



Review

Glucose and glycogen in the diabetic kidney: Heroes or villains?


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ARTICLE INFO

Article history:

Received 3 June 2019

Received in revised form 17 July 2019

Accepted 29 July 2019

Available online 10 August 2019

Keywords:

Glycogen

Diabetes

Kidney disease

Glucose

Glycogen storage disease

ABSTRACT

Glucose metabolism in the kidney is currently foremost in the minds of nephrologists, diabetologists and researchers globally, as a result of the outstanding success of SGLT2 inhibitors in reducing renal and cardiovascular disease in individuals with diabetes. However, these exciting data have come with the puzzling but fascinating paradigm that many of the beneficial effects on the kidney and cardiovascular system seem to be independent of the systemic glucose lowering actions of these agents. This manuscript places into context an area of research highly relevant to renal glucose metabolism, that of glycogen accumulation and metabolism in the diabetic kidney. Whether the glycogen that abnormally accumulates is pathological (the villain), is somehow protective (the hero) or is inconsequential (the bystander) is a research question that may provide insight into the link between diabetes and diabetic kidney disease.

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1. Introduction

Globally, there are currently over 400 million people estimated to have diabetes. However, diabetes incidence is predicted to further

increase, largely due to increases in type 2 diabetes. Both type 1 and 2 diabetes are characterized by a breakdown in blood-glucose homeostasis. Type 1 (insulin-dependent) diabetes, accounting for ~7–12% of diabetes cases [1], is a chronic autoimmune disease precipitated by the destruction of insulin producing pancreatic β -cells. The deficiency in insulin secretion seen in type 1 diabetes greatly diminishes the ability of muscle and adipose tissue to store glucose in the form of glycogen. This in conjunction with increased gluconeogenesis, fuels chronic hyperglycemia [2]. Type 2 diabetes, which accounts for 87–91% [1], involves a number of pathologies, including

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insulin resistance and pancreatic β -cell dysfunction. Resistance to insulin decreases skeletal muscle uptake of glucose while hepatic insulin resistance increases endogenous glucose production [3,4]. Although the pancreas increases β -cell insulin secretion to compensate, this is eventually overwhelmed, resulting in relative insulin insufficiency, with many individuals ultimately requiring exogenous insulin supplementation. β -cells are also damaged by glucose toxicity [5]. A genetic propensity for a decrease in β -cell function has been linked to an increased risk for type 2 diabetes [6].

Diabetes is the predominant cause of chronic kidney and end-stage renal disease, with ~20–40% of people with diabetes diagnosed with kidney disease (DKD) [7]. DKD is most commonly characterized by a thickening of the glomerular basement membrane, an expansion of the mesangial matrix, nodular glomerulosclerosis and arteriolar hyalinosis [8]. Histologically, there are also concomitant changes within the tubulointerstitium including extracellular matrix accumulation, basement membrane thickening, cast formation and interstitial inflammation. Functionally, these result in changes in glomerular filtration rate (GFR), initially hyperfiltration followed by a progressive decline in GFR and the urinary excretion of protein, most commonly assessed as urinary albumin excretion [8]. The mechanisms that lead to kidney disease development and progression are still being fully determined. One hypothesis involves a tubule-centric view which highlights the importance of abnormalities in tubuloglomerular feedback as a precipitating factor in DKD. Another alternative view is that diabetes results in mitochondrial damage and that this is central to diabetes-related kidney damage [9]. Alternatively, the importance of early glomerular changes in the pathogenesis of DKD has also been identified. Of course, it is likely that all these factors, along with others, play an important role in the development and progression of DKD.

Having DKD also greatly increases the chance of cardiovascular disease and mortality [10].

The kidneys are increasingly recognised as important regulators of blood glucose homeostasis. This is because they not only actively reabsorb filtered glucose into the bloodstream, but also produce glucose via gluconeogenesis. It has been estimated that in the post-absorptive state, the kidneys are responsible for ~20–25% of the total body release of glucose, making the kidneys responsible for ~40% of all gluconeogenesis in the body [11]. *De novo* synthesis of glucose from fatty acids also occurs in various kidney compartments. In addition, glucose is actively used as fuel in the kidney both via oxidative phosphorylation and glycolytic pathways [12].

