Glycogen storage disease type 1 and diabetes: Learning by comparing and contrasting the two disorders

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Abstract

Glycogen storage disease type 1 (GSD1) and diabetes may look at first like totally opposite disorders, as diabetes is characterized by uncontrolled hyperglycaemia, whereas GSD1 is characterized by severe fasting hypoglycaemia. Diabetes is due to a failure to suppress endogenous glucose production (EGP) in the postprandial state because of either a lack of insulin or insulin resistance. In contrast, GSD1 is characterized by a lack of EGP. However, both diseases share remarkably similar patterns in terms of pathophysiology such as the long-term progression of renal dysfunction and hepatic steatosis leading to renal failure and the development of hepatic tumours, respectively. Thus, much may be learned from considering the similarities between GSD1 and diabetes, especially in the metabolic pathways underlying nephropathy and fatty liver, and perhaps even more from their differences. In this review, the differences between diabetes and GSD1 are first highlighted, as both are characterized by alterations in EGP. The molecular pathways involved in liver pathologies, including steatosis, hepatomegaly (glycogenic hepatopathy) and the development of liver tumours are also compared. These pathologies are mainly due to the accumulation of lipids and/or glycogen in hepatocytes. Finally, the similar pathways leading to nephropathy in both diabetic and GSD1 patients are described. In conclusion, comparisons of these pathologies should lead to a better understanding of the crucial role of EGP in the control of glucose and energy homeostasis. Moreover, it may highlight similar therapeutic targets for the two disorders. Thus, this review suggests that the treatment of adult patients with either GSD1 or diabetes could be carried out by the same specialists–diabetologists.

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Résumé

Apprendre en comparant le diabète et la glycogénose de type 1.

La glycogénose de type 1 et le diabète peuvent apparaître comme deux maladies « miroir » puisque le diabète se caractérise par une hyperglycémie non contrôlée, alors que la glycogénose de type 1 se caractérise par des hypoglycémies à jeun sévères. Le diabète est dû notamment à un défaut de suppression de la production endogène de glucose (PEG) à l’état postprandial, lié à l’absence de la production d’insuline ou à une résistance à l’insuline. Au contraire, les glycogénoses de type 1 sont caractérisées par une absence de production de glucose par l’organisme. Cependant, ces deux maladies partagent un profil physiopathologique à long terme très similaire, avec une progression de la dysfonction rénale conduisant à une insuffisance rénale et une stéatose hépatique, conduisant au développement de tumeurs. La comparaison de ces deux pathologies va permettre de mettre en exergue de grandes similitudes entre les glycogénoses de type 1 et le diabète, en particulier au niveau des voies métaboliques qui soutiennent la néphropathie et la stéatose hépatique. Dans cette revue, nous allons d’abord souligner les différences entre ces deux pathologies, qui sont toutes deux caractérisées par des défauts de la PEG. Ensuite, nous comparerons les voies moléculaires impliquées dans les pathologies hépatiques, notamment la stéatose, l’hépatomégalie (hépatopathie glycénique) et le développement de tumeurs hépatocellulaires. Ces pathologies sont...
1. A rare disease compared with an epidemic

