

# Diabetic-induced alterations in hepatic glucose and lipid metabolism: The role of type 1 and type 2 diabetes mellitus (Review)

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Received July 12, 2019; Accepted March 6, 2020

DOI: 10.3892/mmr.2020.11175

**Abstract.** Diabetes mellitus (DM) is a growing health concern in society. Type 1 and type 2 DM are the two main types of diabetes; both types are chronic diseases that affect glucose metabolism in the body and the impaired regulation of glucose and lipid metabolism promotes the development and progression of DM. During the physiological metabolism process, the liver serves a unique role in glucose and lipid metabolism. The present article aimed to review the association between DM and glucose metabolism in the liver and discuss the changes of the following hepatic glucose fluxes: Gluconeogenesis, glucose/glucose 6-phosphate cycling, glycogenolysis, glycogenesis and the pentose phosphate pathway. Moreover, the incidence of fatty liver in DM was also investigated.

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## 1. Introduction

Glucose plays an important role in metabolism. It is not only the source of energy, but also the substrate of cell composition biosynthesis (1). The metabolic dysregulation of glucose homeostasis is the main consequence of the development of diabetes and the major cause of diabetic morbidity and mortality. There are two common types of diabetes: Type 1 and type 2. Type 1 diabetes mellitus (T1DM) is characterized by the insufficient secretion of insulin and the excessive release of glucagon, which promotes hepatic lipolysis and ketogenesis (2) and counteracts hepatic anabolism. Type 2 diabetes mellitus (T2DM) is the more common type of DM and is characterized by undetectable levels of insulin, increased liver fat content, impaired insulin clearance and hepatic insulin resistance (3).

DM is associated with various liver abnormalities, including non-alcoholic fatty liver disease (NAFLD) (3) and excessive hepatic glycogenesis (4). The liver serves a unique role in glucose metabolism and is crucial for systemic glucose homeostasis (5); it contributes to the management of an enteral glucose load by inhibiting its own glucose output, which aids the disposal of exogenous glucose by extrahepatic tissues, such as adipose and skeletal muscle (6). The dysregulation of liver signaling and metabolism predisposes individuals to NAFLD and/or T2DM, thus certain liver-derived biomarkers (fetuin-A, alpha-hydroxybutyrate and C-reactive protein) can be used for the diagnosis and prognosis of DM and DM-associated complications (7). Therefore, the liver is also an important target organ that regulates glucose homeostasis and can be targeted by the administration of specific diabetic drugs (8).

In the present review, the physiology and molecular pathways of liver glucose homeostasis were investigated, as well as

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**Abbreviations:** T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; TG, triglycerides; G/G6P, glucose/glucose 6-phosphate; GK, glucokinase; G6Pase, glucose 6-phosphatase; STZ, streptozotocin; 13C-NMRS, 13C nuclear magnetic resonance spectroscopy; HbA1c, glycated hemoglobin; GP, glycogen phosphorylase; GS, glycogen synthase; HGP, hepatic glucose production; TCA cycle, tricarboxylic acid cycle; PPP, pentose phosphate pathway; G6PD, glucose-6-phosphate dehydrogenase; L-PK, liver pyruvate kinase; FAS, fatty acid synthase; ACC, acetyl-CoA carboxylase; PFK1, phosphofructokinase; GAPDH, Glyceraldehyde 3-phosphate dehydrogenase; NADH, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; NADP<sup>+</sup>, nicotinic adenine dinucleotide phosphate

**Key words:** diabetes, sugar, insulin resistance, glucose metabolism, lipid metabolism

the glucose metabolic disorders noted in DM. Hepatic lipogenesis was also investigated since lipid-induced hepatic insulin resistance is one of the main pathophysiological processes of hepatic glucose metabolism disorder in T2DM.

