises with higher fiber intake (p=0,010). However this rise is only significant between the groups with the highest and lowest fiber intake (p=0,017) (table 7). The group with the highest fiber intake has a broader distribution than the other two. In this group there is also an outlier with a K⁺ intake of 253,3 mg/kg/day (figure 5).

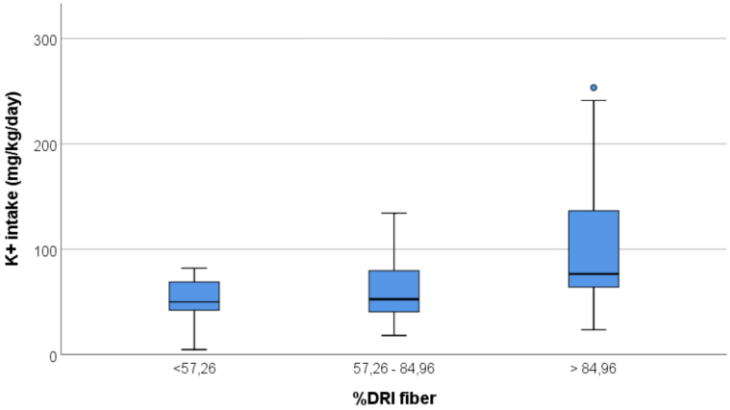

Figure 5: Boxplots of K⁺ intake by %DRI fiber; percentile 33 of %DRI fiber = 57,26%, percentile 66 of %DRI fiber= 84,96%

Table 7: K^+ intake by %DRI fiber

%DRI fiber		n	K+ intake (mg/kg)
Low (<57,26)		17	50,2 [40,3;69,2]
Moderate (57,26-84,96)		17	52,6 [39,1;81,2]
High (>84,96)		18	76,6 [62,9;136,8]
	p		*0,010*
Low & Moderate	*p*		*1,000*
Moderate & High	*p*		*0,050*
Low & High	*p*		*0,017*
Results are presented as n or median [25th; 75th percentile]			

3. Serum K^+ concentration and impact of potassium binding resins

The mean K^+ serum concentration $[K^+]s$ in this population is 4,6 ± 0,6 mmol/L (table 6). This fits within the reference values of 3,5-5,5 mmol/L for $[K^+]s$ in adults and children (neonates excluded). Only five patients did not meet these reference values. One patient from CKD stage 1-2 had a $[K^+]s$ of 3,3 mmol/L and four patients of CKD stage 3 had a $[K^+]s$ of more than 5,5 mmol/L (figure 6).

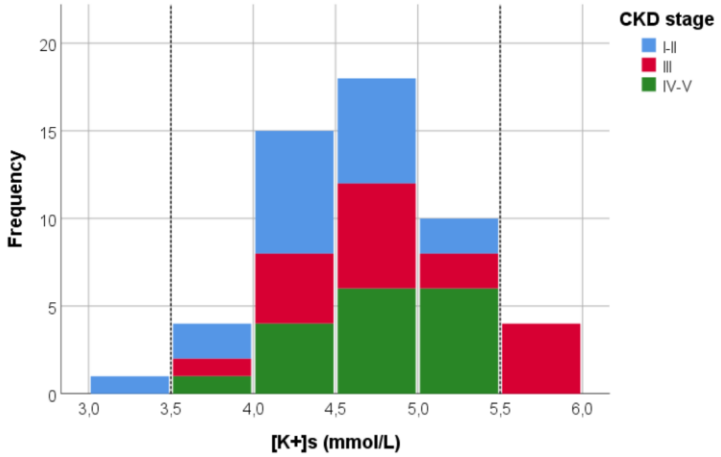

Figure 6: Stacked histogram of [K+]s (mmol/L) by CKD stage, reference lines of 3,5 and 5,5 mmol/L are given

Figure 7 shows that there is a significant difference in serum $[K^+]$ between the CKD stages (p=0,041). However, no significant difference can be seen between CKD stage 3 and 4-5 (p=0,816), nor between CKD stage 1-2 and 4-5 (p=0,156). CKD stage 3 has a significantly higher $[K^+]s$ than CKD stage 1-2 (p=0,042).