In the absence of diabetes, very low levels of kidney glycogen have been reported. However, in individuals with diabetes, there is significant renal glycogen accumulation [13–15]. This glycogen has been described to occur as part of Armani-Ebstein lesions, which derive from swollen epithelial cells in diabetic kidneys and have even been reported to be the cause of death in some instances [16]. Whether renal glycogen accumulation in the diabetic kidney results in abnormalities akin to glycogen storage diseases (GSDs) such as GSD I (von Gierke's disease) and Fanconi-Bickel disease remains unknown.

This review will summarise the current literature regarding renal glycogen accumulation and place this in the broader context of diabetes, kidney glucose metabolism and glycogen storage diseases.

2. Main text

2.1. Glycogen as a key molecule regulating blood glucose concentrations

Maintenance of blood glucose concentrations between 3.0 and 9.0 mmol/L is critical to human health. High blood glucose (hyperglycemia) is characteristic of conditions such as diabetes and increases the risk of chronic complications including diabetic kidney disease (DKD), peripheral neuropathy and retinopathy, premature atherosclerosis, in addition to acute potentially life-threatening episodes of diabetic ketoacidosis. Low blood sugar (hypoglycemia) concentrations can also

result in various pathologies, including neurological dysfunction as well as coma and death [17].

An intricate system of hormones and receptors control blood glucose homeostasis. Insulin, secreted by pancreatic β -cells, is a key hormone that is acutely increased in response to food consumption (postprandially), when blood glucose levels are elevated [18]. This glucose is distributed around the body via the bloodstream, with ~14 separate glucose transporters (GLUTs) directing uptake into various tissues. The degree of glucose uptake by insulin dependent mechanisms is also tissue-specific, with some tissues expressing predominantly insulin sensitive GLUTs (eg GLUT4), while others rely on insulin-independent transport via GLUTs such as GLUT2.

2.2. Structure of glycogen and functional properties

The fate of the majority of blood glucose postprandially is storage via conversion into glycogen. Glycogen is a highly-branched polymer of glucose, allowing large quantities of glucose to be efficiently sequestered for later usage. The importance of efficient glycogen storage is highlighted by the often severe symptoms that accompany genetic alterations in enzymes involved in glycogen metabolism, as summarised in a recent review [19].

Glycogen has several novel features which allow it to remain soluble, thereby rapidly storing or releasing glucose molecules as required. This includes frequent branch points, resulting in short chain lengths of ~10–14 glucose units. The formation of longer glucose chains in glycogen results in its pathological accumulation seen in diseases such as Lafora Disease and Anderson's Disease [20], where glycogen forms insoluble double helices which precipitate and are unable to release the stored glucose [21].

Glycogen particles have 3 main structural levels (see Fig. 1). The first level is the chemical bond between individual glucose molecules via (1 \rightarrow 4)- α glycosidic linkages. These linkages form a tree-like framework, with new branch points formed by (1 \rightarrow 6)- α glycosidic bonds. This concerted action of glycogen chain elongation carried out by the enzyme glycogen synthase and branching catalysed by glycogen branching enzyme, results in the synthesis of a biological glucose storage macromolecule of ~50,000 individual glucose units termed β particles. β particles are roughly spherical in shape and are visible inside cells by electron microscopy (20–30 nm in diameter). In some tissues, such as the liver and heart [22], a third level of glycogen structure is apparent, where β particles are synthesized into larger more complex α particles of around 200 nm in diameter, roughly the size of a small lysosome [23]. There is evidence that these particles are held together via a protein glue [24,25], which is postulated to be glycogenin [26].

The specific metabolic structure of glycogen is directly related to tissue function. Larger α particles, as seen in the liver and heart, degrade more slowly and provide a more stable and sustained release of glucose [27], which is dependent on the degradation enzyme glycogen phosphorylase [28]. By contrast, the predominance of the smaller β particles in skeletal muscle, allows for the rapid release of glucose to fuel the fibre contractions that enable movement [27].