## 2. Metabolic processing of glucose in the liver under diabetic conditions

During glucose homeostasis, the liver serves an important role in carbohydrate synthesis, storage and redistribution (9). The liver performs opposite functions during hyperglycemic (glucose uptake and glycogen synthesis) and hypoglycemic states (glycogenolysis and gluconeogenesis), thus the physiological regulation of hepatic glucose production is a complex process (6). Patients with T2DM and T1DM demonstrate increased hepatic glucose production (HGP), of which multiple extrahepatic mechanisms contribute to the physiological regulation of HGP (10). However, DM is a bi-hormonal disease and is not simply the result of insulin deficiency (11,12). The pancreatic endocrine cell hormones, glucagon (13) and insulin (14), both serve central roles in the regulation of both glucose and lipid metabolism. Insulin inhibits the secretion of glucagon and promotes the storage of lipids and carbohydrates, whereas glucagon facilitates gluconeogenesis and glucose efflux from the liver (15). Previous studies have reported that every type of diabetes is associated with hyperglucagonemia, the suppression of which can reduce hyperglycemia (10,16). For example, insulin exerts a strong regulatory effect on the secretion of glucagon and causes the suppression of secretion of glucagon from pancreatic  $\alpha$ -cells; it has been reported that the absence of this paracrine regulatory mode contributes to the development of hyperglucagonemia and the increase of HGP in DM (11,17). The main processes that contribute to glucose homeostasis, include glycogenolysis, glycogen synthesis, glycolysis and gluconeogenesis, all of which are regulated by independent mechanisms (6,9). The dysregulation of these processes is discussed in detail in the following section.

*Increased hepatic glucose/glucose 6-phosphate (G/G6P) cycling in DM.* In hepatocytes, glucose is converted into G6P by glucokinase (GK; the gatekeeper for glucose metabolism in hepatocytes), and G6P is subsequently trapped in hepatocytes (8). The affinity of GK (also known as hexokinase IV) for glucose is low ( $S_{0.5}$ ; half-saturating concentration,  $\sim 5$  mmol/l) and the reaction rate exhibits a sigmoidal dependence on the intracellular glucose concentration (18). When the blood glucose levels are  $< 5$  mmol/l (90 mg/dl), GK will not stimulate the production of large amounts of G6P and subsequent steps are blocked to ensure that hepatic glycogen synthesis is only highly active when blood glucose levels are high (19). G6P is subsequently converted to excess glycogen when insulin levels are high enough to activate glycogen synthase (GSb) and inactivate glycogen phosphorylase (GP $\alpha$ ) (Fig. 1). In a diabetic state, it was demonstrated that the glucose uptake in hepatocytes from diabetic mice was significantly lower compared with the control animals, which may be a result of the repressed GK synthesis in response to a decreased insulin: Glucagon ratio (20). Glucagon has been demonstrated to modify hepatic glucose uptake; for example,

a previous animal study indicated that under hyperglycemic and hyperinsulinemic conditions, the physiological changes noted in arterial blood glucagon dramatically changed the net hepatic glucose balance (21), whereas another study revealed that elevated blood glucagon levels impaired the ability of the liver to absorb and store glucose (22). Elevated blood-glucose in the postprandial state was found to activate GK activity and subsequently increase hepatic G6P production (23) (Fig. 1). In T2DM (24), impaired liver glucose uptake has been reported, which subsequently lead to postprandial hyperglycemia following the discovery that faulty hepatic GK activation could lead to impaired glucose uptake in T2DM (25). A more recent study demonstrated that the nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylase sirtuin-2 (Sirt2) promoted hepatic glucose uptake through deacetylating the GK regulatory protein. Similarly, in high fat diet-fed obese diabetic mice, the overexpression of hepatic Sirt2 increased the glucose uptake in the liver, attenuating impaired glucose tolerance (26).

Elevated G6P levels promote the upregulation of glucose 6-phosphatase (G6Pase) (27) and the gene expression levels of lipogenic enzymes, such as liver pyruvate kinase (L-PK), fatty acid synthase (FAS), and acetyl-CoA carboxylase (ACC) (28). Elevated levels of G6Pase suppress G6P levels during the fasting state (29). In the fed state, G6P is the precursor of glycogen synthesis and it is also metabolized to generate pyruvate through glycolysis (9). The alterations in the G/G6P cycle have been observed in both humans and animals with T2DM (30,31) as well as in animals with T1DM (20). For example, a previous study compared the levels of glucose in isolated hepatocytes from fasted, normal rats with the corresponding levels in hepatocytes from streptozotocin (STZ)-induced diabetic rats. The results indicated that glucose was absorbed by the liver and phosphorylated in normal fasting rats, whereas in diabetic hepatocytes, additional levels of the G6P precursor were subsequently dephosphorylated and released into the blood circulation (32). Thus, through downregulating the expression levels of GK or upregulating the activity of G6Pase, the concentration of G6P is disturbed, which may be the reason for the decline noted in the glucose metabolism responsiveness of diabetic subjects (20,23,33).