Glycogen storage disease type 1 (GSD1), also known as von Gierke disease, is an autosomal-recessive metabolic disorder with an estimated incidence of one in 100,000 live births. The genetic disorder is caused by a deficiency of glucose-6-phosphatase (G6Pase) activity leading to loss of endogenous glucose production (EGP) [1–3]. G6Pase is an enzyme complex that hydrolyzes glucose-6-phosphate (G6P) into glucose and inorganic phosphate in the terminal step of both gluconeogenesis and glycogenolysis (Fig. 1). This involves the coupled transport of G6P into the lumen of endoplasmic reticulum, facilitated by G6P translocase (G6PT, encoded by SLC37A4) and dephosphorylation of G6P, catalyzed by the G6Pase catalytic subunit (G6PC, encoded by G6PC1). G6PT is ubiquitously expressed, whereas G6PC is expressed only in the liver, kidneys and intestines, the body’s sole gluconeogenic organs [4,5]. Patients with GSD type 1a (GSD1a) have G6Pase deficiencies, while those with type 1b (GSD1b) have G6PT defects. To date, 85 mutations have been identified in GSD1a patients, resulting in a total or partial deficiency of G6Pase activity [2,6–8]. In the case of GSD1b, 81 mutations have been described, resulting in a lack of G6P transport and causing a loss of G6Pase activity despite the presence of active G6PC [1,2]. GSD1a is the most prevalent subtype and represents approximately 80% of GSD1 cases [3]. Both GSD1a and GSD1b patients show broadly similar manifestations, including fasting hypoglycaemia with lactic acidemia, growth delay, hyperlipidaemia, hypercholesterolaemia and hyperuricaemia. The accumulation of glycogen in hepatocytes and proximal renal tubules leads to hepatomegaly and nephromegaly. Hepatomegaly is further exacerbated by accumulation of neutral lipids in the liver leading to marked hepatosteatosis. Later complications include hepatic adenomas that may undergo malignant transformation, chronic renal disease, gouty arthritis, osteoporosis and pulmonary hypertension [2,9,10]. However, GSD1b patients display myeloid dysfunction not seen in patients with GSD1a [1,2].

Rates of diabetes worldwide have reached alarming proportions and the disease is now considered the epidemic of the 21st century, according to the International Diabetes Federation (IDF). The IDF expects that, by 2030, the number of people living with diabetes will reach 472 million, with almost 80% living in the low- and middle-income countries, compared to about 30 million diabetics worldwide only 20 years ago. Experts say diabetes is the cause of around three million deaths globally each year, a number that will continue to rise as the number of people affected increases. Diabetes is a group of diseases characterized by chronic hyperglycaemia (overnight fasting blood glucose above 126 mg/dL or 7 mM) and hyperinsulinaemia due to deterioration of glucose control. This deterioration combines resistance to the action of insulin to stimulate glucose uptake by adipose tissue and skeletal muscle, suppression of EGP and defects in the secretion of insulin from the endocrine pancreas [11,12]. The most common form is type 2 diabetes, which is strongly associated with obesity and a sedentary lifestyle. It is estimated that 80–90% of individuals with type 2 diabetes are obese, and the risk of developing type 2 diabetes is directly associated with an increase in body mass index (BMI) [13]. Long-term complications of diabetes such as heart disease, kidney disease, liver disease, neuropathy, retinopathy and peripheral vascular disease can all seriously compromise the quality of life of the diabetic patient [14,15].

2. Altered endogenous glucose production

Glucose homoeostasis is notably achieved by coordination of the signalling pathways that regulate glycogen synthesis, glycogenolysis and gluconeogenesis. During nutrient intake, glucose is taken up from the circulation and stored in hepatocytes and muscle as glycogen. In the postabsorptive state, glycogen phosphorylase catalyzes the release of glucose from liver glycogen chains to maintain blood glucose. As this glycogen store is depleted, de novo glucose is synthesized from lactate, amino acids and glycerol by the liver, with glutamine being a key glucose precursor in the kidneys and intestines [16–18]. Although hepatic glucose production is often assimilated into EGP, the kidneys and intestines are capable of maintaining glucose production during long-term fasting. Indeed, it was recently shown that mice with a liver deficiency of G6Pase (L.G6pc−/− mice) are viable, exhibit normoglycaemia in the fed state and can even resist fasting due to a compensatory induction of intestinal and renal glucose production [19].

