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REVIEW

Renal gluconeogenesis in insulin resistance: A culprit for hyperglycemia in diabetes

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Abstract

Renal gluconeogenesis is one of the major pathways for endogenous glucose production. Impairment in this process may contribute to hyperglycemia in cases with insulin resistance and diabetes. We reviewed pertinent studies to elucidate the role of renal gluconeogenesis regulation in insulin resistance and diabetes. A consensus on the suppressive effect of insulin on kidney gluconeogenesis has started to build up. Insulin-resistant models exhibit reduced insulin receptor (IR) expression and/or post-receptor signaling in their kidney tissue. Reduced IR expression or post-receptor signaling can cause impairment in insulin's action on kidneys, which may increase renal gluconeogenesis in the state of insulin resistance. It is now established that the kidney contributes up to 20% of all glucose production *via* gluconeogenesis in the post-absorptive phase. However, the rate of renal glucose release excessively increases in diabetes. The rise in renal glucose release in diabetes may contribute to fasting hyperglycemia and increased postprandial glucose levels. Enhanced glucose release by the kidneys and renal expression of the gluconeogenic-enzyme in diabetic rodents and humans further point towards the significance of renal gluconeogenesis. Overall, the available literature suggests that impairment in renal gluconeogenesis in an insulin-resistant state may contribute to hyperglycemia in type 2 diabetes.

Key Words: Renal gluconeogenesis; Insulin-resistance; Insulin; Insulin receptor signaling; Diabetes; Gluconeogenic enzymes

Core Tip: Recently, investigators have begun elucidating the role of renal gluconeogenesis in physiology and pathology. Recent evidence suggests a significant role of the kidney in glucose metabolism under pathological conditions, such as insulin resistance

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and diabetes. This review summarizes the findings from the literature that have enhanced our knowledge related to the significance of renal gluconeogenesis in normal and pathological states.

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INTRODUCTION

Gluconeogenesis is the process of glucose production by non-carbohydrate carbon substrates. During the process, glucose-6-phosphate is produced from precursors, like lactate, glycerol, and amino acids, with subsequent hydrolysis by glucose-6-phosphatase (G6Pase) to glucose. Previously, kidney was not considered to significantly contribute to the overall glucose release[1], however, re-evaluation using the net balance techniques suggested up to 20% contribution to overall glucose production[2]. The rate of renal gluconeogenesis varies in response to physiological activities, such as fasting, postprandial, exercise, stress, and pathological stimuli, like diabetes and insulin sensitivity[3-5].

The liver, kidney, and intestine are the three tissues that express the key gluconeogenic enzymes, including phosphoenolpyruvate carboxykinase (PEPCK), fructose-1,6-bisphosphatase (FBPase), and G6Pase. G6Pase helps in the final release of glucose into the circulation by dephosphorylating glucose-6-phosphate. PEPCK is involved in the phosphorylation of oxaloacetic acid and FBPase dephosphorylates fructose-1,6 bisphosphate to fructose-6-phosphate.The activity of these enzymes is regulated by insulin. Besides, insulin also regulates the other rate-limiting step, like the availability of gluconeogenesis substrates[6-8]. Renal gluconeogenesis is more sensitive to insulin activity than hepatic gluconeogenesis[3]. Impaired insulin action due to inefficient receptor expression/signaling may blunt insulin's suppressive effect on gluconeogenesis. It could contribute to hyperglycemia as seen in insulin-resistant and diabetic rat models and humans[9-15]. Patients with type-2 diabetes mellitus exhibit an increase of about 300% in glucose production[16,17]. Glucose-induced glucose release by the kidneys may potentially contribute to postprandial hyperglycemia in diabetic patients[3].Renal gluconeogenesis contributes to normal glucose levels in the post-absorptive state and plays a key role in postprandial hyperglycemia in diabetic patients[5].