Overall, the imbalance between hepatic glucose release and glucose uptake is an important factor in the development of DM; therefore, the drugs used to treat of DM should be designed to increase glucose uptake by activation of GK. Unfortunately, the majority of the drugs that target GK activation for the treatment of T2DM have not been clinically successful due to side effects, such as hypoglycemia, steatohepatitis and loss of efficacy over time (8). However, TTP399, a hepato-elective GK activator, was assessed in a recently reported double-blind, 6-month study and it was found that TTP399 did not cause hypoglycemia and exhibited limited or no detrimental effect on plasma lipids or liver enzymes (34). Moreover, it is a liver specific GK activator without side effects of hypertension, highlighting the importance of liver selectivity when targeting GK activity (34).

*Hepatic glycogenesis is reduced in T2DM, whilst in T1DM, it is associated with insulin therapy.* Net glycogen deposition in the liver depends on the coordinated inhibition of

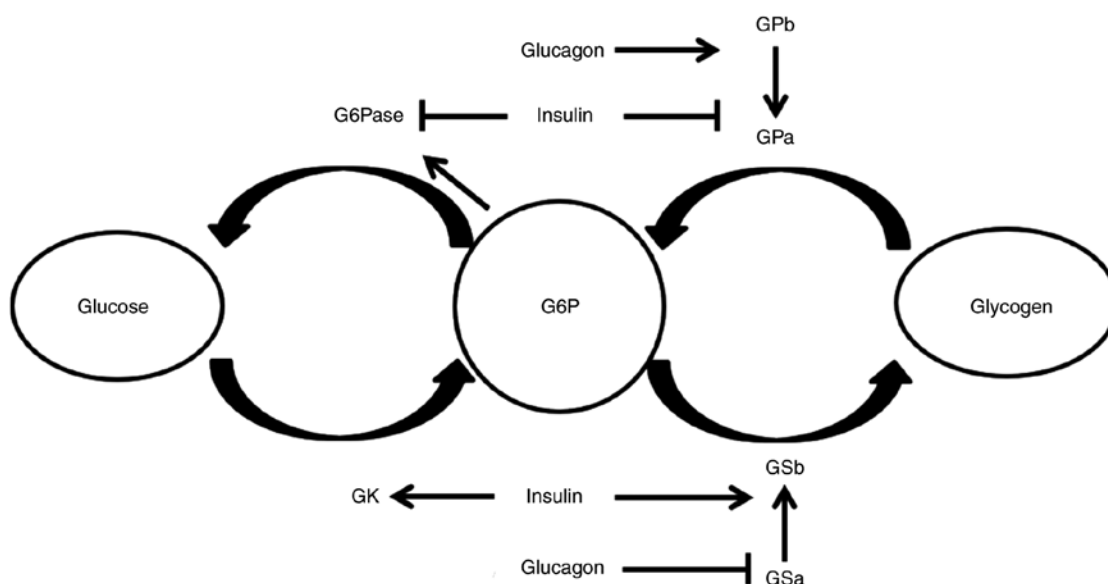


Figure 1. Metabolite cycle of glucose to glycogen. Under the regulation of insulin and glucagon, the liver aids the maintenance of blood glucose homeostasis. Insulin activates the uptake of glucose and the synthesis of glycogen, while inhibiting glycogenolysis and gluconeogenesis. Glucagon inhibits glycogenesis and promotes glycogenolysis. G6P is a key intermediate enzyme of the pathways and elevated G6P levels increases the activity of G6Pase, facilitating the production of glucose. GP is the active form of GP and GPb is the inactive form. Conversely, GSb is the active form of GS and GSa is its inactive form. G6P, glucose 6-phosphate; GP, glycogen phosphorylase; GS, glycogen synthase; GK, glucokinase; G6Pase, glucose-6-phosphatase.

glycogenolytic molecules and the stimulation of glycogen synthesis molecules, of which glycogenolysis and glycogen synthesis are regulated by complex mechanisms (35,36). Generally, a useful simplification is that glucose is the main inhibitor of hepatic glycogenolysis and insulin is the main activator of hepatic glycogen synthesis. This has been demonstrated in healthy individuals, using  $^{13}\text{C}$  nuclear magnetic resonance spectroscopy ( $^{13}\text{C}$ -NMRS) measurements of GS and glycogen phosphorylase flux in the liver (37).

