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Mini Review

Glucose Homeostasis - what Role does the Human Kidney Play?

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Abstract

Glucose homeostasis is the result of the supply of glucose to blood and its consumption in cells. In the postprandial period, circulation requires a constant supply of glucose, which is an essential source of energy for tissues such as brain cells. Only the liver and kidneys can supply glucose to the circulation through the gluconeogenesis process, which involves de novo glucose synthesis from non-glucose substrates; and through glycogenolysis, i.e., the breakdown of stored glycogen. The kidneys play an important role in maintaining glucose homeostasis. The main mechanisms by which the kidneys are involved in maintaining glucose homeostasis are gluconeogenesis, renal glucose consumption, and glucose reabsorption in proximal tubules. The glucose reabsorption system in the kidney is mediated by two Sodium-Dependent Glucose Cotransporters (SGLTs). Cotransporter SGLT 1, is situated in the S3 segment, and SGLT 2 is situated in the S1 segment.

Keywords: Glucose homeostasis; Endogenous glucose production; Gluconeogenesis; Glycogenolysis; Glucose reabsorption; Sodium-dependent glucose cotransporters (SGLTs); SGLT 2 Cotransporter inhibitors

Introduction

Glucose homeostasis is the result of the supply of glucose to blood and its consumption in cells. For circulation, glucose is supplied from the digestive tract, and is also produced in the body in the process of gluconeogenesis. Glucose that enters the body with food is partly metabolized in the process of glycolysis to cover the current needs of the body. It is partly stored in the form of glycogen in the liver and muscles (glycogenesis). In the postprandial period, circulation requires a constant supply of glucose, which is an essential source of energy for tissues such as brain cells. Only the liver and kidneys can supply glucose to the circulation through the gluconeogenesis process, which involves *de novo* glucose synthesis from non-glucose substrates; and through glycogenolysis, i.e. the breakdown of stored glycogen. Glucose produced in the body is another source besides glucose supplied externally. The liver is recognized as the main organ in which glucose production takes place. This process occurs in two ways. One is glycogenolysis, or the breakdown of liver glycogen, the other is gluconeogenesis, which is the synthesis of glucose from non-glucose substrates. In the liver, the main substrate for glucose production is alanine and lactate. These substances are found in the lactic acid cycle (Corich cycle) and in the alanine-glucose cycle. In physiological and pathological conditions, the kidneys play a large role in maintaining the body's metabolic homeostasis. This is due to their participation in the process of glycolysis and gluconeogenesis, as well as two very important functions: filtration of glucose in the glomeruli, and its reabsorption in the tubules. In kidneys, glutamine is the main substrate for gluconeogenesis. The glucose synthesis process takes place in the glucose-glutamine cycle. The process of gluconeogenesis depends on the concentration of glucose in blood in the given moment, and the inflow of substrates. Moreover, it is subject to humoral regulation [1-5]. Figure 1 illustrates glucose production in the liver and kidneys.

After overnight fasting, the gluconeogenesis process in the kidneys provides 20%-25% of the glucose released. In the postprandial period, renal gluconeogenesis increases and provides about 60% of the endogenous glucose released. This glucose is reabsorbed into the circulation. Among the factors playing an essential role in

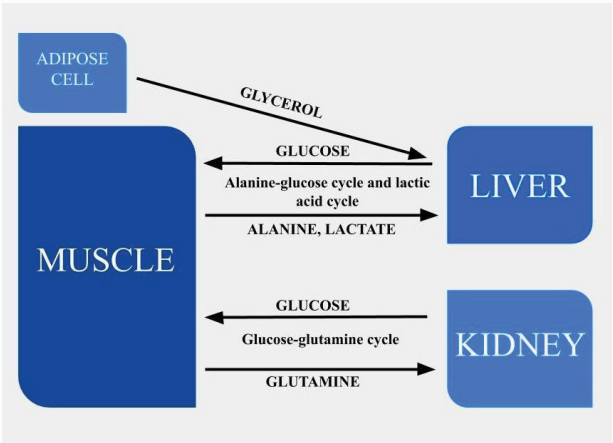

Figure 1: Glucose production in the process of gluconeogenesis in the liver (alanine-glucose cycle and lactic acid cycle) and in the kidney (glucose-glutamine cycle).

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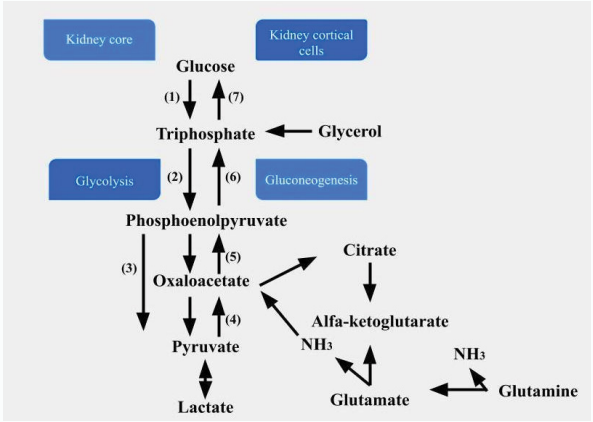