GLUCOSE PRODUCTION AND UTILIZATION BY THE KIDNEYS

The kidneys' substantial contribution to systemic glucose levels *via* gluconeogenesis has now been recognized[18-20]. The first evidence of glucose release by the kidneys emerged in 1938 when Bergman *et al*[21] reported doubled glucose utilization in the hepatectomized animals along with nephrectomy. Several studies confirmed that renal cortex can produce glucose from non-carbohydrate precursors[9,22-25]. The primary sources for renal glucose production involve lactate from cellular respiration, glutamine from protein, and glycerol from triglyceride breakdown[26]. Other than the *in vitro* studies, incorporating these precursors into glucose by the human kidney has also been quantitated[27,28]. Studies using the isotopic approach in human subjects suggested lactate to be the most important renal gluconeogenic substrate, followed by glutamine and glycerol[3,28,29]. Several studies have suggested kidney's role in maintaining glucose homeostasis through gluconeogenesis[18,19,26]. Early human studies using a combination of net renal glucose balance and isotopic measurements have demonstrated that the kidney releases significant amount of glucose in post-absorptive state[30]. The kidney was once thought to contribute mainly to whole-body glucose production only during acidosis or prolonged starvation[6,18,26]. The role and contribution of the glucose production by the kidney in other physiological and pathological conditions have emerged[18,31]. The kidney accounts for 10% systemic gluconeogenesis in the absorptive phase; the rate rises to as much as 25% in the post-

absorptive phase[32]. Moreover, in the case of prolonged fasting, the kidney prevents and reverses hypoglycemia by a counter-regulatory process of increased gluconeogenesis and inhibition of glucose uptake[33]. Besides such adaptive changes, impaired renal insulin signaling/sensitivity affects renal gluconeogenesis[15]. Improving renal insulin sensitivity may reduce systemic glucose levels *via* gluconeogenesis inhibition [34]. In the postprandial state, the renal glucose release accounts for approximately 50% of the endogenous glucose release for several hours. These observations suggested that increased renal glucose release may play an important role in facilitating efficient liver glycogen repletion by permitting substantial suppression of hepatic glucose release. Hormones (notably insulin and catecholamines), substrates, enzymes, and glucose transporters are some of the other factors which affect glucose production by the kidney[31,35-39].

The kidney differentially regulates glucose levels in the medulla and the cortex, with glucose utilization in the renal medulla and glucose production in the kidney cortex[19]. The separation of these processes is based on the differences in the distribution of various enzymes. The nephrons present in the renal medulla have glucose-phosphorylating and glycolytic enzymes; thus, they are involved in the phosphorylation and accumulation of glycogen. However, these cells lack gluconeogenic enzymes, and therefore, cannot synthesize or release free glucose into the circulation. On the other hand, renal cortex cells, more precisely the proximal tubule cells, possess gluconeogenic enzymes, and can produce and release glucose[26,40]. Therefore, the net equilibrium of glucose in the kidney is represented by the difference between renal glucose release by the cortex and renal glucose uptake by the medulla (Figure 1).

LOCALIZATION AND REGULATION OF KEY GLUCONEOGENIC ENZYMES IN THE KIDNEYS

PEPCK, FBPase, G6Pase, and pyruvate carboxylase catalyze the irreversible steps in gluconeogenesis. All these key enzymes are exclusively expressed in the S1–S3 segments of the proximal tubule[41-43]. PEPCK enzymes exist in two isoforms: cytosolic and mitochondrial. These enzymes are encoded by the two nuclear genes. According to human data, 60% of PEPCK is confined to mitochondria, while 40% to cytosol[44]. The cytoplasmic form is regulated at the transcriptional level by nutritional and hormonal stimuli, whereas the expression of mitochondrial form remains constitutive[45] (Figure 2). These three key enzymes are rate-limiting and, under metabolic alterations, PEPCK has been most extensively reported to be regulated. For example, in acidotic conditions, the expression and the activity of renal PEPCK have been found to be upregulated, while G6Pase and FBPase were marginally regulated[15,23,46]. Similarly, under insulin resistance conditions, PEPCK expression increased significantly compared to the levels of FBPase and G6Pase[12,15]. Further, the PEPCK/PCK1 activity in the kidney and the liver of diabetic patients correlates with the levels of PCK1 mRNA, with PEPCK and G6P being regulated at the post-transcriptional level, while FBP being regulated at the pre-or the post-translational level[8,47,48]. PEPCK and G6Pase have been shown to be transcriptionally regulated by a complex network of transcription factors and cofactors, including CREB, HNF-4α, and FOXO1[49].