The synthesis of glycogen occurs through a process called glycogenesis, which requires ATP and uridine-5'-triphosphate (23). Glycogen can be synthesized directly from glucose (from glucose to G6P to UDP-glucose to glycogen) or indirectly (from glucose to G6P to pyruvate to G6P to UDP-glucose to glycogen) in the liver (23). These pathways have similar effects on hepatic glycogen synthesis (38). Three regulated enzymes have been identified that exert a high degree of control over glycogen metabolism in the liver: GK (39), GS and GP (40). The changes in GK activity are achieved by regulating GK protein expression or the dissociation of GK from the GK regulatory protein (41). The activities of GS and GP are determined by phosphorylation and dephosphorylation, which serve opposite actions on the activity levels of GS and GP enzymes, leading to a large change in glycogen synthesis. After phosphorylation, GP has activity to decompose glycogen, while after dephosphorylation, GS has activity to promote glycogen synthesis (Fig. 1) (23).

Under T1DM conditions, blood glucose levels are high and exogenous administration of insulin is elevated, which leads to increased hepatic glycogen production and excessive glycogen storage in the liver (42). Hepatic glycogenosis is a relatively benign disease and does not progress easily to fibrosis (43); glycogenosis is the hepatic response to the excess circulating insulin and glucose load in patients with T1DM, whereas non-alcoholic steatohepatitis is the more common diagnosis

when elevated insulin and glucose levels occur in adults with T2DM (43). The possible pathogenesis of hepatic glycogenosis is considered to occur following the accumulation of hepatic glycogen in patients with unstable DM as a result of the increased flux of glucose into the hepatocytes (44).

T1DM is associated with abnormal hepatic glycogen metabolism; for example Hwang *et al* previously demonstrated that the net hepatic glycogen synthesis was impaired in poorly controlled patients with T1DM during mixed meals (45). It is also important to note that glycogen synthesis was significantly reduced in patients with poorly controlled T1DM without elevated insulin levels (46). This occurred during the course of a day following the consumption of three isocaloric mixed meals by lean young T1DM [glycated hemoglobin (HbA1c)  $8.8 \pm 0.3\%$ ] and non-diabetic subjects (HbA1c  $5.4 \pm 0.1\%$ ) (46).

Moreover,  $^{13}\text{C}$ -NMRS and variable infusion dual-tracer methodologies were used to study patients with T2DM and non-diabetic volunteer control subjects, which demonstrated that postprandial glycogen synthesis was decreased in mildly overweight patients with T2DM (47). This was accompanied by the impaired inhibition of hepatic glucose production. Patients with T2DM also exhibited a 35% reduction of hepatic glycogen content (47). Del Prato *et al* (48) also reported that glycogen synthesis was reduced in patients with T2DM. These results suggested that the reduced glycogen storage in the liver may lead to postprandial hyperglycemia in patients with T2DM. Furthermore, in mice, a previous study highlighted that T2DM hepatic glycogen was present as large aggregates, which may have aided the inhibition of the interconversion between glucose and glycogen in T2DM. In the same study, it was also found that the size of branched glycogen particles was correlated with the glucose release rate (49).

In patients with DM, hepatic glycogen synthesis is impaired; in T1DM, insufficient insulin is responsible for the reduced glycogen synthesis, whereas T2DM is accompanied

by reduced hepatic glycogen synthesis due to the diminished insulin signaling induced by lipid accumulation in various organs (50). GP inhibitors could thereby increase glycogen synthesis and have been previously used to treat T2DM (8,51).

*Decreased hepatic glycogenolysis in DM.* Glycogenolysis is not a simple reversal of glycogenesis but a separate pathway, of which two pathways of glycogen breakdown have been identified. The first glycogen breakdown pathway is the canonical glycogenolysis route, including GP and glycogen debranching enzymes (52) (Fig. 1). The other pathway is associated with autophagy (52). Autophagy-dependent glycogen decomposition produces non-phosphorylated glucose through lysosomal 1,4- $\alpha$ -glucosidase (52); however, the mechanism by which hepatocytes sense the decline in blood glucose levels and activate selective glycophagy remains poorly understood (53). Hepatic-specific autophagy serves a role in the regulation of blood glucose levels, while insulin has a dominant role over glucagon in the control of liver autophagy (54).