A summary of glycogen synthesis and degradation is given in Fig. 2. Glycogen chains are elongated one glucose unit at a time via the action of glycogen synthase (GS), using the energetically favourable UDP-glucose as the substrate. This reaction results in the addition of one glucose unit to the chain, with the UDP being removed in the process. When the growing chain of glucose units gets to a certain size it is cleaved by the enzyme glycogen branching enzyme, with the smaller fragment of the glycogen chain being reattached along the side of a glycogen chain, resulting in a branch point. This elongation and branching continues until you have a large, highly branched macromolecule with tens of thousands of glucose units.

After the initial autoglucosylation of a glycogenin dimer, glycogen synthase (GS) is able to attach new D-glucose units using the substrate UDP-glucose. Once the chain reaches a specific length, glycogen branching enzyme (GBE) cleaves a portion of the chain and reattaches

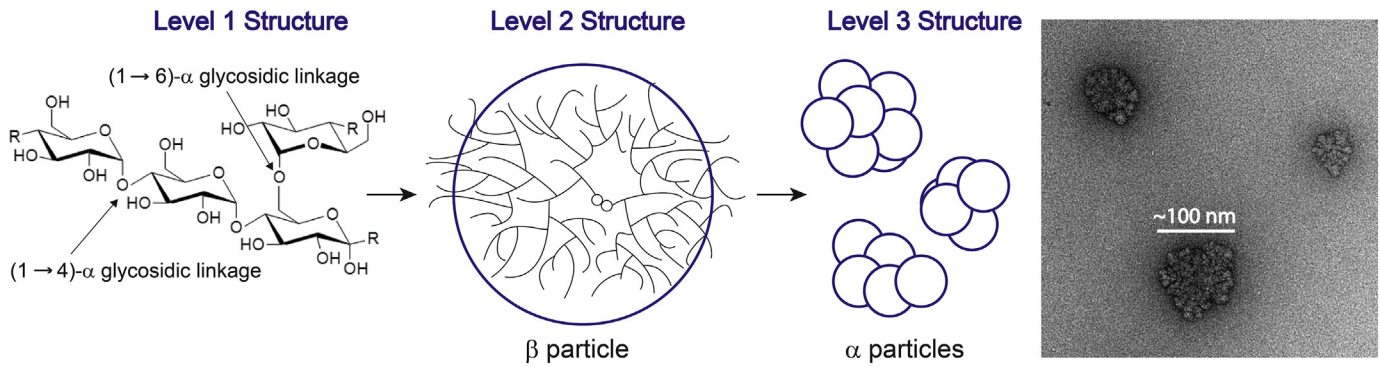


Fig. 1. The three levels of glycogen macromolecular structure. A transmission electron microscopy (TEM) image of rat liver glycogen shows α particles.

it via an α -(1 \rightarrow 6) linkage, creating a new branch point. The combination of GS and GBE activity result in the highly branched β particle [29]. During glycogen degradation, glycogen phosphorylase (GP) sequentially cleaves glucose units, with the help of orthophosphate (P_i), releasing glucose-1-phosphate. When a chain length reaches 4 glucose units glycogen debranching enzyme completes the branches removal [30].

Insulin not only plays a role in glucose uptake in the muscle and heart, but specifically stimulates glycogen synthesis. This stimulation is via protein kinase B, resulting in an inactivation of glycogen synthase kinase-3, an inhibitory regulator of glycogen synthase via phosphorylation [31]. Insulin also lowers cyclic AMP thereby stimulating glycogen synthase activity and inhibiting glycogen phosphorylase activity, facilitating glycogen storage [32]. Insulin signalling can also increase protein phosphatase-1 (PP-1) activity, which directly activates GS by cleaving its inhibitory phosphate [33]. A summary of some of the key enzymes and metabolites involved in glucose/glycogen metabolism is given in Fig. 3.

