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CKJ Review

CKJ REVIEW

Gluconeogenesis in the kidney: in health and in chronic kidney disease

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ABSTRACT

Chronic kidney disease (CKD) is a global health issue with increasing prevalence. Despite large improvements in current therapies, slowing CKD progression remains a challenge. A better understanding of renal pathophysiology is needed to offer new therapeutic targets. The role of metabolism alterations and mitochondrial dysfunction in tubular cells is increasingly recognized in CKD progression. In proximal tubular cells, CKD progression is associated with a switch from fatty acid oxidation to glycolysis. Glucose synthesis through gluconeogenesis is one of the principal physiological functions of the kidney. Loss of tubular gluconeogenesis in a stage-dependent manner is a key feature of CKD and contributes to systemic and possibly local metabolic complications. The local consequences observed may be related to an accumulation of precursors, such as glycogen, but also to the various physiological functions of the gluconeogenesis enzymes. The basic features of metabolism in proximal tubular cells and their modifications during CKD will be reviewed. The metabolic modifications and their influence on kidney disease will be described, as well as the local and systemic consequences. Finally, therapeutic interventions will be discussed.

LAY SUMMARY

We review the modifications of metabolism during chronic kidney disease with a special focus on glucose production through gluconeogenesis.

Keywords: chronic kidney disease, fatty acid oxidation, gluconeogenesis, glycolysis

INTRODUCTION

Chronic kidney disease (CKD) refers to a group of various disorders affecting the function and structure of the kidney for >3 months [1, 2]. Recently, several studies have highlighted major modifications of tubular cell metabolism during CKD. These changes involve modifications in glucose and fatty acid (FA) homeostasis in proximal tubule cells. These modifications likely impact mitochondrial and cellular function, thus potentially playing a role in CKD progression and complications [3–11]. The kidney is one of the largest consumers of energy after the heart [12]. Kidney tubular cells use energy from glycolysis and FA oxidation (FAO) and proximal tubule cells are able to produce glucose through the process of gluconeogenesis [13–16].

Glycolysis is a pathway that converts glucose into pyruvate through a succession of enzymatic reactions. Glycolysis thus produces adenosine triphosphate (ATP) by the conversion of pyruvate to acetyl coenzyme A (acetyl-CoA) and by its use in the