In the absence of G6Pase activity, GSD1 patients mainly suffer from severe hypoglycaemia and hyperlactataemia, both of which appear after only a few hours of fasting. Initial symptoms are due to hypoglycaemia and are seen shortly after birth. In GSD1, hypoglycaemic episodes are not corrected by glucagon administration, and untreated and severe cases can be fatal. However, since the 1980s, the life expectancy of patients with GSD1 has been considerably improved by dietary control, although various complications arise with ageing. The disease may be well controlled by intensive dietary treatment aiming to maintain normoglycaemia through frequent meals during the day and gastric drip-feeding or uncooked cornstarch at night [10]. The use of uncooked cornstarch in adult patients with GSD1
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Moreover, in diabetic patients, the excess release of glucose into the circulation is a major cause of chronic hyperglycaemia. Indeed, the inability to suppress hepatic glucose production because of insulin secretion deficiency or insulin resistance is the key defect of diabetes [11,20,21]. Induction of EGP marks the transition between the state of glucose intolerance and the development of frank diabetes [12]. Using the glucose tracer dilution technique, several studies have shown that EGP is increased under basal conditions in diabetic patients and that this increase in EGP correlates with the severity of fasting hyperglycaemia [22–24]. The increase of EGP in patients with type 2 diabetes is predominantly due to an increase in the rate of gluconeogenesis compared with non-diabetic subjects, as glycogenolysis is largely unchanged [24,25]. In addition to insulin resistance, diabetics also show resistance to the inhibiting effect of hyperglycaemia on EGP [26]. Moreover, many patients with diabetes show fasting hyperglucagonaemia and abnormal suppression of glucagon secretion after a meal [27]. This hyperglucagonaemia is secondary to the absence of regulation of glucagon secretion by insulin following the failure of β cells in diabetic patients [28,29]. Given the stimulatory role of glucagon on glycogenolysis and hepatic gluconeogenesis, several studies have suggested a role for hyperglucagonaemia in fasting hyperglycaemia in type 2 diabetes [27,30].

EGP is a crucial function for maintaining blood glucose at around 100 mg/dL (5.5 mM) during postprandial and fasting periods. It is noteworthy that although the liver has always been considered the main source of EGP via glycogenolysis and gluconeogenesis, the kidneys and intestines are two other important sites for maintaining glucose homeostasis [19]. Interestingly, it was recently shown that intestinal gluconeogenesis is paradoxically beneficial for glucose and energy balance, as it initiates a gut–brain–liver neural circuit to regulate both hunger and liver insulin sensitivity [31]. On the other hand, increased hepatic glucose production is sufficient to induce altered glucose tolerance, hyperinsulinaemia, decreased hepatic glycogen content and modification of lipid homeostasis in rats [32]. These data should open up new therapeutic strategies for diabetes.

3. Hepatic steatosis

Non-alcoholic fatty liver disease (NAFLD) refers to a wide spectrum of disorders characterized by hepatic fat accumulation. Although often considered benign, it is now recognized that hepatic steatosis can progress to chronic liver inflammation, or steatohepatitis, a severe condition of inflamed fatty liver that can further progress to fibrosis and cirrhosis and, finally, the development of hepatocellular carcinoma (HCC) [33]. Several mechanisms can account for the excess hepatic triglyceride accumulation, including increased free fatty acid delivery to the liver, defective mitochondrial long-chain fatty acid oxidation, increased de novo lipogenesis and decreased very-low-density lipoprotein (VLDL) export [34,35]. Previously, transcription factor SREBP-1c (sterol regulatory element-binding protein-1c) had emerged as a major mediator of insulin action on lipogenic genes such as acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS). However, SREBP-1c activity alone
is not sufficient to account for the stimulation of glycolytic and lipogenic gene expression in response to carbohydrate loads. It requires another transcription factor, the so-called carbohydrate-responsive element-binding protein (ChREBP). ChREBP is activated by increased hepatic G6P in the liver and, together with SREBP-1c, drives the expression of genes involved in fatty acid synthesis and esterification [35].

The mechanisms that lead to the accumulation of lipid droplets in the liver of GSD1 and diabetic patients are different. In addition to its role in glucose production, G6Pase has an important regulatory function in buffering the cell content of G6P, an important regulator of both glycogen metabolism and transcription of glycolytic and lipogenic genes. The increase of glycolytic and lipogenic pathways by G6P involves activation of ChREBP [36]. In GSD1, the massive accumulation of G6P leads to accumulation of glycogen and overactivation of de novo lipogenesis (Fig. 2A). The resultant considerable hepatic steatosis is mainly due to increased fatty acid uptake and synthesis together with decreased fatty acid oxidation and triglyceride release [37,38]. Pharmacological inhibition of G6P'T (with S4048) in mice invalidated for either LXRα or ChREBP has revealed the importance of ChREBP in the induction of lipogenesis in patients with GSD1 [39].