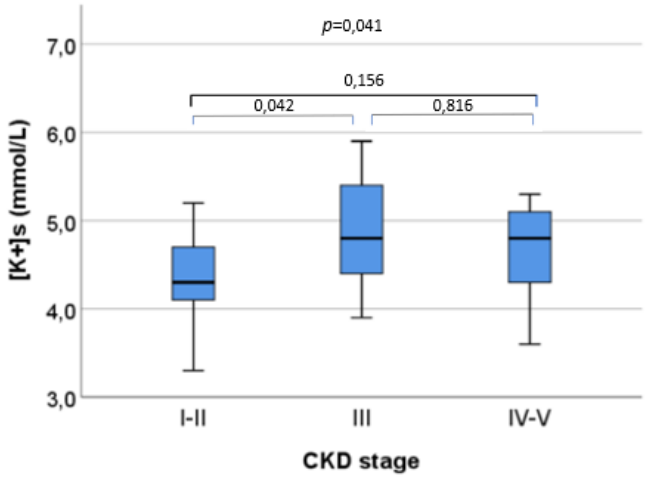

Figure 7: Boxplots of [K+]s (mmol/L) by CKD stage

To research the impact of potassium binding resins on [K^+]s, patients on kayexalate were matched with patients who were not on kayexalate, based on primary kidney disease and eGFR. For primary kidney disease category, CAKUT (hypoplasia/dysplasia and obstructive anomalies) were taken together. From the seven patients on kayexalate (table 5), two were transplant patients and therefore not included. One patient could not be matched based on primary kidney disease and eGFR. Finally, only four patients were matched (table 8). These patients show no consistent effect of kayexalate on [K^+]s. For patients with the same cause of primary kidney disease and closely matched eGFR and K^+ intake, [K^+]s is nearly the same regardless of kayexalate intake. Despite lower or higher K^+ intake, serum potassium is higher in the patients on kayexalate. Nevertheless, no statistical evidence is provided due to the small number of patients.

Table 8: eGFR, K^+ intake and [K^+]s in matched patients with or without kayexalate

	No kayexalate				Kayexalate			
Primary kidney disease category	eGFR (ml/min/1.73m²)	K+ intake (mg/kg)	[K+]s (mmol/L)		**Primary kidney disease category**	eGFR (ml/min/1.73m²)	K+ intake (mg/kg)	[K+]s (mmol/L)
Obstructive	10,57	59,22	4,80		Obstructive	11,46	53,86	4,80
Hypoplasia/dysplasia	25,96	69,46	4,30		Obstructive	27,16	81,99	4,70
Obstructive	13,52	25,65	5,00		Hypoplasia/dysplasia	15,37	26,04	5,10
Other non glomerular	35,66	67,92	4,80		Other non glomerular	32,84	44,20	5,60

4. Association of serum K^+ concentration and K^+ intake

Figure 8 shows the serum [K^+] for low and high K^+ intake by CKD stage. K^+ intake was divided in two groups by the median K^+ intake (61,85 mg/kg/day). It is remarkable that [K^+]s is lower with high K^+ intake for CKD stage 3 (p=0,035) (table 9). In CKD stages 1-2 (p=0,165) and 4-5

(p=0,951) there is no significant difference in [K⁺]s between high and low K⁺ intake. Note that the distribution of [K⁺]s is more extensive for low than for high K⁺ intake in CKD 3 and CKD 4-5 (figure 8). In CKD 1-2 it is the other way around. Furthermore, table 9 shows no significant difference in [K⁺]s between the CKD stages within the groups based on low or high K⁺ intake.