RENAL GLUCONEOGENESIS IN THE POST ABSORPTIVE AND POSTPRANDIAL STATE

As discussed in the above sections, kidneys contribute significantly towards the total endogenous glucose production in normal physiological conditions, including fasting and postprandial states[26,50]. After an overnight fast, 75% of glucose entering the circulation is released by the liver, and the remaining 25% is released by the kidney[19,32,51].After a prolonged fast of 48 h, liver glycogen stores are depleted, and renal gluconeogenesis becomes the major source of glucose that is released into the circulation[51,52].Thus, as the duration of fasting increases, the overall proportion of glucose released *via* renal gluconeogenesis increases[53]. A few studies based on glucose release and glucose uptake by metabolic tissues suggest that the postprandial phase is also important in regulating glucose homeostasis. For example, a 61% decrease in overall glucose release *via* hepatic glycogenolysis was reported previously

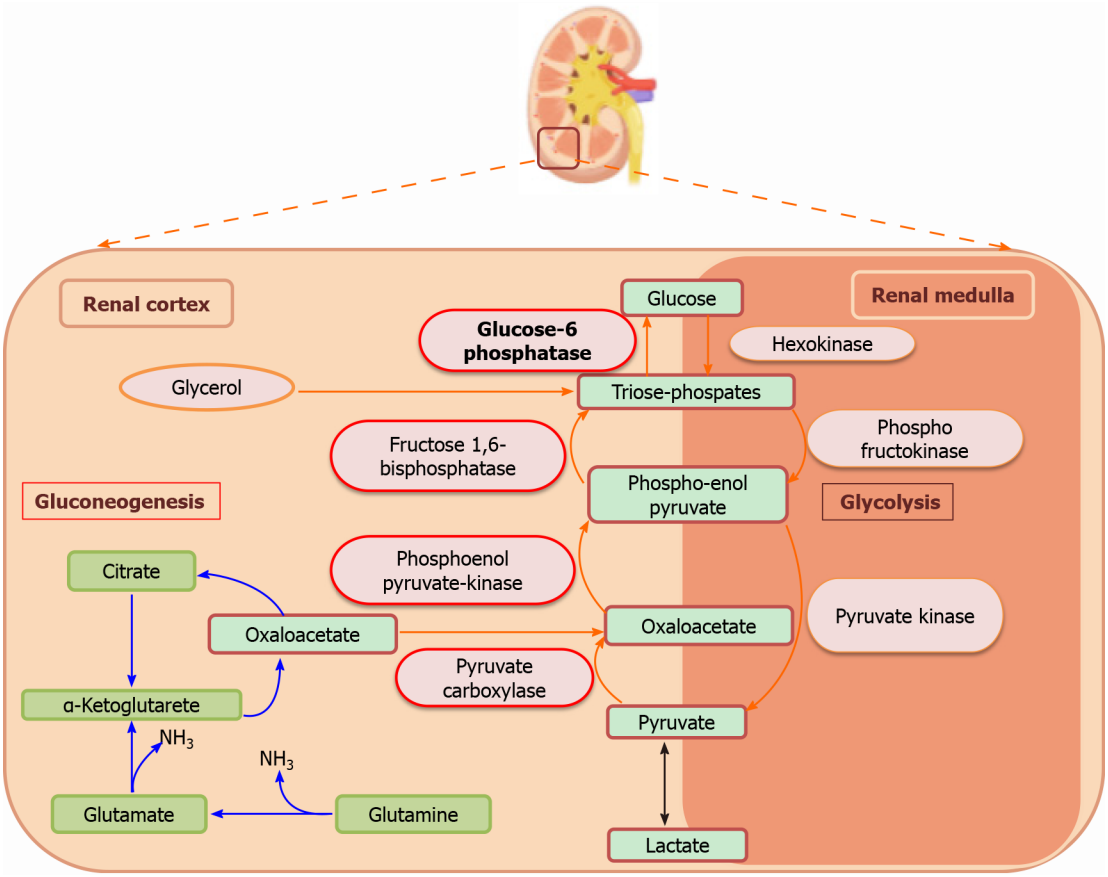

Figure 1 Schematic overview of renal gluconeogenesis and glycolysis pathway and enzyme localization. The key enzymes of gluconeogenesis (1) pyruvate carboxylase; (2) phosphoenolpyruvate carboxykinase; (3) fructose-1,6-biphosphatase; and (4) glucose 6-phosphatase are predominantly localized in the renal cortical cells whereas, the glycolytic key enzymes (1) hexokinase; (2) phosphofructokinase; and (3) pyruvate kinase are found in the renal medulla.