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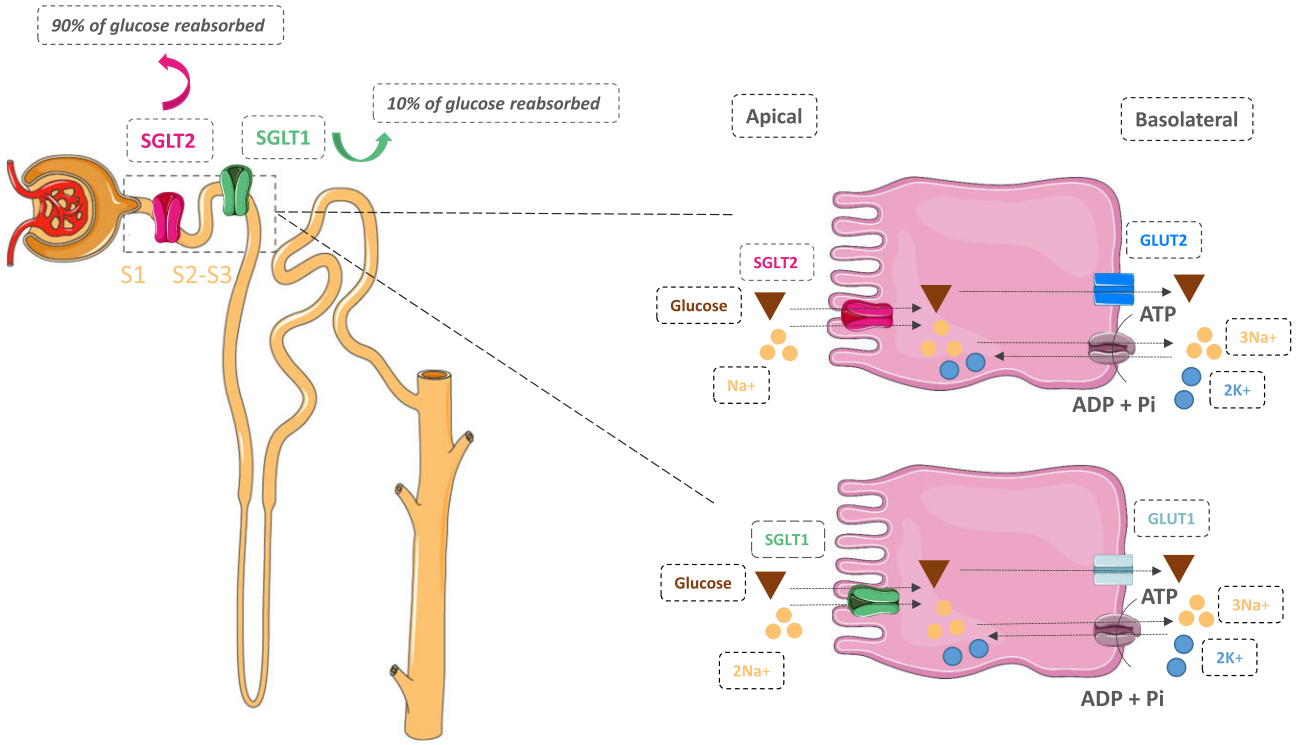

Figure 1: A total of 160–180 g of filtered glucose is reabsorbed by the proximal tubules at the apical membrane through SGLT2 at the S1 and S2 segments (90%) and through SGLT1 at the S3 segment (10%). The glucose is then released into the blood by GLUT1 and GLUT2 located in the basolateral membranes of proximal tubule cells due to the concentration gradient.

tricarboxylic acid cycle (TCA). FAO is the breakdown of FAs that generates acetyl-CoA, which is then also used as substrate in the TCA cycle to produce ATP. In contrast to glycolysis, gluconeogenesis is the metabolic pathway in which glucose is produced from non-hexose precursors such as lactate, pyruvate, glycerol and glycogenic amino acids [14]. Gluconeogenesis was classically attributed to the liver, but it is now well accepted that the kidneys can generate up to 28% of body glucose by gluconeogenesis in the post-absorptive phase and 40–50% in stress conditions [17].

During CKD, modifications of metabolism include a partial loss of the ability to perform FAO in proximal tubule cells, a loss of the ability to produce glucose through gluconeogenesis and an increase in glycolysis needs [18]. The modification of this metabolism switch and its established and potential consequences will be described. Finally, perspectives on nephroprotection will be discussed.

ROLE OF THE KIDNEY IN GLUCOSE METABOLISM DURING HEALTH

The maintenance of blood glucose levels is essential for healthy physiological functioning and involves various organs, among which the liver is well known. Nevertheless, the kidney is also an important player in glucose homeostasis. Due to its activity, the kidney is one of the largest consumers of energy after the heart (400 kcal/kg tissue/day) [12]. In addition, the kidney participates in glucose metabolism through its role in glucose filtration and reabsorption, endogenous glucose production through gluconeogenesis and glucose utilization through glycolysis [13–16]. These different mechanisms allow the kidney to contribute to the maintenance of systemic glucose levels.

Glucose filtration and reabsorption

One of the main functions of the kidney is the filtration and reabsorption of essential metabolites. Under physiological conditions, the kidneys are able to filter ≈180 L of blood per day, corresponding to 160–180 g of glucose [19]. This filtering activity represents ≈30% of the daily energy expenditure [19].