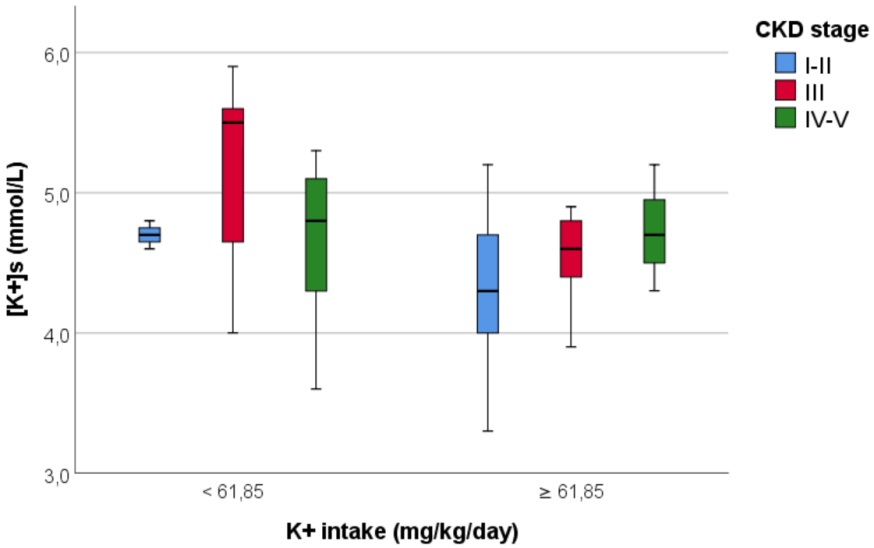

Figure 8: Clustered boxplots of serum [K⁺] by K⁺ intake and by CKD stage; median K⁺ intake= 61,85 mg/kg/day

Table 9: Serum [K⁺] by K⁺ intake and by CKD stage

CKD Stage	K+ intake <61,85 mg/kg		K+ intake ≥ 61,85 mg/kg		
	n	[K+]s (mmol/L)	n	[K+]s (mmol/L)	*p*
Stage I-II	4	4,70 ± 0,08	14	4,29 ± 0,56	*0,165*
Stage III	8	5,18 ± 0,69	9	4,52 ± 0,34	*0,035*
Stage IV-V	14	4,71 ± 0,48	3	4,73 ± 0,45	*0,951*
p		*0,208*		*0,271*	
Stage I-II & III *p*		*0,197*		*0,495*	
Stage III & IV-V *p*		*0,257*		*0,790*	
Stage I-II & IV-V *p*		*0,994*		*0,328*	
Results are presented as n or mean ± SD					

5. Association of serum K⁺ concentration and fiber intake

For the association between fiber intake and [K⁺]s, the cohort was divided into two groups by the median %DRI fiber (68,8%). Figure 9 shows the [K⁺]s for low and high %DRI fiber by CKD stage. [K⁺]s seems not affected by %DRI fiber. Table 10 shows no significant difference in [K⁺]s between low and high %DRI fiber for the CKD stages. Also there is no significant difference in [K⁺]s between the CKD stages within the groups based on low (p=0,149) or high (p=0,217)

%DRI fiber. In the group of CKD stage 1-2 with low %DRI fiber, there is an outlier with a [K⁺]s of 3,3 mmol/L (figure 9).

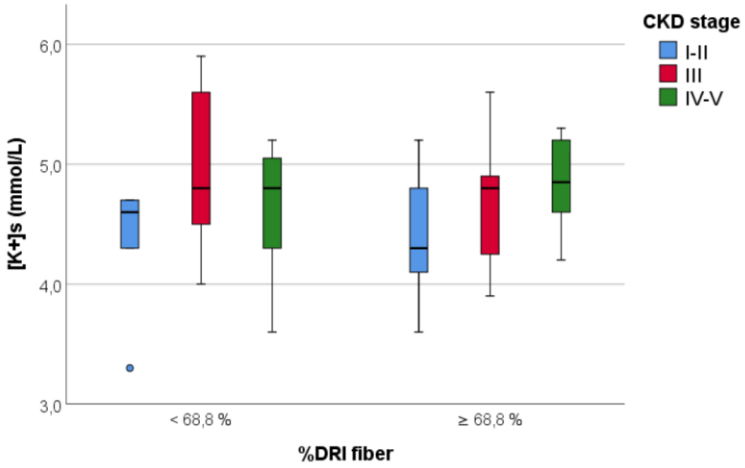

Figure 9: Clustered boxplots of serum [K⁺] by %DRI fiber and by CKD stage; median %DRI fiber = 68,8%

Table 10: [K⁺]s by %DRI fiber and by CKD stage

CKD stage	%DRI fiber <68,8		%DRI fiber ≥68,8		
	n	[K+]s (mmol/L)	n	[K+]s (mmol/L)	*p*
Stage I-II	5	4,6 [3,8;4,7]	13	4,40 ± 0,51	*0,921*
Stage III	10	4,95 ± 0,64	7	4,66 ± 0,58	*0,349*
Stage IV-V	11	4,65 ± 0,50	6	4,83 ± 0,40	*0,467*
p		*0,149*		*0,217*	
Stage I-II & III *p*		*0,135*		*0,537*	
Stage III & IV-V *p*		*0,479*		*0,809*	
Stage I-II & IV-V *p*		*0,536*		*0,217*	
Results are presented as n, mean ± SD or median [25th; 75th percentile]					