2.3. Diabetes and tissue specific glycogen accumulation

Diabetes has been shown to affect the content of glycogen in numerous tissues (see Fig. 4). For example, the deficiency of insulin seen in type 1 diabetes leads to a decrease in liver and muscle glycogen levels [36]. After the initial hyperinsulinemia seen with type 2 diabetes, there

is a similar decrease in liver and muscle glycogen content, again due to decreasing insulin signalling [37]. Conversely, diabetes increases the amount of glycogen stored at other sites such as in the heart and in pancreatic β -cells [38]. Another study found that obese patients with insulin resistance had higher levels of adipose tissue glycogen and provided evidence that this excess accumulation may be pathological, via an increase in inflammation [39]. Not only has diabetes been shown to affect the amount of glycogen within a tissue, it results in structural changes to the glycogen molecule (Fig. 4). For example, studies have shown that *db/db* mice, a model for type 2 diabetes, produce α particles that are more chemically fragile and therefore more easily broken down than non-diabetic controls [40,41]. It has been hypothesised that this contributes to poorer glucose control since the lower surface area to volume ratio of smaller glycogen particles [28] allows for these particles to degrade and release glucose more quickly [27]. Whether this phenotype applies to individuals with diabetes and contributes to poorer glycemic control warrants further investigation. Glycogen from *db/db* mouse liver was also shown to have a higher proportion of longer chains than the control mice [41].

2.4. Glucose metabolism in the kidney

The contribution of the kidneys to glucose homeostasis has historically been overshadowed by the liver, although it was acknowledged

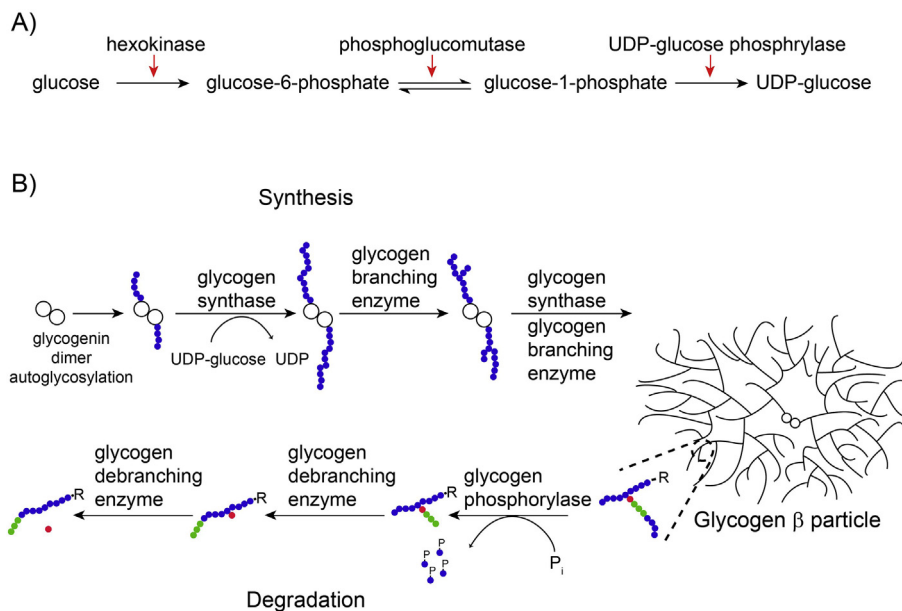


Fig. 2. Key enzymes involved in glycogen metabolism. A) The enzymes involved in converting glucose to UDP-glucose; B) The enzymes involved in the synthesis and degradation of glycogen molecules. Blue, green and red circles are all glucose units with the different colours being used to help demonstrate what is happening during degradation.

