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A Predictive Study on the Chemical Relationship between Human Kidney Function and Hyperglycemia

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Abstract: Type 2 diabetes mellitus (DM) affects 18-20% of adults over 65 years old globally. Diabetic kidney disease (DKD) is one of the most common and dangerous complications of type 2 DM, impacting about one-third of patients. In addition to the pancreas, liver, intestines, and adipose tissue, the kidneys also play an important role in blood sugar regulation through gluconeogenesis and glucose reabsorption. In this review article, an interdisciplinary group of experts in endocrinology, diabetology, and nephrology discuss the relationship between diabetes and kidney disease. They address diagnosis, challenges with glycemic control, and potential treatments for different stages of DKD. Glucose homeostasis is severely disrupted in DKD patients, putting them at high risk of both hyperglycemia and hypoglycemia. Abnormal high and low blood sugar levels associate with higher morbidity and mortality in this population. Factors increasing hypoglycemia risk include reduced kidney gluconeogenesis, altered metabolic pathways, and decreased insulin clearance. Decreased glucose filtration/excretion and inflammation-induced insulin resistance predispose to hyperglycemia. Careful blood sugar monitoring and control tailored to diabetes patients with kidney disease is required to avoid hypoglycemic and other glucose disorders. Understanding the physiology and pathophysiology of DKD has become essential for all specialties treating diabetic patients. Disseminating this knowledge and evidence will be vital to advance research and improve care for these patients.

Keywords: Blood sugar, Diabetes, kidney disease, Glycemic control and Diabetes complications.

1. Introduction

The prevalence and frequency of diabetes mellitus (DM) has grown significantly worldwide, principally due to a higher prevalence of type 2 DM [1]. Type 2 DM affects 18–20% of adults over 65 years old globally. It is estimated that about 285 million people, between 20 and 79 years old, currently have DM, 70% of whom reside in middle- and low-income countries [2]. This increase in type 2 DM (DM2) occurs disproportionately, impacting mainly developing countries, thereby bringing huge challenges in public healthcare for these patients [3]. The expectation is for this number to surge by over 50% in the next 20 years if preventive programs are not implemented. By 2030, it is estimated that almost 438 million people, or 8% of the adult population, will have DM. Diabetic kidney disease (DKD) is one of the most common and dangerous complications of DM2, impacting about one-third of patients. In addition to the increasing complexity of outpatient care for DM patients, DKD results in more hospitalizations and mortality, especially due to cardiovascular complications [4]. DKD also increases the need for renal replacement therapies, like dialysis and

kidney transplants. The combined economic and social costs of this disease are high and concerning to global health systems. [5].

DM2 is an illness characterized by persistent hyperglycemia, resulting from partial or complete insulin deficiency, and it is linked with a clinical picture of insulin resistance [6]. Recently, other organs have been recognized as being involved in the pathogenesis of hyperglycemia in DM2, and it is now known that not only dysfunction of the pancreas, but also of the liver, adipose tissue, intestine, kidneys, and central nervous system may contribute to this hyperglycemic state [7]. Insulin resistance (IR) is one of the pillars dictating the pathogenesis of DM2 and may differ according to body tissues. However, where does IR begin? Some authors argue it starts in the liver, others in the muscle, and others in the brain. What we know is that IR is present in various body tissues (liver, peripheral muscle, central nervous system, adipocytes, etc.) of patients with DM2, preventing glucose entry into the cell and causing hyperglycemia. Several studies show that insulin has an anorexigenic action in the central nervous system [8]. However, the caloric intake in obese individuals is enhanced even in the presence of hyperinsulinemia, suggesting a clinical picture of IR in the brain. Regarding peripheral IR, it is well established that IR directly correlates with deposits of visceral and intramyocellular (within the myocyte) fat [9]. This can be explained by the inflammatory role of adipocytes in producing interleukin-6 and tumor necrosis factor-α, among other pro-inflammatory substances that alter intracellular signaling through the insulin receptor and consequently decrease the expression of glucose transporters of the cell membrane (GLUTs), leading to IR [10]. In the muscle, when deposition of intramyocellular fat occurs, especially in the cytoplasm far from mitochondria, cytoplasmic diacylglycerol production increases, which leads to a decreased membrane expression of GLUT4, subsequent reduction of muscle glucose uptake, and hyperglycemia [11].