Discussion

From 52 non-dialysis pediatric CKD patients, we collected cross-sectional information on eGFR, dietary potassium and fiber intake, serum potassium concentration and use of a potassium binding resin. Because of scarce data on this matter, the describing analyses of these measurements is valuable. The main findings of our study are: 1/ Potassium and even more fiber intake is low in pediatric CKD patients, which is most pronounced in advanced CKD stages. 2/ There is a moderate association between K^+ and fiber intake. 3/ Serum potassium is within the normal range and is constant across CKD stages. 4/ Kayexalate has no consistent effect on serum potassium. 5/ Serum potassium is not dependent upon K^+ nor fiber intake.

First, we found that potassium and even more fiber intake in pediatric CKD patients is low and is dependent upon renal function. Up to now, little research was performed on dietary fiber and potassium intake in pediatric CKD patients and their effect on disease progression and overall health. This leads to vaguely described and little substantiated nutrition guidelines. KDOQI (8) recommends dietary potassium restriction in children with CKD 2-5D who have or are at risk of hyperkalemia, without further defining ‘at risk of hyperkalemia’. As dietary potassium restriction they recommend a potassium intake of 40-120 mg/kg/day, which is based on recommendations in adults. Two previous studies have shown that many pediatric CKD patients did not meet this recommendation (49, 50). Our study confirms this as 15 out of 52 patients did not meet recommended dietary potassium intake. For fiber intake, KDOQI guidelines (8) refer to recommendations in healthy children, which differ between countries (35). Hence, to assess fiber intake in this study, guidelines of the High Health Council of Belgium (23) were used. This recommendation was not met by 39 out of 52 patients. This is in line with data on fiber intake in adults and children with CKD (31, 37, 51), which demonstrated that more than half of adult CKD patients and 77% of pediatric CKD patients did not meet fiber intake guidelines. In our study, potassium as well as fiber intake was significantly lower for patients in CKD 4-5 compared to those in CKD 1-2. This indicates an association between both potassium and fiber intake, and renal function which can be explained by the potassium restricting diets as generally advised in advanced CKD stages. Two patients in CKD stage 1-2 showed an outlier when it came to potassium intake. For one patient, this high dietary potassium can be explained by the cause of CKD. The patient suffered from cystinosis which is a potassium losing condition and was therefore on potassium citrate. The second patient was on a potassium containing food supplement called nutrinidrink multifiber because of bad weight gain.

Second, an association was found between potassium and fiber intake. Potassium intake was significantly higher in the group with high fiber intake compared to low fiber intake. This could explain low fiber intake in advanced CKD stages due to potassium restricting diets. No significant difference in K^+ intake was seen between moderate and low fiber intake or moderate and high fiber intake. The fact that not all foods rich in potassium are rich in fiber and vice-versa might skew the association.

Third, we found that [K^+]s was within the normal range and constant across CKD stages. For 47 out of 52 patients in our cohort, [K^+]s was within the normal range of 3,5 to 5,5 mmol/L. In CKD 3 [K^+]s was significantly higher than in CKD 1-2. Although not significant, mean [K^+]s was higher in CKD 3 than in CKD 4-5, which is surprising as renal K^+ excretion lowers with decreasing eGFR (52). These results could be explained by the fact that all four of the patients with hyperkalemia were in CKD stage 3. Two of them were transplant patients and therefore were on tacrolimus, which decreases K^+ excretion. This could explain hyperkalemia in these patients. No explanation for hyperkalemia in the other two patients, was found.