During insulin resistance, glucose inactivates the stimulated form of GP (GP $\alpha$ ) and thereby inhibits glycogenolysis (23). During the period of energy restriction in patients with T2DM, the decrease in fasting blood glucose levels is largely due to decreased glycogenolysis, while the change in gluconeogenesis is not significant (55). A previous study aimed to compare the size distribution, degradation kinetics and branching structure of normal and diabetic liver glycogen; it was observed that T2DM hepatic glycogen existed as large, loosely bound aggregates that were not present in the normal liver, which may have resulted in the inflexibility of glucose and glycogen interconversion in T2DM (49).

Impaired glycogenolysis is also noted in T1DM; hepatic glycogen breakdown was significantly reduced in patients with poorly controlled T1DM, as measured by 13C-MNRS (46). In another study, the contribution of net hepatic glycogenolysis during insulin-induced hypoglycemia was quantitatively analyzed using 13C-MNRS in 10 non-diabetic and 7 T1DM subjects (HbA1c 6.5 $\pm$ 0.2%) and it was concluded that in intensively treated T1DM subjects, hypoglycemia failed to stimulate hepatic glycogen decomposition or activate endogenous glucose production (56).

*Increased rates of hepatic gluconeogenesis in both T1DM and T2DM subjects.* Gluconeogenesis, is essentially a reverse process of the glycolytic pathway. In humans, gluconeogenesis occurs predominantly in the liver (57) and is regulated by a slower mechanism through changes in gene expression (23) in response to hormones, notably insulin and glucagon (36).

Increased glucose production is a consistent feature of T2DM, which can be attributed to increased gluconeogenesis rather than glycogenolysis rates (58,59). The possible influencing factors include: i) Hepatic resistance to the action of insulin, leading to the inappropriate inhibition of hepatic glucose output (60); ii) high levels of glucagon, leading to the overactivation of signaling pathways, which are usually activated during fasting when glucose supply is required (60); and iii) the indirect regulation of gluconeogenesis by excess circulating free fatty acids (FFAs) through the insulin receptor independent pathway (61,62). A previous study using normal blood glucose and hyperglycemic clamps provided

evidence for deficiencies in the rapid inhibition of hepatic glucose production in T2DM (63). Non-invasive 13C-NMRS studies have demonstrated that hepatic glycogen decomposition was low and gluconeogenesis was increased in patients with T2DM (58,64). In one study, specific small molecules (SR-18292) were used to increase the acetylation of the peroxisome proliferator-activated receptor gamma coactivator 1- $\alpha$  (PGC-1 $\alpha$ ). The study demonstrated that these molecules inhibited the activity of PGC-1 $\alpha$ -dependent gluconeogenesis, thereby increasing insulin sensitivity and lowering blood glucose levels in T2D mice (65).

T1DM rats were discovered to have ~90% lower insulin and leptin levels, as well as 90% higher glucagon levels in the plasma compared with control non-diabetic rats (66). Glucagon stimulates hepatic glucose production by activating enzymes involved in gluconeogenesis and glycogenolysis (60). In animal experiments, the inhibition of glucagon action prevented the metabolic disorders noted in T1DM mice (67). Another study indicated that moderately controlled patients with T1DM exhibited increased glucose production during both rest and exercise, which may account for the increased gluconeogenesis rates (68).

Increased glucose production in the liver that occurs due to enhanced gluconeogenesis is the major contributor to the high blood glucose levels observed in DM (69). Thus, inhibiting gluconeogenesis may provide the most direct route for decreasing glucose production in the liver; for example, Metformin is the most commonly used therapy for T2DM, since it decreases gluconeogenesis in the liver without increasing insulin secretion (70). However, the underlying mechanism by which metformin inhibits hepatic gluconeogenesis remains unknown. The addition of metformin to insulin therapy in T1DM is still under debate and previous findings of metformin in patients with T1DM have resulted in conflicting results (71).

*Hepatic glycolytic activity is weakened in DM.* Glycolysis is mainly regulated through glucose, insulin and glucagon (9). In addition to increasing hepatic gluconeogenic activity, the inhibition of hepatic glycolysis was found to contribute to elevated blood glucose levels; Henly *et al* (32) demonstrated that the glycolytic flux in diabetic rat hepatocytes was only 40% of that noted in normal rat hepatocytes, with a larger proportion of G6P being reconverted to glucose without glycolysis. In a human study, including 7 patients with non-insulin-dependent DM, Del Prato *et al* (48) demonstrated that glucose uptake was reduced by 54%, with both glycolysis and glucose oxidation being reduced in patients compared with control subjects. In an animal study, STZ-treated mice exhibited significant decreases in GK, phosphofructokinase (PFK1) and pyruvate kinase activity compared with those of control subjects (72).