In obese type 2 diabetic patients, hepatic steatosis has been demonstrated to be highly associated with insulin resistance [40]. On the one hand, insulin resistance in muscle and adipose tissue can increase the influx of carbohydrates and free fatty acids into the liver, thereby promoting de novo hepatic lipogenesis and triglyceride synthesis (Fig. 2B). On the other hand, the accumulation of lipid derivatives such as diacylglycerol (DAG), ceramides, fatty acyl-CoAs and their metabolites can activate several protein kinase cascades and/or endoplasmic reticulum stress, ultimately leading to the disruption of insulin signalling and, thus, exacerbation of insulin resistance. Paradoxically, while insulin action on the hepatic gluconeogenic pathway is impaired, the action of insulin on SREBP-1c expression and the lipogenic pathway remains intact or is hyperstimulated [41,42]. Several hypotheses have been suggested to explain the paradoxical activation of SREBP-1c in insulin resistance. As mammalian target of rapamycin complex 1 (mTORC1) is required for stimulation of lipogenic gene expression, but not for inhibition of gluconeogenesis in rat liver, there may be a bifurcation in the insulin signalling pathway involved in lipogenic and gluconeogenic programming [43]. Another hypothesis proposes activation of SREBP-1c and lipogenesis by means of increased endoplasmic reticulum stress, as the unfolded protein response (UPR) induces maturation of SREBP-1c [44,45]. It is also possible that a significant part of hepatic lipogenesis is independent of insulin signalling.

Recent studies suggest that NAFLD may be more common in type 1 diabetes than was previously thought and may serve as an independent risk marker for some chronic diabetic complications [46]. The pathogenesis of NAFLD remains obscure, but it has been hypothesized that hepatic fat accumulation in type 1 diabetes could be due to lipoprotein abnormalities, hyperglycaemia-induced activation of transcription factors ChREBP and SREBP-1c, upregulation of glucose transporter 2 (GLUT2) with subsequent intrahepatic fat synthesis, or a combination of these mechanisms.

The metabolic consequences of steatosis differ in GSD1 and diabetes. Indeed, fatty liver is associated with insulin resistance in diabetes, but not in GSD1. This supports the possibility of a dissociation between hepatic steatosis and hepatic insulin resistance, an idea that has recently been discussed elsewhere [47,48]. In fact, new studies suggest the crucial importance of hepatic fatty acid composition to the metabolic consequences of steatosis. The harmful effects of saturated fatty acids and particularly of palmitate on insulin signalling have been documented in several cell types, including liver, muscle and pancreatic cells [49–52]. These effects could be reversed by concomitant treatment with oleate [53–55]. In rats, dietary enrichment with oleate was associated with improved insulin sensitivity [56]. Interestingly, invalidation of the enzyme ELOVL6 along with an enrichment ratio of palmitoleate/palmitate resulted in accumulation of palmitate and palmitoleate at the expense of stearate. The mice fed a high-fat/high-sucrose diet developed fatty liver, but had improved insulin sensitivity compared with control mice [51]. In another study, adenoviral overexpression of a constitutively active form of ChREBP in mouse liver improved glycaemic control and restored hepatic insulin sensitivity in obese and diabetic mice despite exacerbation of hepatic lipid accumulation. The improvements were associated with an increased ratio of oleate/palmitate in the livers of mice overexpressing ChREBP [57]. These studies clearly show the influence of the composition of liver lipid content on alterations of insulin sensitivity.

