## Contents

**WORLD JOURNAL OF DIABETES**

**Monthly Volume 12 Number 5 May 15, 2021**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>514</td>
<td>Euglycemic diabetic ketoacidosis: A missed diagnosis</td>
<td>Nasa P, Chaudhary S, Shrivastava PK, Singh A</td>
</tr>
<tr>
<td>524</td>
<td>New insights into renal lipid dysmetabolism in diabetic kidney disease</td>
<td>Mitrofanova A, Burke G, Merscher S, Fornoni A</td>
</tr>
<tr>
<td>541</td>
<td>Recent advances in new-onset diabetes mellitus after kidney transplantation</td>
<td>Montada-Atin T, Prasad GVR</td>
</tr>
<tr>
<td>556</td>
<td>Renal gluconeogenesis in insulin resistance: A culprit for hyperglycemia in diabetes</td>
<td>Sharma R, Tiwari S</td>
</tr>
<tr>
<td>569</td>
<td>Fear of hypoglycemia, a game changer during physical activity in type 1 diabetes mellitus patients</td>
<td>Cigrovski Berkovic M, Bilic-Curcic I, La Grasta Sabolic L, Mrzljak A, Cigrovski V</td>
</tr>
<tr>
<td>578</td>
<td>Chronic care model in the diabetes pay-for-performance program in Taiwan: Benefits, challenges and future directions</td>
<td>Chen TT, Oldenburg B, Hsueh YS</td>
</tr>
<tr>
<td>590</td>
<td>Advanced-glycation end-products axis: A contributor to the risk of severe illness from COVID-19 in diabetes patients</td>
<td>Rojas A, Lindner C, González I, Morales MA</td>
</tr>
<tr>
<td>603</td>
<td>Current advances in using tolerogenic dendritic cells as a therapeutic alternative in the treatment of type 1 diabetes</td>
<td>Rios-Rios WJ, Sosa-Luis SA, Torres-Aguilar H</td>
</tr>
<tr>
<td>616</td>
<td>Role of insulin and insulin resistance in androgen excess disorders</td>
<td>Unluhizarci K, Karaca Z, Kelestimur F</td>
</tr>
<tr>
<td>630</td>
<td>Impact of spiritual beliefs and faith-based interventions on diabetes management</td>
<td>Onyishi CN, Ilechukwu LC, Victor-Aigbodion V, Eseadi C</td>
</tr>
<tr>
<td>642</td>
<td>COVID-19 and hyperglycemia/diabetes</td>
<td>Michalakis K, Ilias I</td>
</tr>
</tbody>
</table>
FINAL ARTICLE

Basic Study

658 Diabetes-related intestinal region-specific thickening of ganglionic basement membrane and regionally decreased matrix metalloproteinase 9 expression in myenteric ganglia


Observational Study

673 Relationships between emissions of toxic airborne molecules and type 1 diabetes incidence in children: An ecologic study

Di Ciaula A, Portincasa P
ABOUT COVER
Editorial Board Member of World Journal of Diabetes, Fernando Cordido, MD, PhD, Full Professor, Department of Medicine, University A Coruña, A Coruña 15006, Spain. Cordido.Carballido@sergas.es

AIMS AND SCOPE
The primary aim of World Journal of Diabetes (WJD, World J Diabetes) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

INDEXING/ABSTRACTING
The WJD is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for WJD as 3.247; IF without journal self cites: 3.222; Ranking: 70 among 143 journals in endocrinology and metabolism; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE
Production Editor: Ya-Jie Ma; Production Department Director: Xiang Li; Editorial Office Director: Jia-Ping Yan.

NAME OF JOURNAL
World Journal of Diabetes

ISSN
ISSN 1948-9358 (online)

LAUNCH DATE
June 15, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Timothy Koch

EDITORIAL BOARD MEMBERS

PUBLICATION DATE
May 15, 2021

COPYRIGHT
© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/gerinfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2021 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com  https://www.wjgnet.com
Renal gluconeogenesis in insulin resistance: A culprit for hyperglycemia in diabetes

Rajni Sharma, Swasti Tiwari

ORCID number: Rajni Sharma 0000-0002-3966-8003; Swasti Tiwari 0000-0002-1701-2636.

Author contributions: Sharma R and Tiwari S contributed to the conception of the review; Sharma R performed the literature search and drafted the manuscript; Tiwari S and Sharma R performed the editing and proofreading of the manuscript; both authors approved the final version of the manuscript for submission.

Supported by: The Indian Council of Medical Research, No. 55/4/4/CARE-KD/2018/NCD-II; and the Council of Scientific & Industrial Research, No. 09/590/(0159)/2016-EMR-I.

Conflict-of-interest statement: Authors declare no conflicts of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the

Rajni Sharma, Swasti Tiwari, Department of Molecular Medicine and Biotechnology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226014, India

Corresponding author: Swasti Tiwari, PhD, Professor, Department of Molecular Medicine and Biotechnology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, 4th Floor, PMMSY Building, Lucknow 226014, India. tiwaris@sgpgi.ac.in

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

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

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.
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.

**Citation:** Sharma R, Tiwari S. Renal gluconeogenesis in insulin resistance: A culprit for hyperglycemia in diabetes. *World J Diabetes* 2021; 12(5): 556-568


**DOI:** https://dx.doi.org/10.4239/wjd.v12.i5.556

**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 patients. Patients with type-2 diabetes mellitus exhibit an increase of about 300% in glucose production[9-15]. The primary sources for renal glucose production involve lactate from cellular respiration, glutamine from protein, and glycerol from triglyceride breakdown[16]. 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 have shown lactate to be the most important renal gluconeogenic substrate, followed by glutamine and glycerol[3,25,29]. 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].

**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 hepatectomy 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 have shown lactate to be the most important renal gluconeogenic substrate, followed by glutamine and glycerol[3,25,29]. 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[5,47,48]. 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].

RENNAL 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
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 GLUCONEGENESIS**

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
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.

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 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 another study, 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].
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 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[12,61,85,99]. 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
diabetes. However, more research is warranted in this area to further elucidate the associated mechanism.

ACKNOWLEDGMENTS

We would like to thank Mr. Shashank Mathur for helping with the Figures 1 and 2. We would also like to thank Dr. Maurice B Fluitt (Assistant Professor, Endocrinology and Metabolism, Department of Medicine, Howard University College of Medicine, Washington, DC, United States) and Dr. Kath Clark (Lecturer, Biological Sciences, Department of Molecular and Cell Biology, University of Leicester, University Road, Leicester, LE1 7RH, United Kingdom) for proofreading the manuscript.

REFERENCES


Sharma R et al. Renal gluconeogenesis in metabolic syndrome

10.1152/ajpregu.1998.275.6.F915


Renal gluconeogenesis in metabolic syndrome

Sharma R et al. WJD 2020; 73: 693-705

48: e219 [PMID: 26964835 DOI: 10.1038/emm.2016.6]


Hashimoto S, Maoka T, Kawata T, Mochizuki T, Koike T, Shigematsu T. Roles of Insulin Receptor

79  

80  

81  

82  

83  

84  

85  

86  

87  

88  

89  

90  

91  

92  

93  

94  

95  

96  

97  

98  


Williamson JR. Mechanism for the stimulation in vivo of hepatic gluconeogenesis by glucose. Biochem J 1966; 101: 11C-14C [PMID: 4291353 DOI: 10.1042/bj0101011c]