The pyruvate produced by glycolysis is an important intermediate product in the conversion of carbohydrates to fatty acids and cholesterol (73). The hepatic abnormal regulation of pyruvate metabolism has been reported in DM and NAFLD (74). In insulin-resistant conditions, pyruvate is used for gluconeogenesis and fatty acid synthesis rather than ATP generation, which is promoted by the tricarboxylic acid (TCA) cycle, resulting in hyperglycemia and hepatic steatosis (75,76). The TCA cycle is affected by DM and the glycolytic activity

is weakened during the development of DM (77). The activation of the pyruvate dehydrogenase complex promotes the conversion of pyruvate to acetyl-CoA by oxidative decarboxylation (78). Go *et al* (76) reported that by inhibiting pyruvate dehydrogenase kinase 2, the activity of the hepatic pyruvate dehydrogenase complex was increased, ameliorating hepatic steatosis and improving insulin sensitivity through regulating the TCA cycle.

Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) is an important enzyme used to catalyze the sixth step of glycolysis, which is the step between the energy-requiring phase and the energy-releasing phase (79). GAPDH is a major target protein involved in oxidative stress (80) and it is inactivated due to the accumulation of reactive oxygen species (81). It is well known that oxidative stress serves an important role in the incidence of diabetic complications and hyperglycemia (82). Moreover, it leads to the excessive production of mitochondrial superoxide, resulting in a 66% decrease in GAPDH activity (83). The imbalance of the nicotinamide adenine dinucleotide (NADH)/NAD<sup>+</sup> redox status in DM was revealed to inhibit both GAPDH and dihydrolipoamide dehydrogenase in the pyruvate dehydrogenase complex (84) and the impairment of glycolysis led to the accumulation of glyceraldehyde 3-phosphate (G3P), as reported in microvascular and cardiovascular studies (85-87). Therefore, all intermediate products prior to G3P (including G3P) must be converted through the branch pathways of the glycolytic pathway (82,87,88). Moreover, in a previous study GAPDH inactivation resulted in a shift in metabolic flux from glycolysis to the pentose phosphate pathway (PPP) (89); however, to the best of our knowledge, no direct evidence of decreased hepatic GAPDH activity in DM has been previously reported.

In brief, hepatic glycolytic activity is weakened in both T1DM and T2DM, which can enhance hepatic glucose utilization for targeting hepatic glucose output. The alteration of mitochondrial uncoupling can also enhance glucose utilization in the liver by increasing fatty acid and glucose oxidation (90).

*Role of the PPP in the diabetic liver is not clear.* In the majority of organs, 80-90% of glucose oxidation occurs via glycolysis and the remaining 10-20% occurs via the PPP (91); the percentage of glucose metabolized by PPP varies from 5 to 30% in different tissues (92). In lipid- and steroid-synthesizing tissues, such as the liver, lactating mammary glands, white adipose tissue, adrenal glands and gonads, in addition to the erythrocytes, the PPP produces the highest proportion of glucose flux (92). PPP is usually divided into an oxidative and a nonoxidative pathway and the activity of the former is generally higher than that of the latter (93). G6P dehydrogenase (G6PD) is a rate limiting enzyme of the PPP and produces the majority of nicotinamide adenine dinucleotide phosphate (NADPH) in the cell, which is the most abundant reducing coenzyme in the cells (94). NADPH is an important cofactor involved in several enzymatic reactions in the cell, such as nitric oxide production, fatty acid synthesis/oxidation and the production of glutathione by glutathione reductase (95). In addition, NADPH is required to remove excess hydrogen peroxide from the glutathione system (94).