in a human study, virtually ceasing in 4 to 6 h[54]. This finding was attributed to the need for replenishing the liver glycogen stores and to limit postprandial hyperglycemia. Moreover, unlike the liver, renal gluconeogenesis increases by approximately two-folds and accounts for 60% of endogenous glucose release in the postprandial phase[54]. The tight hormonal regulation helps maintain a homeostasis between the renal glucose release and uptake. Postprandial plasma glucose levels are majorly regulated by insulin and glucagon levels[32]. In another study, a four-fold increase in insulin and up to 50% decrease in plasma glucagon levels were observed after glucose ingestion in humans[55,56]. This process of mutual-regulation of glucose homeostasis is termed as hepatorenal glucose reciprocity. The term can be defined as a physiological or pathological decrease in glucose release by either one of the tissues-kidney or liver- with a linear increase in glucose release by the other[5]. Such situation is encountered during anhepatic phase post-liver transplantation, prolonged fasting, acidosis, meal ingestion, and insulin overdoses in diabetes mellitus[5,57,58].

INSULIN-MEDIATED REGULATION OF RENAL GLUCONEOGENESIS

Insulin has been demonstrated to attenuate enhanced renal gluconeogenesis in rodent models of type 1 diabetes[59,60-66]. Insulin is a known suppressor of gluconeogenesis in both, liver and kidney; however, kidneys are more sensitive to the suppressive effects of insulin[67]. Using the combined isotopic and net balance approach, insulin was shown to suppress renal glucose release and stimulated renal glucose uptake by 75% in conscious dogs[28]. A human study also showed that administration of insulin inhibitor increased renal glucose production in type 1 diabetic patients[19]. At molecular levels, insulin has been demonstrated to reduce the mRNA expressions of PCK1 and G6P[59]. This inhibitory effect is mediated through phosphorylation of FOXO1 *via* the IRS/Pi3k/Akt/FOXO1 pathway[59,68].Insulin inhibits the availability of gluconeogenic substrates or redirect the substrates to the oxidative pathways