Hyperglycemia is not observed in a clinical picture of impaired glucose tolerance or pre-diabetes, since hyperinsulinemia can still compensate for insulin resistance and maintain normal blood glucose levels. When hyperinsulinemia can no longer compensate for insulin resistance and insulin secretion begins to decline, the disruption of these variables results in hyperglycemia and a diagnosis of DM [12]. In the early stages of DM2, the clinical picture of hyperinsulinemia persists. However, reduced insulin secretion is mainly responsible for the clinical picture of hyperglycemia. In the later stages of the disease, insulin resistance persists. However, the clinical picture, characterized by deficient insulin secretion, worsens, thus exacerbating the loss of glycemic control. The gold standard to evaluate insulin resistance is the euglycemic insulin clamp technique. However, this technique is difficult to perform, expensive to apply, and is only used in clinical studies. More simply, we can estimate insulin resistance using formulas that correlate with the clamp, such as the homeostatic model assessment (HOMA-IR): [fasting insulin (mU/mL) × fasting blood glucose (mmol/L)]/22.5 [13]. It is important to remember that HOMA-IR assesses hepatic insulin resistance, as the calculation involves fasting blood glucose and insulin levels. On the other hand, the Matsuda index can estimate hepatic and peripheral insulin sensitivity, using blood sugar and insulin levels obtained through an oral glucose tolerance test. In addition to insulin resistance, insulin deficiency is essential to manifest hyperglycemia in DM2. There are several factors involved in the process of insulin secretion, and incretins are one of the most important. Incretins are hormones secreted by the gut that have different functions upon binding to their receptors, expressed in various organs and tissues. After a meal, 60% of insulin secretion depends on the stimulation of incretin hormones [14]. There are two main incretins: glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1). Both are involved in glucose homeostasis. However, GLP-1 is more important than GIP, since it also inhibits glucagon secretion, slows gastric emptying, and inhibits hunger, whereas GIP does not. Therefore, GLP-1 is a target of several incretin therapies for the treatment of DM2. GLP-1 is secreted by the L-cells of the ileum and has a half-life of 2 minutes; it is inactivated by dipeptidyl dipeptidase-4 enzyme. When released into the circulation, GLP-1 binds to its receptor, which is expressed in different tissues, and promotes different actions [15]. The GLP-1 receptor is a G-protein-coupled receptor, and binding activates adenylyl cyclase, leading to a subsequent increase in cyclic adenosine monophosphate, which activates protein kinase A and increases insulin release. It is worth noting that incretins stimulate glucose-dependent insulin secretion, i.e., only if blood glucose

is elevated. The GLP-1 receptor is expressed in multiple organs besides the pancreas, such as the intestine, kidneys, heart, and central nervous system [16]. It exerts different functions in different tissues: (1) in the central nervous system, it decreases hunger and increases satiety; (2) in the pancreas, after a meal, it stimulates insulin secretion from β cells and decreases glucagon release by α cells; (3) in the liver, it reduces glycogenolysis and gluconeogenesis by decreasing postprandial glucagon; (4) in the heart, it plays a cardioprotective role; and (5) in the vessels, it acts as a vasodilator [17].

2. Concentration of blood glucose

According to biological variation, to avoid patient misclassification, glucose measurement should have an analytical imprecision ≤2.9%, a bias ≤2.2%, and a total error ≤6.9%. Ideally, glucose analysis should minimize total analytical error, and methods should be without measurable bias. Enzymatic methods for glucose analysis are well standardized. A survey by the College of American Pathologists (CAP) reveals that hexokinase or glucose oxidase is used in nearly all U.S. analyses, with few laboratories using glucose dehydrogenase. Glucose is stable for 8 hours in samples collected with an antiglycolytic agent. In plasma, serum, and other fluids already separated from cells, glucose levels are stable for 3 days at 2–8°C if no bacterial contamination occurs [18]. Important factors interfering with glucose measurement: Bilirubin levels >10 mg/dL produce negative interference when the endpoint method is used. For samples with triglyceride concentrations >1100 mg/dL, the turbidity effect can be minimized by diluting with 150 mmol/L NaCl (0.85%) and repeating the measurement. With the kinetic method, bilirubin ≤10 mg/dL, hemoglobin ≤150 mg/dL, and triglycerides ≤3500 mg/dL do not significantly interfere. Ascorbic acid above 100 mg/dL also interferes with the reaction, falsely lowering results [19]. For the exam: Fasting for 8–12 hours with water intake is recommended. Normal physical activity and diet the day before plus a standard 150 g carbohydrate diet is advised [20].