Comparing GSD1a and diabetes also highlights the intricate relationship between hepatic lipid and glucose metabolism. In normal circadian physiology, hepatic lipogenesis and gluconeogenesis are mutually exclusive. Recent studies of histone deacetylase 3 (HDAC3) showed that hepatic HDAC3, which controls the circadian rhythm of hepatic lipogenesis [58], promotes gluconeogenesis by inhibiting lipid synthesis and sequestration [59]. In addition, although hepatic gluconeogenesis competes with lipid synthesis for metabolic intermediates, it depends on lipid oxidation for energy and cofactors. A blocked gluconeogenesis flux shunts intermediates into lipogenesis and promotes steatosis. In contrast, excessive enhancement of lipogenesis attenuates gluconeogenesis, leading to reduced glycogen storage and hypoglycaemia [59]. In type 2 diabetes, the simultaneous activation of gluconeogenesis and lipogenesis produces far more lipid than the liver can handle, resulting in lipotoxicity and worsening insulin resistance. For this reason, Sun et al. [59] recently suggested that the intensity of hepatic insulin resistance is determined by the variable capacity of lipid droplets to sequester enough lipids to prevent the cytosolic accumulation of deleterious lipid species.

4. Liver cancer

In the liver, long-term complications of G6Pase deficiency include focal nodular hyperplasia and, more often, hepatocellular adenoma (HCA) with a risk of malignant transformation [10,60]. Despite massive hepatic steatosis, neither fibrosis
Fig. 2. Liver metabolism in GSD1a and type 2 diabetes. A. In GSD1, accumulation of G6P in the cytosol induces glycolysis, glycogen synthesis and de novo lipogenesis, and activation of glycolysis induces lactate production. Insulin plasma levels are rather low, and glucagon activates lipolysis through an increase of hepatic fibroblast growth factor 21 (FGF21) [126], leading to high plasma levels of free fatty acids (FFAs). FFAs are taken up from plasma into hepatocytes to produce triglycerides (TG). Accumulation of G6P activates TG synthesis in hepatocytes, leading to steatosis. In the postprandial state, insulin stimulates dephosphorylation of glycogen synthase (GS) by protein phosphatase 1 (PP1) and inhibits phosphorylation of protein GS DK3 and protein kinase 1 (PKA), leading to massive glycogen synthesis and nephromegaly. B. In type 2 diabetes, insulin resistance blocks both glycogen synthesis and inhibition of lipolysis, whereas hyperglucagonaemia activates glycogen degradation and lipolysis through FGF21 [126]. FFAs are taken up from plasma into hepatocytes to produce TG. At the same time, activation of de novo lipogenesis by high hepatic G6P levels leads to steatosis, while activation of G6Pase leads to hyperglycaemia.

nor cirrhosis has been observed in GSD1 patients. This could be explained by the limited β-oxidation-induced oxidative stress and a strong antioxidative defence [61]. HCA develops predominantly during and after puberty, and more than 70% of GSD1 adult patients have multiple HCAs [62,63]. The clinical problems related to HCA are the risks of haemorrhage, spontaneous rupture and malignant transformation into HCC. A recent study provided a molecular characterization of GSD1-related
HCA that displayed a high frequency of β-catenin mutation, suggesting that a significant proportion of HCAs are at high risk of malignant transformation [60,64]. In addition, more than 50% of HCAs were classified as inflammatory adenomas mainly caused by an IL6ST mutation activating gp130, whereas no HNF1A mutation was observed in the series [60]. As expected, L.G6pc−/− mice developed HCAs over time. The first nodules were detected after 9 months of G6pc deletion and, after 18 months, all L.G6pc−/− mouse livers showed multiple lesions [65]. In about 20% of cases, L.G6pc−/− mice presented with dysplasia after 18 months of gene deletion (unpublished data). It is important to note that the development of adenomas appeared rather late, while liver steatosis tended to worsen [65]. Moreover, recent data show that the development of hepatic tumours in L.G6pc−/− mice is enhanced by a high-fat enriched diet (unpublished data).