The filtered glucose contained in the primary urine is entirely reabsorbed by the proximal tubules at the apical membrane through the sodium–glucose transporters (SGLTs) and then released into the blood at the basolateral membrane via the facilitated glucose transporters (GLUTs). Using the transmembrane gradient generated by the sodium/potassium ATPase pump, 90% of glucose is reabsorbed at the S1 and S2 segments by SGLT2 and 10% by SGLT1 at the S3 segment. Then, due to the concentration gradient, glucose is released into the blood by GLUT1 and GLUT2 (Fig. 1). In normal conditions, glucose is either absent or at very low concentrations in the urine of healthy adults (range 0.03–0.30 g/day) [20–22].

When the capacity of the kidney to reabsorb glucose is exceeded, urinary glucose excretion ensues. The plasma concentration at which this occurs is referred to as the renal threshold for glucose excretion, with a range of 180–240 mg/dl in healthy individuals [23–26]. In pathological conditions, the level of glucose in the blood, and thus filtration, can be greatly increased. The increase of the reabsorption occurs through an increase in SGLT2 capacity in segments of the proximal tubule in response to cytokine secretions, which may be considered maladaptive [26].

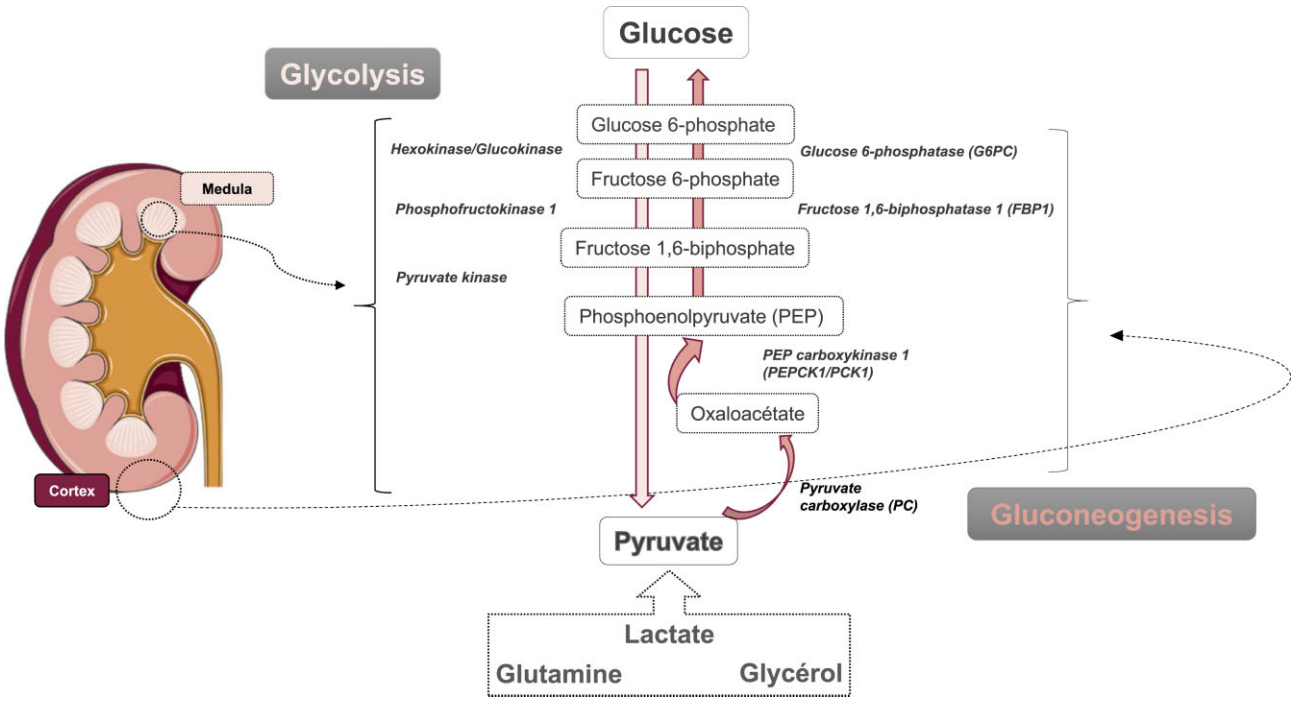

Figure 2: Overview of the gluconeogenesis and glycolysis pathways. Glycolysis is a pathway with 10 reactions, with a final production of pyruvate. Three reactions catalysed by hexokinase/glucokinase, phosphofructokinase and pyruvate kinase are rate limited. Gluconeogenesis is the reversed reaction of glycolysis, with four specific reactions catalysed by G6Pase, FBP1, PEPCK and PC.

Endogenous production of glucose through gluconeogenesis

Although historically the liver has been considered as the almost exclusive source of glucose production, numerous studies have revealed that the kidney may in fact contribute to ≈40–50% of endogenous gluconeogenesis under stress, acidosis or fasting, making it the second most important organ for this process [17, 27].