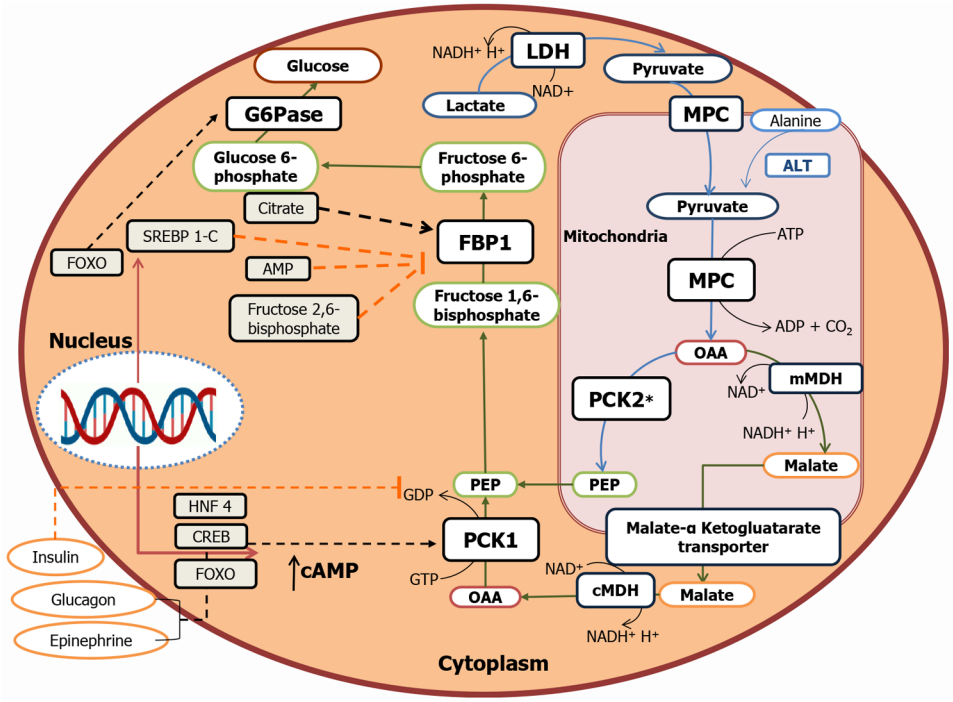

Figure 2 Gluconeogenesis Pathway and cellular compartmentalization of the gluconeogenic enzymes. Pyruvate from lactate enters mitochondria by mitochondrial pyruvate transporter. Pyruvate provided by alanine transamination or lactate dehydrogenation is converted to oxaloacetate (OAA) by mitochondrial pyruvate carboxylase. OAA is either reduced to malate and exported out in the cytoplasm by malate ketoglutarate transporter or directly converted to phosphoenolpyruvate (PEP) by phosphoenolpyruvate carboxykinase (PCK) 2 (mitochondrial isoform) and exported out in the cytoplasm. In the cytoplasm, malate is first oxidized to OAA and then converted to PEP by PCK1 (cytoplasmic isoform). Fructose-1,6-bisphosphate (FBP) is then converted to fructose-6-phosphate by cytoplasmic FBP1. Glucose-6-phosphatase in the cytoplasm ultimately dephosphorylates glucose-6-phosphate to release glucose. G6Pase: Glucose-6-phosphatase; LDH: Lactate dehydrogenase; MPC: Mitochondrial pyruvate carrier; ALT: Alanine aminotransferase; FBP: Fructose-1,6-bisphosphate; OAA: Oxaloacetate; PCK: Phosphoenolpyruvate carboxykinase; PEP: Phosphoenolpyruvate; mMDH: Malate dehydrogenase; cAMP: Cyclic adenosine monophosphate.

[6,26,28]. Moreover, it indirectly affects glucose release *via* reduction of free fatty acid uptake[6,69,70]. A few reports have documented an inhibitory effect of insulin on renal gluconeogenesis through the substrates glycerol and glutamine in the post-absorptive state in humans[6,28]. However, regulation of renal gluconeogenesis by insulin, glucagon, and epinephrine is not widely studied in humans[6,71,72].

In the liver, the role of insulin or insulin receptor (IR) signaling in transcriptional regulation of gluconeogenic genes, that is, PCK1 and G6PC, is well known[73,74]. However, only a handful of studies have investigated the role of insulin *via* IR signaling in renal gluconeogenesis regulation. DeFronzo*et al*[75] reported the inhibitory effect of insulin on renal gluconeogenesis. Previously, we demonstrated high blood glucose and renal gluconeogenic-enzyme upregulation in mice with targeted deletion of IRs from the proximal tubule[13,59]. These IR knock-out (IRKO) mice exhibited normal insulin sensitivity, throughout their bodies. Additionally, increased activity and elevated mRNA expression of G6Pase observed in the IRKO mice indicates the role of the IR in regulating renal gluconeogenesis. In another study, reduced IR expression with a concomitant increase in PEPCK levels were reported in the kidney cortex of mice with high-fat-induced insulin resistance[76].In addition, *in vitro* studies in primary human proximal tubule (PT)cells also revealed insulin's inhibitory action on cAMP/DEXA-induced gluconeogenesis, while silencing of the IR attenuated this inhibitory effect[65] (Figure 3). Further down the signaling mechanism, Nakamura *et al*[77] demonstrated that, unlike the liver, insulin-induced inhibition of proximal tubule gluconeogenesis inhibition might be mediated *via* the IRS1/Akt2/mTORC1/2 pathway. In another study, IRS2 (IRS2–/–) knockdown has been shown to result in elevated blood glucose levels in mice[78].However, the post-receptor signaling mechanism for insulin-induced inhibition of renal gluconeogenesis is not yet clear. Nevertheless, these studies indicate the significance of IR signaling in renal gluconeogenesis and suggest that defect in IR signaling to the kidneys may contribute to hyperglycemia in insulin resistance state[9-13,79].