These data are consistent with findings in GSD1 patients showing that poor metabolic control appears to play a role in HCA formation [66,67]. In 2002, guidelines from the European Study on Glycogen Storage Disease Type 1 recommended liver transplantation in patients with GSD1 and non-resectable HCAs that were unresponsive to dietary therapy, particularly if the tumours were associated with serious compression or haemorrhage, or showed signs of transformation into HCC [68].

Type 2 diabetes in association with obesity has been identified as an independent risk factor for the development of HCC [62,69–74]. Analyses of diabetic cohorts have found that the incidence ratio of primary liver cancer was increased by about two- or threefold [75]. Intriguingly, NAFLD is the key link between obesity (and type 2 diabetes) and liver cancer. In most cases, this probably involves the progression of steatohepatitis to cirrhosis and the subsequent development of carcinoma. However, HCC also arises from simple steatosis without cirrhosis, which may imply a special role for lipid metabolism and lipotoxicity in the hepatic carcinogenic process [76,77].

Emerging data support a role for both lipid and glucose metabolism in hepatocellular carcinogenesis that is closely interrelated with inflammatory, proliferative and apoptotic signalling within the liver [78–80]. In type 2 diabetes, the accumulation of lipids within hepatocytes leads to chronic low-grade inflammation, involving various cytokines and adipokines such as interleukin (IL)-6 and tumour necrosis factor (TNF)-α that are tumour-promoting [81]. These cytokines lead to hepatic inflammation and activation of oncogenic transcription factor STAT3 by phosphorylation [82]. Activation of STAT3 induces proliferation, inhibition of apoptosis and cytokine production leading to liver cancer development. However, activation of the IL-6 and TNF-α pathways alone is probably not enough to induce HCC [83]. In humans, the activation of gp130 (a key transducer of IL-6 signals) is mainly associated to benign tumorigenesis and, in malignant liver tumours, gp130 is associated with additional β-catenin-activating mutations [64,85].

In addition to the inflammatory signalling pathways, the AMP-activated protein kinase (AMPK)–mTORC1 pathway is another major signalling pathway involved in hepatosteatosis and hepatocarcinogenesis. Induction of the mTOR pathway in obese diabetic animal models activates SREBP1c, promotes endoplasmic reticulum stress and inhibits autophagy. Indeed, mTORC1 serves as an important checkpoint in autophagy [84,85]. Autophagy in acute liver injury might to a certain degree act ‘hepatoprotectively’ as it rapidly supplies hepatocytes with energy [86]. Knock-out mice with specific deletions in autophagy-related genes show spontaneous development of hepatocellular dysplasia [87,88]. One way to reactivate autophagy in the hepatosteatotic liver is through the use of the antidiabetic drug metformin. Metformin treatment has been associated with a strong and statistically significant reduction of HCC risk among diabetics [69,89–91]. Thus, decreased autophagy function in particular could promote the initial development of hepatic steatosis and progression of steatosis to liver injury in type 2 diabetes [92].

Alteration of lipid metabolism in the liver is a shared feature of both GSD1 and diabetic patients associated with hepatic tumour formation. A recent review highlighted the central role of de novo fatty acid synthesis in tumorigenesis [93]. Increased de novo fatty acid synthesis is required in tumour cells for the construction of highly lipid membranes, and studies with chemical inhibitors of FAS have shown decreased proliferation and increased apoptosis of tumour cells [94]. In addition, proliferating cell metabolism differs from quiescent cell metabolism by having higher rates of glycolysis even in the presence of abundant oxygen (the ‘Warburg effect’), lactate production and biosynthesis of lipids [95]. In fact, metabolic alterations in GSD1 livers confer a preneoplastic status to hepatocytes favouring multiple HCA development in the liver [60].

5. Hepatomegaly

As already mentioned, the massive accumulation of G6P leads to high glycogen stores and hepatomegaly in GSD1. More commonly, the presence of a protruding abdomen due to marked hepatomegaly at around 3 months of age is the first symptom, although in some cases the liver may already be enlarged at birth. The size of the liver increases gradually and its lower border may extend to well below the umbilicus. However, it should be emphasized that hepatomegaly may be missed on physical examination as the liver is soft [2]. The accumulation of intrahepatic lipids also contributes to hepatomegaly in patients with GSD1.