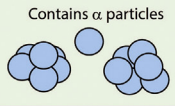
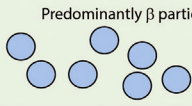
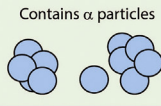
Tissue	Liver	Skeletal Muscle	Heart	Adipose	Kidney
Transporter	GLUT2	GLUT4	GLUT4	GLUT4	SGLT2
No diabetes	Fed ~5-10% tissue weight	~0.5-1.0% of tissue weight	~0.5% of tissue weight	Very low (dramatic transient spike in brown adipose tissue after refeeding from a prolonged fast)	Very low
	Fasted ↓↓	↓	↑		
	Post-exercise ↓	↓↓	↓		
Structure	Contains α particles 	Predominantly β particles 	Contains α particles 	???	???
Diabetes	Type 2 ↓	↓	↑	? (obesity appears to cause an increase)	↑↑
	Type 1 ↓	↓	↑	↓	↑↑
	Structure α particles become molecularly fragile Increase in longer chains	???	???	???	???

Fig. 4. Glycogen in various tissues. The predominant glucose transporter and glycogen content/structure under both diabetic and non-diabetic conditions is summarised for liver, skeletal muscle, heart, adipose and kidney tissue.

lumen exceeds the reabsorption capacity, resulting in excess glucose being expelled into the urine, a condition known as glycosuria. Promising new therapeutic agents to combat hyperglycemia in diabetes increase this expulsion of urinary glucose, achieved by inhibiting SGLT2 and SGLT1 transporters [44], which have potent blood glucose lowering capacity and show cardio-renal protection in major clinical trials [49].

2.5. The kidney as a site for glucose synthesis

The role of the kidney however, is not only to reabsorb glucose filtered from the blood, but to also synthesize new glucose via gluconeogenesis. Surprisingly, in the post-absorptive state, the kidney releases an equivalent amount of newly formed glucose (gluconeogenesis) to that from the liver, but these organs use different amino acid precursors for glucose synthesis, namely glutamine and alanine, respectively [50]. The liver also initially releases glucose from glycogen particles through glycogenolysis, making the total postprandial contribution of glucose into the bloodstream ~80% from the liver and ~20% from the kidneys, under physiological conditions. However, once the majority of liver glycogen has been degraded, the proportional contribution of the kidney increases [17]. One study has shown that increases in kidney gluconeogenesis may account for as much as ~60% of the body's endogenous glucose production under some circumstances [51].

Elevations in circulating insulin decrease endogenous glucose production, with glycogenolysis effectively halting and hepatic gluconeogenesis decreasing by ~82%. As with hepatocytes, insulin also suppresses glucose synthesis and release from the kidney under physiological conditions [52]. However, in diabetes where the actions of insulin are impaired or absent, there are significant increases in renal gluconeogenesis [53]. The accumulation of glycogen found in diabetic kidneys may be explained by these observations [54]. Furthermore, the kidneys are directly involved in the degradation of insulin, such

that at least 25% of the insulin secreted daily is cleared by glomerular filtration and tubular degradation [55]. In addition, deletion of the insulin receptor in renal proximal tubule cells promotes hyperglycemia in preclinical models [56]. Given these findings, it is surprising that renal gluconeogenesis in diabetes has not received greater attention.

2.6. Kidneys as glucose consumers

The kidneys are extremely high consumers of energy, with a high density of mitochondria seen in the renal tubules [57]. The large quantities of ATP generated via oxidative phosphorylation make the kidneys major consumers of molecular oxygen, second only to the myocardium at rest [9]. It is important to note that the preferred fuel of kidney cells varies greatly depending on their position along the nephron, their specific ATP demands and oxygen availability. For example, while the glomeruli and thin descending limb prefer glucose as a fuel substrate, the proximal tubule cells (PTCs) tend to use free fatty acids (FFAs). The use of FFAs consumes comparatively higher levels of oxygen than glucose oxidation, but the yield of ATP per gram is greater, making it an attractive fuel source when oxygen is in greater supply [9].

Early in diabetes, oxygen consumption by the kidney dramatically increases. This is postulated to contribute to hypoxia and ultimately a switch to glycolysis and increases in glucose oxidation at sites such as the proximal tubules [58]. Under these conditions, cells further down the nephron require an even greater amount of glucose for oxidation, with the greatest demand being in the thick ascending limb of Henle's loop [59]. The abnormal accumulation of kidney glycogen in diabetes, described in further detail below, may be a result of this switch to a glucose based fuel system and could actually be a key adaptive mechanism which functionally preserves renal function. The other possibility is that this glycogen is a pathological by-product of excess glucose production, reabsorption and utilisation that directly contributes to kidney damage.