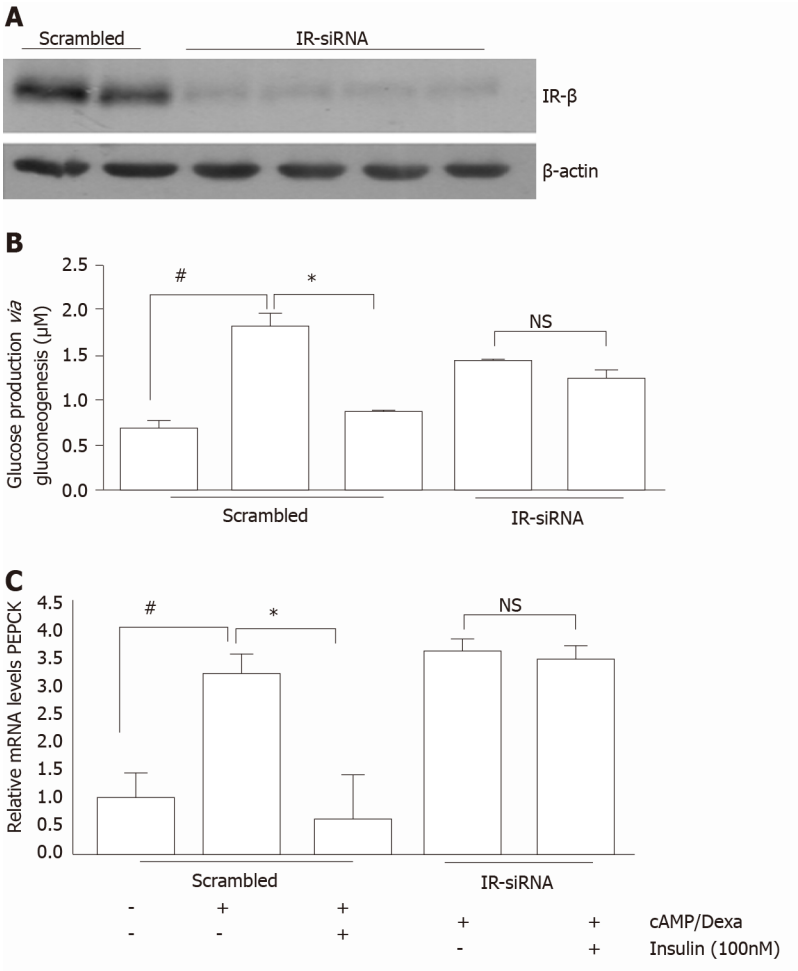

Figure 3 siRNA mediated knockdown of insulin receptor in the human proximal tubule cells increased glucose production *via* gluconeogenesis stimulation. A: Western blot showing reduced insulin receptor insulin receptor (IR) expression in IR-siRNA treated human proximal tubule (hPT) cells relative to scrambled; B:cAMP/Dexa induced gluconeogenesis/glucose production in the hPT cell culture media; and C: Relative phosphoenolpyruvate carboxykinase mRNA transcript levels in scrambled and IR-siRNA treated hPT cells with or without insulin treatment. "Citation: Pandey G, Shankar K, Makhija E, Gaikwad A, Ecelbarger C, Mandhani A, Srivastava A, Tiwari S. Reduced Insulin Receptor Expression Enhances Proximal Tubule Gluconeogenesis. *J Cell Biochem* 2017; 118: 276-285 [PMID: 27322100 DOI: 10.1002/jcb.25632] Copyright © The Author(s) 2017. Published by John/Wiley & Sons, Inc[65]"

RENAL GLUCONEOGENESIS IN CASES OF INSULIN RESISTANCE AND DIABETES

Insulin resistance refers to inefficient sensitivity of primary metabolic tissues towards insulin and is characterized by a reduced insulin action despite hyperinsulinemia [80-82]. Like the other metabolic tissues, kidneys also lose their insulin sensitivity during insulin resistance[14,61,83].The mechanism of insulin resistance is different among different organs and even cells of the same organ. For example, in case of insulin resistance, IRS2 signaling is impaired in liver too. However, in the renal proximal tubules, insulin signaling *via* IRS1 is impaired; however, the signaling *via* IRS2 is preserved[84-87].