In diabetic patients, hepatomegaly is an extremely rare complication. It has been described in cases of ‘glycogenic hepatopathy’, mostly in patients with type 1 diabetes whose glycaemic control has been poor for a long time [96] and in those with poorly controlled type 2 diabetes treated with insulin therapy [97]. The key finding in glycogenic hepatopathy is the accumulation of glycogen in the liver resulting in hepatomegaly and elevated liver enzymes, especially transaminases. On histology, glycogenic hepatopathy is characterized by marked glycogen accumulation leading to pale, swollen hepatocytes, mild fat accumulation, nil or minimal inflammation and an intact hepatic architecture with no significant fibrosis [96]. Although the underlying mechanism(s) through which glycogenic hepatopathy develops have not been fully
clarified, wide fluctuations in both glucose and insulin levels appear to be essential in the pathophysiology. The increase in hepatic glycogen synthesis depends on the presence of high concentrations of glucose and the insulin concentration in the environment.

The other major cause of liver enlargement in diabetes is fatty liver, and it is important to distinguish these two entities, as both their pathophysiology and therapy are different. Fatty liver is associated with hyperinsulinaemia, mild elevations of liver enzymes and a hypodense liver on computed tomography (CT). In contrast, hepatic glycogen loading seen with insulin deficiency is associated with marked elevations of liver enzymes, and the liver appears hyperdense on CT scans [98]. In some cases, a dual gradient-echo magnetic resonance imaging (MRI) sequence could be a clue to the diagnosis of glycogenic hepatopathy [99]. Also, the prognosis for glycogenic hepatopathy is good, as improved glycaemic control reverses glycogen storage disease [99].

6. Renal disease

Chronic renal disease was recognized as a major complication of GSD1a in the late 1980s. Almost all GSD1a patients above 20 years of age manifest kidney complications, including proteinuria. Many also have hypertension, renal stones, nephrocalcinosis, altered creatinine clearance and, eventually, renal failure. Unfortunately, intensive dietary therapy in GSD1a patients fails to prevent the long-term complications of renal disease. In fact, renal disease in GSD1a follows a similar clinical course and pathology as diabetic nephropathy [100]. In both conditions, dysfunction remains silent for a long period of time, with glomerular hyperfiltration being the only demonstrable renal abnormality. Eventually, however, the renal involvement progresses to hypercalciuria, hypocitraturia and urinary albumin excretion. Renal biopsy then reveals tubular atrophy, focal segmental glomerulosclerosis and interstitial fibrosis. In both GSD1 and diabetes, renal fibrosis is the result of excess accumulation of extracellular matrix (ECM) proteins, including fibronectin and collagens types I, III and IV (Fig. 3) [100,101]. It is well established that renal fibrosis is mediated by the angiotensin–transforming growth factor (TGF)-β1 pathway. Indeed, many profibrotic effects of angiotensin II are mediated by the multifunctional TGF-β1 [102], the expression of which is also increased by angiotensin II. In turn, TGF-β1 increases the expression of ECM genes while inhibiting the production of ECM degradative proteins, thereby leading to ECM protein deposition. In patients with diabetic nephropathy, treatment with angiotensin-converting enzyme inhibitors (ACEIs) significantly reduces the risk of nephropathy [103]. In GSD1, a significant decrease in glomerular filtration rate was observed when ACEIs were prescribed to patients with glomerular hyperfiltration. However, no significant effects were observed on microalbuminuria and proteinuria [104,105]. Thus, more investigations are needed to ascertain the effectiveness of this treatment in GSD1 patients.