To the best of our knowledge, the fate of the glucose molecules that are metabolized by the PPP in the liver has not been well studied. In DM, previous findings have demonstrated that

the activity of G6PD is inhibited and the content of NADPH is reduced in the liver of T1DM rats (induced by STZ- and alloxan-treatment) (96). Similar findings have also been reported in the liver of patients with chronic DM (97). In an animal study of mild, moderate and severe hyperglycemia induced by STZ and nicotinamide treatment, it was found that the levels of hepatocyte glucose-6-phosphate dehydrogenase (G6PD) activity in mild hyperglycemia remained similar to the normal values, whereas in moderate and severely hyperglycemia, they were significantly reduced (94). The G6PD:NADPH/nicotine adenine dinucleotide phosphate (NADP<sup>+</sup>) ratio and the glutathione levels exhibited a negative correlation with the blood glucose concentration and a positive direct correlation with insulin levels (94). In addition, in T2DM obese Zucker rats, hepatic G6PD protein levels and activity were significantly higher compared with those noted in lean rats (98,99). Increased G6PD levels have also been noted in high-fat diet STZ-treated-T2D rats (100).

*Hepatic lipogenesis in NAFLD is prevalent in T2DM but not in T1DM.* The liver is the primary site of lipogenesis (101) and increased lipogenesis is the major abnormality found in NAFLD (102), while the contribution of dietary fat and blood free fatty acid production are not considerably altered (103). NAFLD is a broad term that includes net triglyceride (TG) deposition in hepatocytes caused by any factor other than ethanol intake and is defined as the presence of more than and/or equal to 5-10% of fat deposits in hepatocytes (104). The biopsy features in NAFLD include enhanced TG vacuoles, hepatocyte ballooning and necrosis, mixed inflammatory cell infiltration and fibrosis (105).

NAFLD is highly prevalent in T2DM and can also occur in T1DM (106). In children and adolescents with T1DM, NAFLD did not exhibit a significant increase in NAFLD prevalence, as determined by ultrasound screening (107); however, ultrasonography is not the best method to measure fatty liver changes (108). MRI is an accurate imaging technique used for the detection of fatty liver (109). A previous study using MRI with 128 patients with T1DM, 264 patients with T2DM and 67 participants without DM indicated that T1DM was not associated with the increase in the incidence of steatosis (110). Previous studies that used MRI to measure hepatic fat content indicated that the prevalence of NAFLD in adults (111,112) and children patients with T1DM (113) did not increase. In a time-course study of OVE26 mice (a type 1 diabetic model) Oil Red O staining and biochemical methods were used to detect the lipid content in the liver; the data indicated that uncontrolled T1DM did not cause lipid deposition in the liver, which was most likely due to the reduced lipid synthesis as a result of insulin deficiency (114). NAFLD must be distinguished from the more common glycogen hepatopathy, which is responsible for hepatomegaly and liver dysfunction in patients with T1DM (115). In a study by Cusi *et al* (112), the prevalence of NAFLD (hepatic fat content  $\geq 6\%$ ) was low in T1DM (8.8%) and high in T2DM and a higher prevalence was noted in insulin-naïve (75.6%) versus insulin-treated (61.7%) patients with T2DM.

Hepatic metabolic changes in patients with T2DM are characterized via increased liver fat content, impaired insulin clearance and hepatic insulin resistance (3,116). Insulin promotes hepatic lipogenesis and in insulin resistance states,