Fourth, we found no consistent effect of the potassium binding resin kayexalate on [K^+]s. Efficacy and safety of sodium polystyrene sulfonate (kayexalate) is disputed. No robust randomized controlled clinical trials on long term use of this product are available. There are only some trials in adult CKD patients which show a lowering effect of kayexalate on [K^+]s. Though, these trials were of short duration and operated with small sample sizes (53-55). One long-term study showed a fall in [K^+]s after 289 months of low dose kayexalate therapy in adult patients on renin-angiotensin-aldosterone system inhibitors for heart disease (53). Contradictory, one placebo controlled trial showed no difference in [K^+]s and fecal potassium excretion after kayexalate intake in ESKD patients on hemodialysis (53). With the use of kayexalate, many adverse effects among which bowel obstruction, intestinal necrosis, electrolyte disturbances and nausea are described (53-55). In our cohort, neither a difference in [K^+]s nor a lower [K^+]s in patients on kayexalate was seen, but no statistical evidence is provided due to small sample size. The fact that only patients whose baseline [K^+]s is high and thus are at risk of hyperkalemia, are prescribed kayexalate, influences the result. Efficacy of potassium binding resins is an important matter because intake of chronic medication increases the pill burden, which is already high in pediatric CKD patients (41-43). Consequently, this could impact QoL of these patients. Therefore, randomized double-blind controlled trials in patients with marginally elevated serum potassium and not at risk for acute hyperkalemia, are necessary to research efficacy, safety and impact on QoL of chronic potassium binding resins in pediatric CKD patients.

Further, our study has shown no influence of K^+ intake on $[K^+]$s. The impact of dietary potassium restriction has been increasingly questioned due to the many potential health benefits of plant-based foods and fibers (figure 2) (25, 26). It also has an important impact on everyday life of pediatric CKD patients as potassium restricting diets are strict and difficult to follow. It is often reported that children experience dietary restrictions as a nuisance (42, 43). A trial by Aparicio-López et al. (41) showed that 58% of the children on diet restrictions are bothered by them. Therefore we may assume that potassium restriction could influence QoL of these patients, however no evidence on this matter is provided. As with the use of potassium binding resins, potassium restricting diets are based on the assumption that potassium intake and absorption are important determinants of $[K^+]$s in CKD patients. However, only two trials described a rather weak association between dietary potassium intake and pre-dialysis serum potassium in adult hemodialysis patients (25, 39). A recent meta-analysis did show a decline in $[K^+]$s in adult CKD patients on a potassium restricting diet, but this result was based on very-low-quality evidence (40). No research on this matter in a pediatric CKD population is published, according to our knowledge. Thus, our study is the first to describe the association between potassium intake and $[K^+]$s in pediatric CKD patients. No impact of K^+ intake on $[K^+]$s was seen in CKD stages 1-2 and 4-5. Rather unexpectedly, a significantly lower $[K^+]$s was seen with high K^+ intake in CKD stage 3. This paradoxical result could emerge from the fact that all four hyperkalemic patients of CKD stage 3 had low potassium intake. Also, $[K^+]$s did not differ between the CKD stages within the groups of low or high K^+ intake. But $[K^+]$s did slightly differ between CKD stages when potassium intake was not considered. This could thus be interpreted as a trend for an inverse association of K^+ intake and $[K^+]$s. It raises the question of what came first. It can be presumed that patients with high $[K^+]$s are more frequently recommended to follow a potassium restricting diet. As $[K^+]$s is not significantly lower in patients on potassium restriction the role of dietary potassium in $[K^+]$s could be questioned. As mentioned in the introduction, $[K^+]$s is mediated by a variety of determinants among which acidosis, aldosterone, vasopressin, epinephrine, insulin, medication, eGFR and potassium intake. Down to an eGFR of approximately 15 mL/min/1.73m², $[K^+]$s homeostasis is provided by the kidney. When hyperkalemia arises in these patients, it will more likely be controlled by determinants apart from potassium intake, as large amounts of dietary potassium are needed to provoke hyperkalemia. In patients with eGFR <15 mL/min/1.73m², $[K^+]$s is more affected by potassium intake (52). Because of this, a prudent interpretation of our results is necessary. Only three patients of CKD stage 4-5 had a high potassium intake and they all had an eGFR >15 mL/min/1.73m².