Figure 2: Glycolysis and gluconeogenesis in the kidney.

the above-mentioned processes are hormones, mainly insulin and catecholamines, as well as enzymes and glucose transporters [1,2,6-8]. The kidneys are also involved in glucose reabsorption. This process is mediated by sodium-glucose co-transporters (SGLT1 and SGLT2) located in segments S1 and S3 of the proximal tubule. Most renal glucose reabsorption, up to 90%, is mediated by the SGLT2 co-transporter [9]. The Na+/glucose (SGLT1) co-transporter was first described in 1960 [10,11]. The first reports of glucose synthesis in kidneys in experimental animals come from the 1930s [12]. Glucose produced in the process of gluconeogenesis in the renal cortex is used to cover the core's energy needs. The kidneys play an important role in maintaining glucose homeostasis [13]. If we have preserved glomerular filtration, the kidneys can prevent extreme hyperglycemia [14,15]. The main mechanisms by which the kidneys are involved in maintaining glucose homeostasis are gluconeogenesis, renal glucose consumption, and glucose reabsorption in proximal tubules [8,16,17]. Glucose reabsorption is one of the most important physiological functions of the kidneys, enabling full recovery of filtered glucose, elimination of glucose from urine, and the prevention of calorie loss [17]. The course of glycolysis and gluconeogenesis in the kidneys is illustrated in Figure 2.

The key enzymes in the glycolysis process, which are located in the cells of the kidney core, are hexokinase (1), phosphofructokinase (2), and pyruvate kinase (3). The process of gluconeogenesis involves pyruvate carboxylase (4), phosphoenolpyruvate carboxykinase (5), fructose-1,6-bisphosphatase (6), and glucose-6-phosphatase (7), which are enzymes located mainly in kidney cortical cells.

Effect of diabetes on renal glucose metabolism

SGLT2 expression and activity are increased in diabetes, which leads to greater glucose reabsorption, and thus to an increase in hyperglycemia. Chronic elevated plasma glucose may increase β-cell insulin resistance and dysfunction, contributing to glucose homeostasis disorder. Blocking SGLT co-transporters reduces glucose reabsorption and increases renal glucose excretion [14]. Modulation of the activity of SGLT1 and SGLT2 sodium glucose co-transporters may be a potential therapeutic target in patients with diabetes [9,18]. Renal glucose production is regulated by insulin. In the presence of insulin resistance associated with Type 2 diabetes, glucose overproduction occurs [19,20]. Other authors have also discussed the relationship between insulin resistance and glucose intolerance, and the assessment of the renal function based on clinical and experimental studies [21,22]. In recent years, much attention has also been paid to the relationship between renal failure and the degree of metabolic control in patients with Type 1 diabetes, because progressive renal failure is a major complication of Type 1 diabetes [23-27]. It has been established that good glycemic control delays the development of diabetic nephropathy [28]. In the process of gluconeogenesis, approximately 50% of the body's glucose resources are generated, of which 50% is produced in the kidney. It follows that people with chronic renal failure may develop hypoglycemia. Based on the literature provided, Canadian authors have provided a comprehensive discussion of the relationship between hypoglycemia in diabetes and the renal function [29]. Triplitt presents the mechanisms governing the regulation of glucose homeostasis by kidneys [30,31]. The author discusses the mechanisms of glucose release into the circulation, glucose uptake to meet energy needs, and glucose reabsorption in the tubules. The fact that epinephrine stimulation increases renal glucose production indicates the important role of kidneys in the process of hypoglycaemia, in that they increase gluconeogenesis and glucose reabsorption from glomerular filtrate [32]. American authors have confirmed the role of epinephrine in glucose release in the process of gluconeogenesis [33].

Conclusion

As mentioned before, kidneys participate in the maintenance of glucose homeostasis by taking part in gluconeogenesis, glucose filtration, reabsorption and utilization. Each of these processes may be disturbed in diabetes.