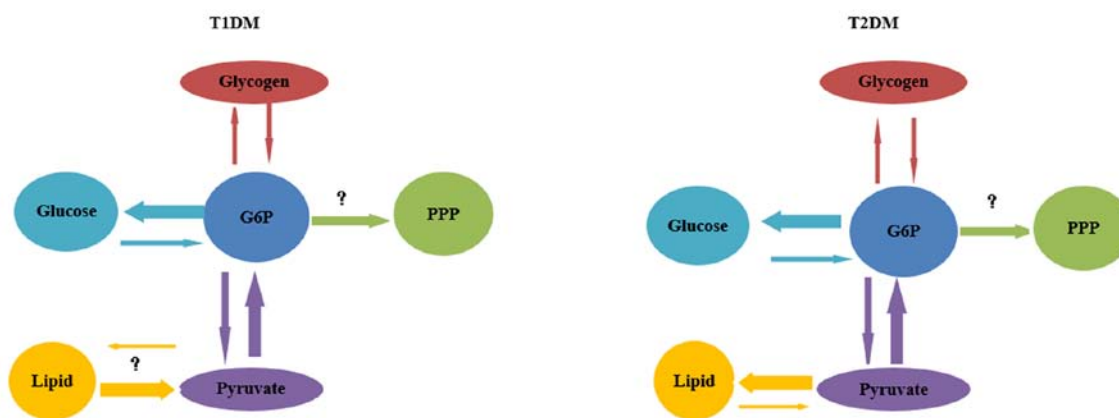


Figure 2. Changes in hepatic glucose metabolic flux in DM. Thick arrows indicate increased flux, whereas thin arrows indicate reduced flux. T1DM: In T1DM, due to the lack of insulin, glycogen synthesis and glycolysis are decreased. The loss of insulin also causes the inactivation of the paracrine regulation of glucagon, which contributes to the development of hyperglucagonemia and to an increase in gluconeogenesis, which in turn leads to hyperglycemia. The changes in hepatic lipolysis in T1DM are not clear. T2DM: Insulin resistance exists in T2DM, leading to decreased glycogen synthesis and glucose metabolism via the TCA cycle, thereby increasing lipogenesis. Moreover, gluconeogenesis flux increases as a result of hyperglucagonemia. The changes in the PPP in both T1DM and T2DM are still not clear. T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TCA, tricarboxylic acid; PPP, pentose phosphate pathway; G6P, glucose 6-phosphate; ?, unclear.

this action is maintained, whereas its ability to reduce hepatic gluconeogenesis is reported to be impaired (103,117). The production of glucose from non-carbohydrate sources was increased in patients with NAFLD, a phenomenon known as selective insulin resistance (103). This is one explanation for the occurrence of NAFLD in T2DM, whereas another hypothesis is that NAFLD may develop independently of insulin in the liver. Vatner *et al* (118) reported that in T2DM, the main source of hepatic lipid synthesis was the esterification of preformed fatty acids, which was mainly dependent on the transport of substrates and was largely independent of hepatic insulin action. These findings demonstrated that plasma was the main source of TG synthesis in T2DM albeit the role of insulin in fatty acid esterification (if any) was not clear (119).

Increased liver fat has been discovered to be associated with decreased insulin clearance and sensitivity in patients with T2DM (116,120), whereas in T1DM, which is characterized by decreased insulin secretion, the lipid synthesis in patients with T1DM was reduced (11,114,121). T1DM is characterized by insufficient insulin secretion and excessive glucagon production (2) and the mechanism of NAFLD in T1DM may be complicated; Regnell and Lernmark (122) proposed three hypotheses to explain the occurrence of hepatic steatosis in patients with T1DM. In the present review, two possible reasons are highlighted: Initially, the establishment of insulin therapy was found to promote lipogenesis (113) and weight gain in patients with T1DM (123) and secondly, the increased presence of hepatic lipids may be associated with hyperglycemia that directly influence insulin and glucagon secretion (122). Abnormal autophagy may also have an important role in aggravating lipid metabolic disorders contributing to steatohepatitis in diabetes; Singh *et al* (124) demonstrated that the inhibition of autophagy in cultured hepatocytes and in mouse liver tissues increased TG storage in lipid droplets.

In brief, hyperglycemia in both T1DM and T2DM may be explained by increased G/G6P cycling or by increased flux through the gluconeogenesis pathway. Reduced flux of glycolysis and glycogenolysis may also explain the inefficiency

of acute regulation of hypoglycemia in fasting and of hyperglycemia following a meal (Fig. 2).

### 3. Conclusion

In the current review, the findings suggested that the dysregulation of hepatic glucose and lipid metabolism may be the primary factor underlying the pathogenesis of T2DM and T1DM. These two chronic diseases affect the body's ability to regulate glucose and result in different hepatic pathological conditions. Overall, it is evident that the liver is crucial for systemic glucose homeostasis and that the disorders of glucose metabolism may contribute to the initiation, progression and exacerbation of DM; however, there are still several unanswered questions and gaps in our knowledge that must be addressed in the future.

### Acknowledgements

Not applicable.

### Funding

The present work was supported in part by grants from the Basic Scientific Research Projects of Wenzhou Municipal Science and Technology Bureau (CN) (grant no. Y20180253 to SZJ), NIEHS (T32-ES011564 to JY) and China-U.S. University of Louisville Paediatric Research Exchange Training Program. Personnel expenses and partial research-related expenses for Dr Saizhi Jiang and Dr Kai Wang were provided by the First Affiliated Hospital of the Wenzhou Medical University through a collaborative research agreement between the University of Louisville and the First Affiliated Hospital of the Wenzhou Medical University, Wenzhou, China.

### Availability of data and materials

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

## Authors' contributions

SJ, LC, JLY, KW and YQ conceived and designed the present study. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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