In the kidney, gluconeogenesis is mainly performed in the renal cortex, and more specifically in the proximal tubule, which is the only segment expressing the required machinery for this process [28]. Gluconeogenesis allows the synthesis of glucose-6-phosphate from non-hexose precursors such as lactate, pyruvate, glycerol and glutamine through a succession of 11 enzymatic reactions. In the kidney, the main precursor for gluconeogenesis under physiological conditions is lactate (50%), followed by glutamine (20%) and glycerol (10%) [27, 29]. During metabolic acidosis, glutamine becomes the most significant precursor for gluconeogenesis [30]. Among gluconeogenic reactions, seven are inverse steps to glycolysis and four are specific to gluconeogenesis. The specific steps are catalysed by four rate-limiting enzymes: pyruvate carboxylase (PC), phosphoenolpyruvate carboxykinase (PEPCK), fructose-1,6-bisophosphatase (FBP1) and glucose-6-phosphatase (G6Pase) [28]. The first reaction of gluconeogenesis is the conversion of pyruvate to oxaloacetate via PC. In the cytosol, oxaloacetate is then decarboxylated and phosphorylated by PEPCK (also called PCK1). Then FBP1 catalyses the hydrolysis of FBP1 to fructose-6-phosphate. Finally, the enzyme G6PC dephosphorylates glucose-6-phosphate to glucose [31–33] (Fig. 2).

Gluconeogenesis is classically regulated by hepatocyte nuclear factor 4 alpha (HNF4α), peroxisome proliferator-activated receptor alpha (PPARα) and forkhead box protein O1 (FOXO1) [34–37]. This pathway can also be modulated by certain stimuli, such as fasting, hypoglycaemia, acidosis and diabetes, as well as by hormones such as catecholamine, hydrocortisone and insulin [38, 39]. In the kidney, acidosis is a major regulator of the pathway by its stimulation of PEPCK and of glutamine catalysis [40, 41]. Insulin decreases glucose release through inhibition of gluconeogenesis enzymes and through the availability of gluconeogenic substrates [38]. Catecholamine may also increase gluconeogenesis by stimulating enzymes and increasing precursors involved in this pathway [42–45]. The role of glucagon in the kidney is unclear, but in an experiment, an infusion of stress hormones in dogs (combining hydrocortisone, epinephrine, norepinephrine and glucagon) showed an increase in gluconeogenesis [46]. The presence of glucagon receptors in the proximal tubule cells is still debated [47].