References

1. Ficek R, Chudek J, Więcek A. Blocking glucose reabsorption in the renal tubules as a new potential treatment for diabetes in Cukrzyca w populacji wieku rozwojowego - co nowego? Otto Buczkowska E (ed). Wrocław, Poland: Cornetis; 2009. p. 244-50.
2. Kelly L, Almutairi MM, Kursan S, Pacheco R, Dias-Junior E, Castrop H, et al. Impaired glucose tolerance, glucagon, and insulin responses in mice lacking the loop diuretic-sensitive Nkcc2a transporter. Am J Physiol Cell Physiol. 2019;317(4):C843-C856.
3. Otto Buczkowska E. The role of the human kidney for glucose homeostasis. Wiad Lek. 2004;57(3-4):158-60.
4. Otto-Buczkowska E, Tucholski K. Kidneys function in glucose homeostasis regulation and its therapeutic implications. Fam Med Pri Care Rev. 2013;15(1):34-7.
5. Otto-Buczkowska E. Sodium glucose cotransporter-2 inhibitors – a novel class agents for the treatment of diabetes. Forum Med Rodz. 2014;8(5):181-4.
6. Alsahli M, Gerich JE. Renal glucose metabolism in normal physiological conditions and in diabetes. Diabetes Res Clin Pract. 2017;133:1-9.
7. Marsenic O. Glucose control by the kidney: an emerging target in diabetes. Am J Kidney Dis. 2009;53(5):875-83.
8. Mather A, Pollock C. Glucose handling by the kidney. Kidney Int. 2011;79;Suppl(120):S1-S6.
9. Liu B, Wang Y, Zhang Y, Yan B. Mechanisms of Protective Effects of SGLT2 Inhibitors in Cardiovascular Disease and Renal Dysfunction. Curr Top Med Chem. 2019;19(20):1818-49.
10. Wright EM, Loo DD, Panayotova-Heiermann M, Hirayama BA, Turk E, Eskandari S, et al. Structure and function of the Na+/glucose cotransporter. Acta Physiol Scand Suppl. 1998;643:257-64.
11. Wright EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. Physiol Rev. 2011; 91(2):733-94.
12. Braga VA. Teaching the renal tubular reabsorption of glucose using two classic papers by Shannon et al. Adv Physiol Educ. 2011;35(2):114-6.
13. Ruan X, Guan Y. Metabolic syndrome and chronic kidney disease. J Diabetes. 2009;1(4):236-45.

14. Girard J. Role of the kidneys in glucose homeostasis. Implication of sodium-glucose cotransporter 2 (SGLT2) in diabetes mellitus treatment. Nephrol Ther. 2017;13 Suppl 1:S35-S41.

15. Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. Diabetologia. 2017;60(2):215-25.

16. Moradi-Marjaneh R, Paseban M, Sahebkar A. Natural products with SGLT2 inhibitory activity: Possibilities of application for the treatment of diabetes. Phytother Res. 2019;33(10):2518-30.

17. Segura J, Ruilope LM. Contribution of the kidney to glucose homeostasis. Med Clin (Barc). 2013;141 Suppl 2:26-30.

18. Fattah H, Vallon V. The Potential Role of SGLT2 Inhibitors in the Treatment of Type 1 Diabetes Mellitus. Drugs. 2018;78(7):717-26.

19. Sullivan MA, Forbes JM. Glucose and glycogen in the diabetic kidney: Heroes or villains? EBioMedicine. 2019;47:590-7.

20. Takeda Y, Fujita Y, Bessho R, Sato M, Abe T, Yanagimachi T, et al. Increment of plasma glucose by exogenous glucagon is associated with present and future renal function in type 2 diabetes: a retrospective study from glucagon stimulation test. BMC Endocr Disord. 2019;19(1):99.

21. Granda ML, Amarapurkar P, Fornoni A. Probing insulin sensitivity in diabetic kidney disease: is there a stronger role for functional imaging? Clin Sci (Lond). 2018;132(11):1085-95.

22. Mak RH. Insulin and its role in chronic kidney disease. Pediatr Nephrol. 2008;23(3):355-62.

23. Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation. 2014;129(5):587-97.

24. Goel G, Perkins BA. Can improved glycemic control slow renal function decline at all stages of diabetic nephropathy? Semin Nephrol. 2012;32(5):423-31.

25. Najafian B, Mauer M. Morphologic features of declining renal function in type 1 diabetes. Semin Nephrol. 2012:32(5):415-22.

26. Thomson HJ, Ekinci EI, Radcliffe NJ, Seah JM, MacIsaac RJ, Jerums G, et al. Elevated baseline glomerular filtration rate (GFR) is independently associated with a more rapid decline in renal function of patients with type 1 diabetes. J Diabetes Complicat. 2016;30(2):256-61.

27. Yang GK, Maahs DM, Perkins BA, Cherney DZ. Renal hyperfiltration and systemic blood pressure in patients with uncomplicated type 1 diabetes mellitus. PLoS One. 2013;8(7):e68908.

28. Meeme A, Kasozi H. Effect of glycaemic control on glomerular filtration rate in diabetes mellitus patients. Afr Health Sci. 2009;9(Suppl 1):S23-26.

29. Alsahli M, Gerich JE. Hypoglycemia, chronic kidney disease, and diabetes mellitus. Mayo Clin Proc. 2014;89(11):1564-71.

30. Triplitt CL. Examining the mechanisms of glucose regulation. Am J Manag Care. 2012;18(1 Suppl):S4-10.

31. Triplitt CL. Understanding the kidneys' role in blood glucose regulation. Am J Manag Care. 2012;18(1 Suppl):S11-6.

32. Mitrakou A. Kidney: its impact on glucose homeostasis and hormonal regulation. Diabetes Res Clin Pract. 2011;93(Suppl 1):S66-72.

33. Meyer C, Stumvoll M, Welle S, Woerle HJ, Haymond M, Gerich J. Relative importance of liver, kidney, and substrates in epinephrine-induced increased gluconeogenesis in humans. Am J Physiol Endocrinol Metab. 2003;285(4):E819-26.