Insulin resistance has frequently been associated with renal abnormalities, such as impaired glucose metabolism[12,79,88]. These studies suggest that impairment of the expression or post-receptor signaling of the IR can enhance renal gluconeogenesis in the diabetic patients. A wide distribution of IR throughout the nephron segments and their reduced expression in renal epithelial cells in insulin resistance models have been reported[14].We and others have demonstrated reduced expression of IR and its phosphorylated form in the kidney cortex of diabetic rodents and humans [14,61,65,89]. In a previous study, newly diagnosed cases of type-2 diabetes were reported to exhibit impaired insulin-induced suppression of gluconeogenesis [9,11,79]. Our recent study also suggested impairment in meal-induced inhibition of renal PEPCK in individuals with reduced insulin sensitivity[15].Thus, insulin resistance might be responsible for high levels of gluconeogenic enzymes found in

renal biopsies from T2D human and rodent models[61,65,90].

Nevertheless, impaired IR signaling to the kidneys also affects kidneys' vital functions, including the endogenous glucose production by the kidneys[13,91-93]. We previously reported altered systemic glucose metabolism in IRKO mice, which further strengthens this proposition[13].Thus, similar to the liver, insulin resistance could impair renal gluconeogenesis in diabetes patients[14,61]. Previous studies on diabetic animal models have reported increased renal gluconeogenic enzyme activity and glucose release[48,94-98]. In 1999, Meyer reported significantly higher systemic glucose levels in diabetic patients compared to normal subjects, of which 40% of glucose content was contributed by renal glucose release[16]. Another *in vitro* study conducted by Eid *et al*[12], for the very first time, reported increased gluconeogenesis in the proximal tubules of obese Zucker rats. Another *in vivo* study reported an intrinsic increase in renal gluconeogenesis and increased PEPCK mRNA levels in type 2 diabetic model[12,61,83,99].The other key enzymes, FBPase and G6Pase, were, however, marginally regulated[12] (Figure 4). Moreover, recent rodent model studies conducted by us and others also indicated the significant role of renal gluconeogenesis in fasting hyperglycemia[13,15,59,65]. Furthermore, increased renal gluconeogenesis contributed to increased level of fasting glucose in T2DM patients and raised postprandial glucose. Furthermore, many human studies also reported an increase in the release of glucose by the kidney in the fasting state in T2DM patients[100-104], which might be attributed to gluconeogenesis[105].Additionally, abnormal postprandial glucose metabolism has also been reported in T2DM patients[16]. In this study, dual-isotope and net balance measurement across kidney, liver, and skeletal muscles revealed an impaired suppression of gluconeogenesis by kidney and liver, leading to increased levels of postprandial glucose. The other possible reasons for this postprandial increase in glucose levels in type 2 diabetic condition include persistently increased glucose levels in the post-absorptive state[106],high levels of free fatty acids, and increased substrate availability[54,61,105,107,108].

CLINICAL MANAGEMENT

Insulin resistance is a known risk factor for developing pre-diabetes, and eventually, type-2 diabetes. Insulin resistance at the kidney level could further contribute to hyperglycemia by enhancing renal gluconeogenesis. Thus, improving insulin sensitivity *via* lifestyle modifications, such as dieting and physical activity, could be a preventive strategy for pre-diabetes and improving glycemic levels in diabetes patients. Two classes of drugs, biguanides and thiazolidinediones, are available commercially for improving insulin sensitivity. In clinical practice, both these agents are in common use for glucose-lowering in patients with type-2 diabetes[26,109,110]. By enhancing renal insulin sensitivity, these agents exhibit great potential in regulation of renal function in T2DM patients[111,112]. Apart from the known insulin sensitizers, SGLT2 inhibitors are emerging as another promising anti-hyperglycemic agent. They induce glucosuria by inhibiting glucose reabsorption in the renal proximal tubules[113]. Inhibition of renal glucose reabsorption and induction of glucosuria by these agents are considered to be effective and safe in patients with T2DM. Moreover, their insulin-independent action lowers hypoglycemia risk commonly associated with other anti-diabetic drugs[26].