Both GSD1 and diabetic kidneys exhibit an increase in the proinflammatory cytokines IL-6 and TNF-α, and oxidative stress (Fig. 3). Enhancement of oxidative stress is mediated by activation of NADPH oxidase, and suppression of the antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) is mediated by the Akt–FoxO (protein kinase B–Forkhead box O) pathway [106]. Metformin activates AMPK and decreases NADPH oxidase activity, and ultimately leads to a decrease in reactive oxygen species (ROS) production in cultured podocytes, the differentiated cells that line the outer layer of the glomerular basement membrane [107]. In type 2 diabetes animal models, it has been shown that metformin treatment ameliorated the tubular injury associated with hyperglycaemia [108].

Another common denominator in both diabetes and GSD1 is the accumulation of glycogen in the kidneys in association with upregulation of the pentose phosphate pathway and de novo synthesis of lipids (Fig. 3). Indeed, diabetic renal disease is associated with lipid deposits in the kidney (in both glomeruli and proximal tubules) mediated by a coordinated upregulation of SREBP1, SREBP2 and ChREBP [109–113]. Lipid deposits include lipid bodies, triglycerides, cholesterol and metabolites such as DAG and ceramides that may possibly induce defects in glucose control [114]. DAG is a potent activator of protein kinase C, which leads to activation of intrarenal angiotensinogen expression [115]. Diabetic patients treated with fibrates, peroxisome proliferator-activated receptor-α agonists that lower serum triglyceride concentrations, also exhibit a significant decrease in proteinuria [116,117]. Up till now, lipid deposits in the kidneys of GSD1a patients have received little attention, but were reported in one GSD1 patient [118]. However, these abnormalities of renal lipid metabolism could play an important role in the pathogenesis of diabetic and GSD1a nephropathy.

Diabetic nephropathy has become a global epidemic, accounting for approximately one-third of all cases of end-stage renal disease—and the problem is expected to grow. Improved management of diabetes is clearly required, including improved glycaemic control to avoid the development of diabetic nephropathy, particularly in high-risk patients [119]. In GSD1, optimal metabolic control is needed to reduce the risks of microalbuminuria and proteinuria. In patients with GSD1, liver transplantation can correct all liver-related biochemical abnormalities and glucose blood level, but its effect on the reversal and/or prevention of renal disease remains unclear [120–122]. Also, renal transplantation can correct only renal abnormalities [123]. Thus, a combined liver–kidney graft is indicated when renal function is compromised in GSD1 patients.

7. Is G6Pase a therapeutic target for glucose control in type 2 diabetes?

On comparing these two pathological conditions, inhibiting hepatic G6Pase activity in the liver appears to be an attractive approach for treating diabetes. However, there are two major limitations. As GSD1 patients develop hypoglycaemia and fatty liver, it might be expected that moderate inhibition of hepatic G6Pase could lead to marked perturbations in the expression of various genes involved in lipogenesis, but this could exacerbate hepatic steatosis in type 2 diabetes patients and lead to the
development of hepatic tumours. On the other hand, mice with heterozygous deletion of G6Pase and so exhibiting half the normal activity of G6Pase do not exhibit marked liver abnormality [65]. To avoid hypoglycaemia in treated type 2 diabetics, it would be necessary to target inhibition strictly to EGP of splanchnic origin and not renal glucose production. This might be achieved by developing drugs that are taken up, but not released, by the liver. In addition, the drugs need to be able to inhibit strongly, but not totally, hepatic G6Pase activity (say, by above 50%). In this case, the increase in renal glucose release might partially compensate for the reduced hepatic and intestinal glucose production. It has previously been shown that replacement of hepatic glucose production by renal glucose production is beneficial for glucose control [124]. It is noteworthy that the first-line oral glucose-lowering drug recommended in the guidelines of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) is metformin. The main action of metformin is to decrease hepatic glucose output by, in particular, suppressing metabolic flux through G6Pase, thereby promoting increased G6P content [125]. The ideal strategy to overcome these complications would be to achieve an effective reduction of hepatic glucose production while limiting the development of steatosis, which is consistent with the mechanisms of action of metformin. On the other hand, a better understanding of the molecular pathways involved in the development of liver tumours and nephropathy in GSD1 patients would allow the development of new therapeutic approaches that could be used for patients with either GSD1 or diabetes.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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