2.7. Kidneys as a site for glycogen synthesis

There are usually negligible levels of glycogen measurable in renal tissue. However, with hyperglycemia, glycogen rapidly accumulates in the kidney, an observation made as early as 1877 [60]. Surprisingly, this renal glycogen accumulation was even reported to be the cause of death in numerous instances [16]. In tubular epithelial cells that accumulate these large quantities of glycogen, Armani-Ebstein lesions are formed. Armani-Ebstein lesions, originally described by Luciano Armani in 1872, are characterized by vacuolization and PAS-positive glycogen accumulation within the cytoplasm of tubular epithelial cells following diastase digestion [61,62], as seen in Fig. 5.

Glycogen deposition in the kidney under physiological conditions is temporal and dependent on the fasting state. In preclinical rodent models of diabetes, renal glycogen temporarily accumulates postprandially, when blood glucose levels are ~24 mmol/L. After a 24 h fast when the blood glucose concentrations were decreased to ~7 mmol/L, renal glycogen returned to the amounts seen in non-diabetic kidneys. However, after a longer duration of diabetes, renal glycogen accumulation does not decline with fasting, even for prolonged periods such as 24 h where blood glucose levels decreased from ~25 mmol/L to ~12 mmol/L [15]. Kidney glycogen accumulation in diabetes is reported as predominantly in the thick ascending limb of Henle's loop and in the distal convoluted tubule. These compartments are downstream of the proximal tubules and highly dependent on glucose metabolism for energy generation which is used for ion and bicarbonate reabsorption. This localisation is consistent with the sites of pathological Armani-Ebstein lesions reported in human diabetic kidneys. In the thick ascending limb of Henle's loop, glycogen accumulation was also evident in some nuclei [64]. One study found that in the distal convoluted tubules there was cytoplasmic glycogen and in the thick ascending limb of Henle's loop the glycogen was nuclear, suggesting that the glycogen accumulation might accumulate as the result of different pathogenic mechanisms [65]. Glycogen also accumulates in the renal proximal tubules of diabetic individuals [13], as well as preclinical rodent models with long duration of diabetes [14,15]. Importantly in these studies, the location and amount of glycogen accumulation was not only related to the degree of hyperglycemia but also diabetes duration. There is also some evidence that diabetes can lead to an accumulation of glycogen in the glomerulus, with an increase in periodic acid-Schiff staining observed in mice with streptozotocin-induced diabetes [66].

Whether the formation of glycogen has an effect on the non-enzymatic glycation of proteins, a pathogenic pathway known to

be associated with diabetes-related kidney complications, is also worth considering since this is highly dependent of glucose and glucose precursor availability. Potentially the sequestering of glucose within the kidney, as glycogen, could decrease the level of glucose available to react with proteins. In this way it is possible that glycogen formation may be protective against the pathological glycation of proteins in the kidney. Conversely, the in situ sequestering of greater amounts of glucose in particular sites within the kidney could also locally facilitate the advanced glycation by increasing substrate availability even at times of low blood glucose.

Glycogen accumulation can also result from defects in the enzymes responsible for glycogen synthesis and breakdown. A study using heterozygous transgenic diabetic "Ren-2" rats showed concomitant increases in glycogen synthase activity, decreases in glycogen phosphorylase activity and increased glycogenin levels, which together would facilitate the accumulation of glycogen. In that study, an anti-fibrotic agent reduced glycogenin mRNA translation thereby decreasing the accumulation of renal glycogen [67]. Another study showed that diabetic kidney disease is characterized by excessive deposition of glycogen and inactivation of glycogen synthase [15]. However, the converse where activation of glycogen synthase kinase β has impaired the action of glycogen synthase, improved kidney function in a mouse model for type 1 diabetes [68]. Hence it is possible that the inactivation of glycogen synthase is a compensatory mechanism to protect against glycogen accumulation in the diabetic kidney.