Interestingly, SGLT2 inhibitors have been postulated to act by modulating insulin sensitivity and/or renoprotective actions in T2DM patients[114]. Dapagliflozin, an SGLT2 inhibitor, has been shown to improve renal function and renal insulin signaling in an animal model of diet-induced obesity[115]. Dapagliflozin, either as monotherapy or add-on therapy to insulin or metformin, was found to reduce glucose and HbA1c levels in T2DM in clinical trials[116]. Also, dapagliflozin or empagliflozin, along with insulin therapy, imparts clinical benefits in patients with type-1 diabetes[117,118]. However, more studies are warranted to confirm their therapeutic potential as an adjunct therapy.

CONCLUSION

Renal gluconeogenesis plays a key role in normal physiology, where its impairment contributes adversely with pathological implications. Overall, this review suggested enhancement or insulin-mediated impairment of renal gluconeogenesis in cases of insulin resistance. Such impairment may further contribute to hyperglycemia in type-2

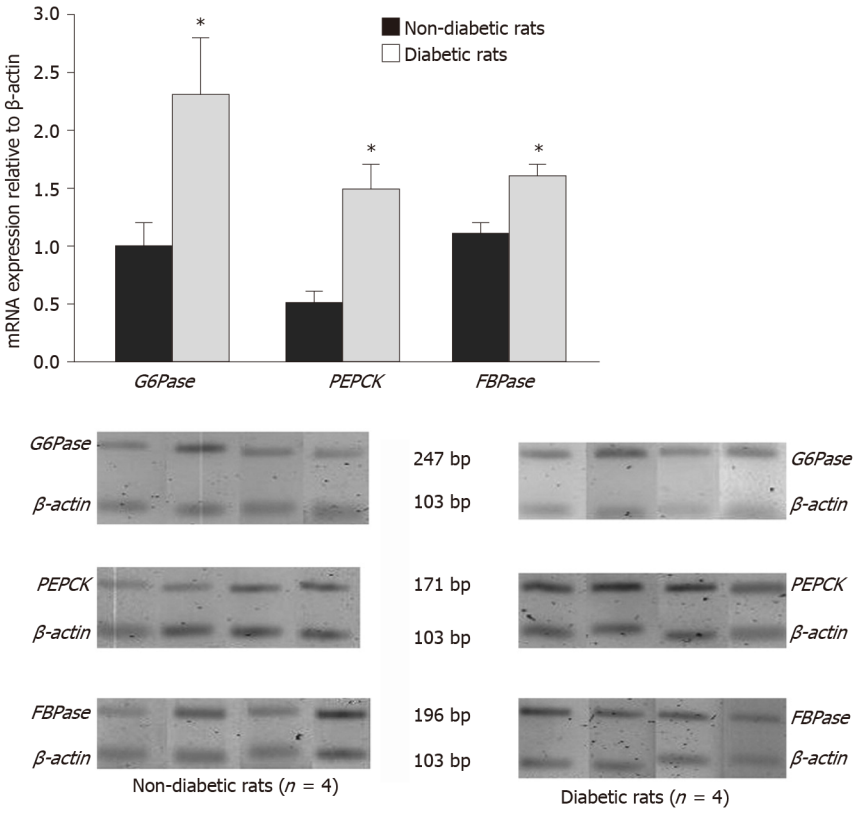

Figure 4 mRNA and protein levels of glucose-6-phosphatase, phosphoenolpyruvate carboxykinase, and fructose-1,6-bisphosphatase in diabetic rats and their non-diabetic controls. "Citation: Eid A, Bodin S, Ferrier B, Delage H, Boghossian M, Martin M, Baverel G, Conjard A. Intrinsic gluconeogenesis is enhanced in renal proximal tubules of Zucker diabetic fatty rats. *J Am SocNephrol* 2006; 17: 398-405 [PMID: 16396963 DOI: 10.1681/asn.2005070742] Copyright © The Author(s) 2006. Published by the American Society of Nephrology Inc[12]"

diabetes. However, more research is warranted in this area to further elucidate the associated mechanism.

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