Glycolysis and FAO

The kidney uses a significant amount of energy to perform the various roles of filtration, reabsorption and excretion. After the heart, the kidney is the second most energetically active organ [12]. At the cellular level, proximal cells are the most important producers and consumers of energy, given their major role in sodium and electrolyte reabsorption and endocytosis [48]. Depending on the segment of the nephron, on metabolic demand and oxygen availability, tubular cells use energy through FAO or glycolysis [21, 49]. Glycolysis is the metabolic pathway that converts glucose to pyruvate. In the presence of oxygen, pyruvate is then converted to acetyl-CoA, which serves as a substrate for TCA and the electron transport chain to produce ATP [50]. In the absence of oxygen, pyruvate is converted to lactate and glycolysis remains the primary source of ATP production [51]. FAO is a catabolic process that converts FAs to acetyl-CoA at the

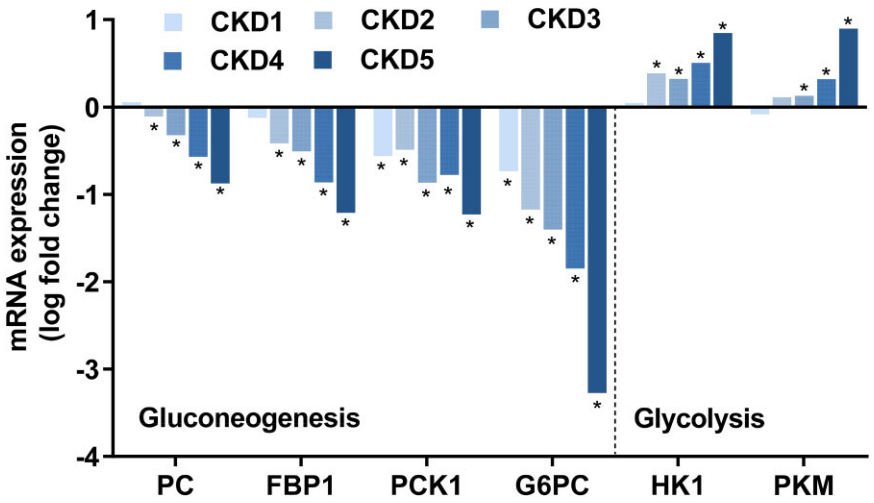

Figure 3: Microarray analysis of the European Renal CDNA bank database sorted by stage of CKD. A stage downregulation of rate-limiting enzymes of gluconeogenesis (PC, FBP1, PCK1, G6PC) is observed with an enhancement of those of glycolysis. (HK1, PKM). Adapted from Verissimo *et al*. Decreased renal gluconeogenesis is a hallmark of chronic kidney disease. *J Am Soc Nephrol* 2022;**33**:810–27.

mitochondrial level. Acetyl-CoA is then oxidized through the TCA cycle and through the electron transport chain to produce ATP [52]. In the kidney, oxygen availability decreases from the cortex to the medulla. This probably explains, in part, why proximal tubules in the cortex perform more oxidative phosphorylation to generate ATP and distal segments of the nephron use more of the glycolytic pathway [53–55].

METABOLISM DYSREGULATION DURING CKD

Downregulation of FAO

In physiological conditions, proximal tubule cells generate ATP mostly by the oxidative phosphorylation of acetyl-CoA from FAO. These cells are almost unable to use glucose as an energetic substrate [56, 57]. The breakdown of FAs depends on the availability of oxygen. Therefore the cells have to use other energy sources than FAO in case of low oxygen conditions. The more distal nephron cells have high glycolytic capacity and less capacity to perform oxidative phosphorylation. This may be the reason why proximal tubule cells, compared with cells of distal segments, have less ability to cope with hypoxic conditions, which make them sensitive to acute and chronic stimuli [56]. Although proximal tubule cells may switch their metabolism from FAO to glycolysis transiently to improve survival in hypoxic conditions, the persistence of the metabolic switch is associated with a worsened kidney prognosis with the loss of mitochondrial genes expression [57, 58]. Persistent loss of FAO has indeed been well described in biopsies from patients with CKD to correlate with CKD severity [4]. It has also been described during acute kidney injury (AKI), where proximal tubule cells are using glycolysis instead of FAO even at late stages post-reperfusion [5]. In biopsies from patients with CKD, transforming growth factor $\beta 1$ was described as a main trigger for the switch in tubular cells, inducing metabolic reprogramming during CKD [4]. Hypoxia and inflammation could also play an important role in the persistence of the metabolic switch [59]. In fact, interleukin-1β and c-myc signalling activation induce glycolysis and promote tubular cell injury [60]. Thus modification of metabolism with mitochondrial dysfunction and a decrease of FAO with a switch to glycolysis are hallmarks of CKD and likely contribute to fibrosis development [4–6, 8, 10, 56, 57, 60, 61].