Despite early evidence, there remains a paucity of data determining if glycogen accumulation directly causes cellular damage in the kidney. Certainly, the structure of the deposited glycogen could elucidate its metabolic state and potential for injury. For example, if the accumulated renal glycogen forms insoluble glycogen, termed polyglucosan bodies, such as those seen in glycogen storage diseases such as Lafora disease and Adult Polyglucosan Body Disease, then it is likely to be pathological. One of the key features of this pathological glycogen is the longer chain lengths, helix formation between chains and precipitation [21]. Hence, the examination of renal glycogen for the presence of these features in diabetes should be actively pursued. In addition, the presence of mismatches between glycogen synthetic and branching enzymes, as seen in other glycogen storage diseases [20], would also provide important evidence of a pathological accumulation of glycogen if seen in concert with a decline in kidney function and other structural damage to the kidney. Indeed at other sites, both the muscle isoform of glycogen synthase (GS) and levels of glucose-6-phosphate (G6P), an allosteric activator of GS, are elevated in diabetes [69,70], with the G6P levels increasing more with age [15], although this is not consistent among all preclinical studies [15]. In humans, diabetes also increases the renal expression of protein targeting to glycogen (PTG) [71], which may lead to an increased level of GS activity. Without an equivalent increase in glycogen branching enzyme (GBE) activity, which is a key enzyme involved in preserving glycogen branching, the chain lengths may become too long, which is a key pathological precursor to polyglucosan body formation. It is also important to note that enzyme activities likely vary across the length of the renal nephron, with the cells experiencing vastly different exposure to metabolites (with glucose being especially relevant). As such, the presence of glycogen in areas of the nephron that under physiological conditions would be exposed to low glucose concentrations such as the loop of Henle, raises the question as to whether these cells are ill-equipped to handle an abnormal influx of glucose as seen during insulin resistance and/or diabetes.

2.8. Kidney's involvement in glycogen storage disorders

Clues as to whether or not abnormal glycogen accumulation in the kidneys can lead to tissue damage may be garnered from known glycogen storage diseases (GSDs). For example, von Gierke's disease (GSD I), resulting from a deficiency of the glycolytic/gluconeogenic enzyme glucose-6-phosphatase, results in a significant accumulation of

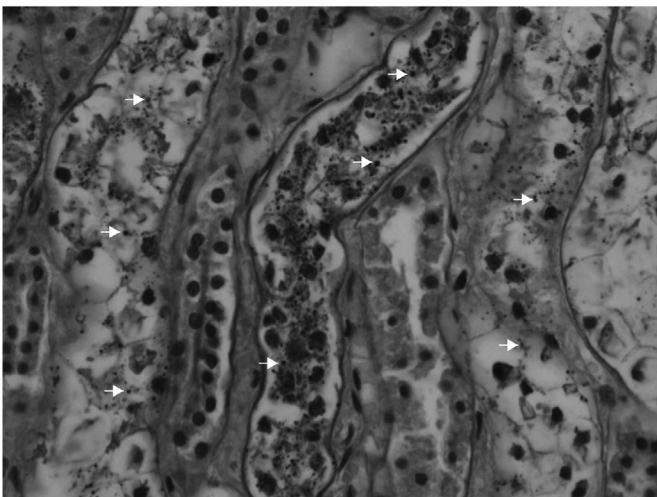


Fig. 5. Armani-Ebstein lesions appear as PAS-positive material (white arrows) in the vacuoles of tubules, more commonly seen in the distal tubules and the thick ascending limb of Henle's loop. Reproduced with permission from [63].

glycogen within the liver, kidney and intestinal mucosa. In addition to symptoms of hypoglycemia, hyperlipidemia, hyperuricemia and hyperlactacemia, GSD I often precipitates renal disease [72]. Interestingly, the pathology reported begins with hyperfiltration and then a progressive loss of GFR, proteinuria and glomerulosclerosis which are common to all CKD including diabetic kidney disease, and in GSD I this commonly progresses to renal failure and death [73]. GSD I nephropathy and diabetic kidney disease also have some similar metabolic perturbations, including increases in circulating glucagon and alanine (liver gluconeogenic precursor) concentrations, lipolysis, lactate production and hepatic very low density lipoprotein [74]. A kidney specific knockout of glucose 6 phosphatase led to early tubular dysfunction and later glomerular destruction, with the development of polycystic kidneys [75].