At last, our study has shown no association between fiber intake and $[K^+]$s. Dietary fiber has shown to provide multiple health beneficial effects. In healthy adults, fiber intake is associated with a reduced cardiovascular risk (32-36). In adult CKD patients it reduces inflammation, cholesterol, uremic toxin concentrations and mortality (figure 2) (20, 28, 30, 31, 51, 56-58). It also reduces serum creatinine and is found to be renoprotective (27, 28, 30, 31, 56, 57, 59). Yet, general fiber intake is low in CKD patients, especially in patients on dietary potassium restriction due to the positive association of fiber and K^+ intake. In the first place, low fiber intake might affect QoL of CKD patients. Due to low dietary fiber, they miss out on many of the health beneficial effects. For example, a common problem in CKD patients is constipation, which can be a side-effect of low fiber intake. QoL of these patients may thus be affected by the lack of fiber-associated health benefits, due to potassium restriction. However, there is little clinical evidence on the efficacy of dietary potassium restriction in pediatric CKD patients and no long term data on overall health are available. This may be the reason for the absence of adjusted fiber intake guidelines in pediatric CKD patients. Secondly, low fiber intake might influence $[K^+]$s in CKD patients. Sufficient dietary fiber intake reduces metabolic acidosis and increases fecal excretion in adult CKD patients, which both can affect $[K^+]$s (figure 2) (27, 29-31, 52, 58). Potassium in high-fiber foods also has a lower bioavailability and potentially promotes intracellular potassium distribution by a stimulating effect of fiber on alkaline and insulin (28, 29). From this we could figure that dietary fiber potentially lowers $[K^+]$s in CKD patients. This could contribute to the negative association found between K^+ intake and $[K^+]$s in CKD stage 3 in our cohort. Literature describes varying results on the association between fiber intake and $[K^+]$s. Tyson et al. (60) described a small increase in $[K^+]$s after two weeks of Dietary Approaches to Stop Hypertension (DASH), which is full of fiber, in adult patients with CKD stage 3. A trial by Goraya et al. (27) showed no increase in $[K^+]$s in adult CKD stage 4 patients with increased fruit and vegetable consumption for one year. The latter is in line with our results. No association between fiber intake and $[K^+]$s was seen. This result may be biased by the small range of fiber intake in our cohort, which is a consequence of low general fiber intake in pediatric CKD patients.

The value of our study lies within the presented data on potassium and fiber intake and their association with $[K^+]$s. Data on fiber and potassium intake in pediatric CKD patients is scarce and to our knowledge, we are the first to describe their association with $[K^+]$s in these patients. A big strength of our study is the detailed quantification of dietary intake. Data on potassium and fiber intake were obtained through 3-day food diaries or 24 hours recall. This is more precise than the frequently used food frequency questionnaires because recall bias is reduced.

Limitations of our study lie within the observational, cross-sectional design, the small sample size and the dietary quantification method. The observational, cross-sectional design of the study makes it difficult to assess causality, as no intervention is performed, regarding the impact of kayexalate, potassium restriction and fiber intake on [K^+]s. Another restriction is the rather small sample size of 52 pediatric CKD patients. Despite the strength of detailed quantification of dietary intake, this method carries the constitutional risk of over- and underreporting potassium and fiber intake. Of the study population, 38,5% kept a 3 day food diary. Preferably this proportion should be larger to reduce daily variability. Seasonal variation was also not taken into account as the baseline was spread throughout the year. For 35 out of 52 patients, dietary anamnesis was performed during winter months (October-March), which may lead to lower reported fiber intake as fewer plant-based foods are consumed during winter. Ideally the measurement would be performed several times throughout the year to get a global view on dietary fiber and potassium intake of a patient. Another limitation is the lack of information on fiber type and source. This can be important due to changing properties in different fiber types. Considering that even healthy children and adults fail to meet recommendations (36), we focused on total dietary fiber intake.

Conclusion

This study shows that fiber intake in non-dialysis pediatric CKD patients does not meet the nutrition guidelines as set for healthy children. Especially with advanced CKD, fiber intake was low. A moderate association is observed between potassium and fiber intake and no consistent effect of the potassium binding resin kayexalate on serum potassium could be demonstrated. No influence of potassium intake nor fiber intake is seen on serum potassium. Except for CKD stage 3 where an inverse relation of potassium intake and serum potassium is described. These incoherent results suggest that there are other important determinants of serum potassium. As our study is first to examine this association, present findings are exploratory. Subsequent research is necessary to validate these hypotheses and identify other determinants of serum potassium, bearing in mind the difference between CKD stages. Dietary potassium restriction stays a prudent approach to reduce risk of hyperkalemia in non-dialysis pediatric CKD patients, especially in patients of CKD 5. Despite, more attention towards fiber intake and validated nutrition guidelines are needed. As potassium restricting diets in pediatric CKD patients are widely used but little substantiated, further research on the efficacy, safety and impact on QoL is needed. Also research on the efficacy and safety of potassium binding resins in pediatric CKD patients is necessary. The ultimate aim is to provide optimal care and improve QoL of patients with regard to dietary restrictions and medication burden.

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