Switch from gluconeogenesis to glycolysis

Loss of FAO and induction of glycolysis were first described as the main metabolism modifications during CKD. However, glycolysis and gluconeogenesis are counterregulated pathways. Therefore an impact of glycolysis induction in proximal tubules on the ability of the kidney to produce glucose could also be expected. This hypothesis is supported by several lines of evidence suggesting a link between kidney function and a risk of systemic hypoglycaemia, such as was observed in the large ACCORD study [8]. Hypoglycaemia and metabolic acidosis due to hyperlactatemia have also been demonstrated in patients with kidney disease on dialysis [62].

During AKI, kidney gluconeogenesis is lost in addition to FAO, resulting in an increased risk of hypoglycaemia and hyperlactatemia. Loss of renal gluconeogenesis was further associated with mortality risk during AKI [63].

Hypothesizing that renal gluconeogenesis was also altered in CKD, glucose metabolism regulation in animals and humans with CKD was investigated. A microarray dataset from the European Renal cDNA bank at different stages of kidney disease was analysed. The highest regulated metabolic genes were part of the gluconeogenesis pathway, with rate limiting genes such as *PC*, *PCK1*, *FBP1* and *G6PC* being markedly downregulated according to CKD stages in all types of CKD. FAO genes were also downregulated as expected, whereas glycolysis gene expression was enhanced (*PKM* and *HK1*) (Fig. 3). To better evaluate the switch from gluconeogenesis to glycolysis and systemic consequences, glucose metabolism in different mice models of chronic injury (ischaemic, proteinuric and unilateral fibrosis) was investigated. The loss of expression of gluconeogenesis genes and proteins and decreased activity of the pathway within the kidney were observed. These regulations led to systemic modifications of glucose and lactate handling in mice with renal disease [64].

In the clinical context, the same parameters were analysed in patients with severe stages of CKD, hospitalised in the intensive unit care. These patients also showed alterations of glucose