Another GSD that results in a renal pathology similar to that seen in diabetes is Fanconi-Bickel syndrome, resulting from a mutation in GLUT2. This results in glycogen accumulating in the liver and kidneys and can involve glomerular hyperfiltration, microalbuminuria and glomerular mesangial expansion. This kidney glycogen accumulation is largely due to the inability of glucose to exit the kidney's proximal tubule cells, which usually have GLUT2 receptors on the basolateral membrane to release reabsorbed glucose back into the bloodstream [76]. However, in Fanconi-Bickel syndrome, the glycogen accumulation is localised to the proximal tubule rather than the further down the nephron as reported in DKD.

3. Conclusions

Diabetes is the principal cause of chronic kidney disease, a major risk factor for cardiovascular disease and mortality. Finding new strategies to inhibit the complications associated with diabetes will greatly decrease the burden of this disease. While kidneys usually contain low amounts of glycogen, a highly branched storage molecule of glucose, large deposits are present in diabetic kidneys. The significance of this accumulation is unknown, including whether the glycogen is metabolically active, contributes to kidney glucose release into the blood stream, is being utilized by the renal cells for fuel generation, or whether the accumulated glycogen forms insoluble glycogen bodies, comparable to those seen in glycogen storage diseases such as Lafora disease. In glycogen storage disorders, these insoluble polyglucosan bodies elicit the significant cellular damage accompanying these conditions. Understanding whether renal glycogen seen in diabetes is pathological or a compensatory pathway to prevent glucose mediated damage may help shed light on future strategies to prevent DKD. If glycogen is found to be pathological, treatments that prevent this accumulation, similar to those currently being developed for diseases such as Lafora disease, may help mitigate diabetes associated kidney damage.

3.1. Outstanding questions

The predominant outstanding question highlighted in this review is whether the glycogen that accumulates in kidneys in individuals with diabetes is pathological, protective or inconsequential to kidney health and function. It is still unknown whether the targeting of glycogen metabolism could be an effective therapeutic treatment strategy aimed at preventing diabetic kidney.

3.2. Search strategy and selection criteria

Articles cited in this review were found using multiple databases, including Web of Science, Scifinder, Scopus and Google Scholar. The search criteria we used included: “kidney + glycogen + diabetes”; “kidney glycogen”; “Armani-Ebstein”; “diabetes + kidney + glucose”; “kidney glycogen metabolism”; “glycogen + podocytes”; “glycogen + tubules”; “diabetes nephropathy”; “diabetic kidney disease”; “glycogen storage disease + kidney”; “kidney glycogen storage disease”; “glucose

metabolism kidney”; “glucose transporters kidney”. We excluded articles that had not undergone peer review or that did not have a version written (or translated) in English.

Author contributions

Both M.A.S and J.M.F. conceived this review and contributed to the writing and editing of the manuscript. M.A.S was responsible for the first draft. J.M.F edited multiple iterations, providing extensive feedback and alterations.

Acknowledgements/funding

We would like to thank Rani Whiddett for proof reading the manuscript. Figs. 3 and 4 were created with BioRender. M.A.S was supported by a National Health and Medical Council of Australia (NH&MRC) CJ Martin Fellowship (GNT1092451), a Mater Research McGuckin Early Career Fellowship and Mater Foundation. J.M.F was supported by the NH&MRC Fellowship (1102935), Mater Foundation and Equity Trustees. The funders had no role in paper design, data collection, data analysis, interpretation and writing of the paper.

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