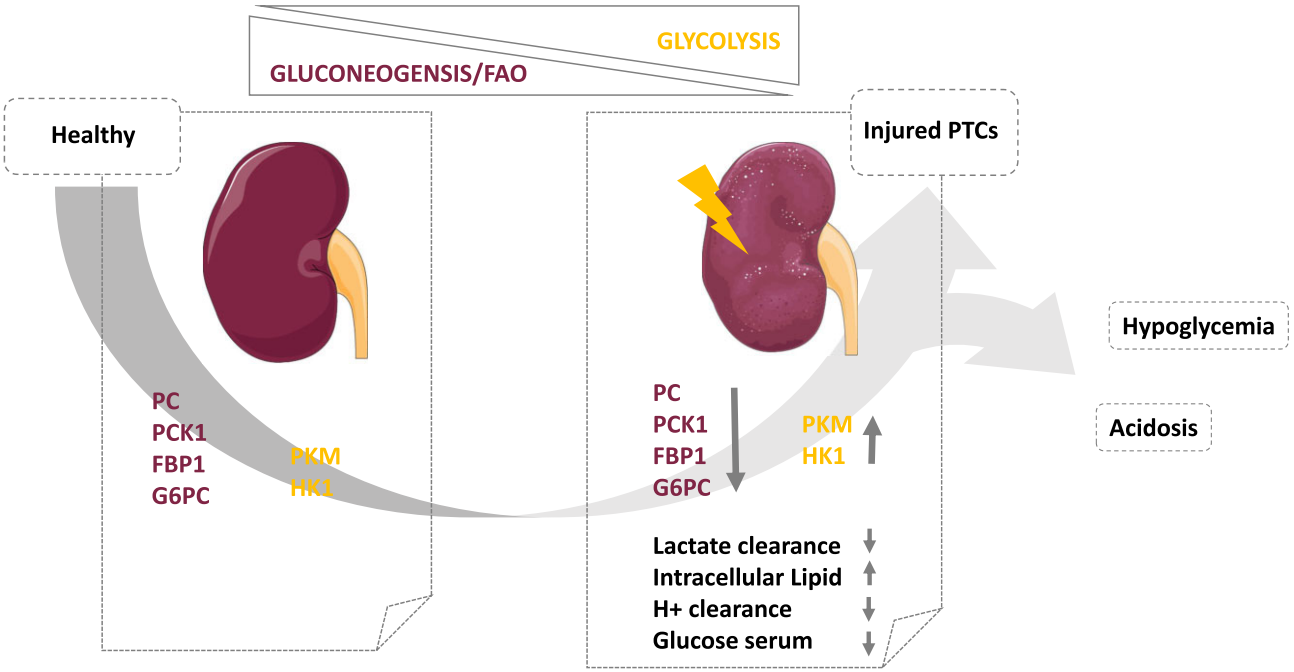

Figure 4: Downregulation of gluconeogenesis genes (*PC*, *PCK1*, *FBP1* and *G6PC*) and upregulation of those of glycolysis (*PKM* and *HK1*) is observed during CKD. Secondary to this switch, accumulation of precursors such as lactate, lipid, H^+ and potentially glycogen is observed. The decrease of kidney gluconeogenesis with its systemic consequences is associated with hypoglycaemia and acidosis.

and lactate parameters in stress conditions [64]. Finally, gluconeogenesis gene expression was associated with renal prognosis in kidney allograft patients, suggesting that the downregulation observed has also local detrimental consequences on the kidney [14]. This is supported by the fact that loss of some gluconeogenesis genes such as *G6PC* are known to induce renal fibrosis and disease progression [65]. The loss of *FBP1* has never been studied in the kidney but it is associated with an elevation of fibrotic gene expression in the liver [66]. Finally, our unpublished data confirm that PCK1 is an important player in CKD progression. The local detrimental consequences observed may thus be related to accumulation of precursors, such as glycogen, but also to the various physiological functions of the gluconeogenesis enzymes, being at the interface of energy production, ammoniagenesis and fibrogenesis [40, 64]. Thus the regulation observed may contribute to several metabolic complications, both locally and systemically, that may alter both general and renal prognosis during CKD (Fig. 4).

CKD AS A STORAGE DISEASE?

The metabolic switches described may lead to the accumulation of metabolic precursors, which may influence kidney disease. In this section, these precursors and their potential contributions to kidney disease will be described.

Lipotoxicity

Loss of FAO is associated with fat droplet accumulation in tubular cells by local accumulation of precursors [67, 68]. Several studies suggest that lipid accumulation in proximal cells can affect the function and structure of kidney cells, including those of proximal cells [67, 69]. The non-esterified FA and dysregulated glycerol derived from impaired FAO in cytoplasm contribute to the decrease of ATP production and mitochondrial energy production [70, 71] . The question is whether the accumulation of FA triglycerides is directly toxic or whether mitochondrial dysfunction secondary to substrate depletion is the true characteristic of the disease?

Recent data showed that in two CKD mice models (diabetic nephropathy and folic acid nephropathy), fat accumulation induced by kidney cell–specific overexpression of CD36 (which is a protein in proximal membrane cells permitting FA uptake [72, 73]) did not generate fibrosis in the kidney [4]. Thus mitochondrial dysfunction and defective energy production seem to be more detrimental than FA accumulation in the cells in this model. Currently, more data to define the causal relationship between lipid accumulation and the decrease in energy production and lipotoxicity during CKD are warranted [73].

Glycogen synthesis during kidney disease

Glycogen levels are usually negligible in kidney tissue. In diabetic kidneys, glycogen accumulation has been reported particularly in the thick ascending limb of Henle's loop and in the distal convoluted tubules [74–76]. The reason for this accumulation is yet unknown and little data exist to determine whether glycogen accumulation directly causes cellular damage in the kidney. Considering that glycogen is metabolically active, this accumulation may be protective, contributing to glucose release and used by kidney cells for fuel generation in conditions of stress. If the glycogen accumulates in an insoluble form, such as those seen in some diseases (Lafora disease or adult polyglucosan body disease), it will be harmful and may contribute to kidney damage [77]. In a recent study on humans with glycogen storage disease type I, the deficiency in G6PC, a major gluconeogenesis enzyme, was highlighted. These patients were especially prone to CKD development due to lipid and glycogen

accumulation in the kidneys and activation of the renin–angiotensin system. Interestingly, this enzyme is involved in gluconeogenesis and downregulated during CKD [78]. Recently, SGLT2 inhibitors were also associated with renal improvement in glycogen storage disease [79]. Thus, similar to fat accumulation, more studies are needed to determine whether glycogen accumulation plays a beneficial or detrimental role in CKD.

Increase in lactate level during kidney disease

Flux analysis of metabolites indicates that the kidney also plays a major role in lactate clearance [80, 81]. In the case of a decrease in gluconeogenesis, as described above, a decrease in lactate clearance occurs and lactate accumulation is expected at the local and systemic levels. Lactate clearance has been associated with mortality and metabolic alterations [14, 82]. A recent article indicated a potential local toxic role of lactate with increased fibrogenesis in the renal cortex [83].

Therapeutic intervention during CKD, the example of SGLT2 inhibition

SGLT2 inhibitors are anti-diabetic drugs that lower blood glucose by enhancing glycosuria. The main purpose of this medication is to prevent glucose reabsorption in the proximal tubule of the kidney. However, SGLT2 inhibitors (gliflozins) are known to be nephroprotective in diabetics but also in non-diabetic patients [84–86]. Nephroprotection occurs through haemodynamic mechanisms, mainly by modulation of tubuloglomerular feedback. Nevertheless, other mechanisms are likely at play a role in explaining the nephroprotection provided against AKI by these drugs and their efficiency in non-proteinuric kidney disease. Metabolic effects of these drugs are expected since they block glucose entry into tubular cells and may therefore avoid a switch to glycolysis during CKD. In addition, it has been described that SGLT2 inhibitors stimulate gluconeogenesis in the kidney by increasing PEPCK and G6Pase. Further studies are needed to determine whether the beneficial renal effect of this drug on the kidney is based on this regulation. In addition, other drugs modulating metabolism in kidney tubular cells should be studied for their nephroprotective abilities.

CONCLUSION AND PERSPECTIVES

Metabolism is modified during CKD with the switch from gluconeogenesis and FAO to glycolysis in the proximal tubule cells. Whether these modifications are to some extent beneficial for cell survival or harmful through defective energy production and substrate accumulation warrants more studies. Renal gluconeogenesis is lost during CKD, likely contributing to local and systemic complications and possibly being a key player in CKD progression.

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AUTHORS' CONTRIBUTIONS

D.D. reviewed the literature, edited the manuscript and drew the figures. T.V. reviewed the literature and edited the manuscript. S.S. designed, supervised and edited the manuscript. All authors contributed to the article and approved the submitted version.

DATA AVAILABILITY STATEMENT

There were no data generated or analysed during the current review.

CONFLICT OF INTEREST STATEMENT

None declared.

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