3. Glycated hemoglobin

Glycation is a nonenzymatic reaction of glucose binding to a protein, in this case, hemoglobin, yielding glycated hemoglobin, or HbA1c. This process is concentration- and time-dependent - the higher the glucose concentration, the higher the HbA1c, while over time, glucose binding to hemoglobin decreases. Unlike plasma glucose, HbA1c represents nonenzymatic glycation dependent on glucose levels inside erythrocytes. Though HbA1c and glucose correlate well in diabetic patients with and without chronic kidney disease (CKD), the variable relationship between HbA1c and average glucose remains a potential concern. Normally, 97% of hemoglobin is HbA. Only 6% of HbA undergoes glycation into HbA1c. Ninety-four percent of HbA has no sugar-induced changes, called HbA0. HbA1c has subtypes - 20% is influenced by fructose-1,6-diphosphate and glucose-6-phosphate, forming HbA1a and HbA1b. The remaining 80% depends on glycemic variation, called HbA1c [21].

Approved HbA1c laboratory methods by the National Glycohemoglobin Standardization Program (NGSP) include: HPLC, boronic acid affinity chromatography, enzymatic, immunoassay, and capillary electrophoresis. Since methods quantify different glycated hemoglobin ratios, results differ. However, an excellent correlation occurs in samples without hemoglobin variants or interfering factors. Via NGSP, HbA1c values can be standardized across methods to equate glycemic status regardless of the method, enabling widespread application of the same criteria. NGSP standardized methods to be comparable to the Diabetes Control and Complications Trial (DCCT), which established the relationship between average blood glucose and vascular risk. NGSP certifies methods and laboratories worldwide that demonstrate acceptable accuracy per DCCT standards [22].

4. Glycated albumin

The measurement of glycated albumin (GA) is gaining attention as a potential marker of glycemic control. GA is a ketoamine formed by the non-enzymatic oxidation of albumin by glucose. Since the half-life of albumin is about 15 days, GA is used as a short-term gauge of glycemic control, that is, 2–3 weeks, and as such, it might serve as an intermediate-term index of glycemic control. Several methods can be utilized for the measurement of GA, including affinity chromatography, ion-

exchange chromatography, HPLC, immunoassay techniques, capillary electrophoresis, and other electrophoretic and enzymatic assays. It is not influenced by sex, red blood cell lifespan, or erythropoietin therapy; however, the findings for serum albumin concentration are conflicting. However, the results can be impacted by age, nutritional status, albuminuria, cirrhosis, thyroid dysfunction, and smoking. GA is inversely affected by body mass index, body fat mass, and visceral adipose tissue [23].

5. Glycated fructosamine

Fructosamine is the generic term for all glycated proteins, of which albumin is the major plasma fraction, after hemoglobin. Although fructosamine measurement can be automated, making it cheaper and faster than HbA1c testing, there is no consensus on its clinical usefulness. The fructosamine level correlates better with average glucose levels over the previous 10–14 days. Since this measures total glycated serum proteins, of which glycated albumin represents about 90%, fructosamine concentrations can be impacted by serum protein concentrations and the profile of different proteins. Moreover, fructosamine is influenced by the concentration of bilirubin and low molecular weight substances, such as urea and uric acid. Fructosamine is not altered by changes in hemoglobin metabolism. However, it is affected by disturbances in protein turnover. The reference values depend on age, sex, sample population, and test method used. Unfortunately, the data show conflicting results regarding the correlation between fructosamine and glucose concentrations in patients with chronic kidney disease (CKD). The values may be influenced by nephrotic syndrome, thyroid diseases, glucocorticoid administration, liver cirrhosis, and jaundice. [24].

Diabetic kidney disease (DKD) progresses with several metabolic changes, which occur alongside the progressive decline in glomerular filtration rate (GFR). Using the euglycemic insulin clamp, DeFronzo et al. showed that glucose utilization by peripheral tissues in response to insulin is reduced in uremia. The increased insulin resistance is related to accumulation of uremic toxins, markers of chronic inflammation, increased visceral fat, oxidative stress, and vitamin D deficiency. Progression to uremia is associated with decreased insulin sensitivity of peripheral tissues, increased hepatic gluconeogenesis, decreased glucose uptake by skeletal muscle cells, and deficiency of intracellular glycogen synthesis and subsequent hyperglycemia. On the other hand, the risk of hypoglycemia is a constant concern, since this is increased in diabetic patients with chronic kidney disease (CKD). The pathogenesis of hypoglycemia in these patients is related to changes in glucose metabolism, decreased insulin degradation, and changes in the metabolism of hypoglycemic agents. With a progressive reduction in GFR, we observed a decrease in the clearance of oral hypoglycemic agents, and sometimes, a longer time of action of these drugs and their active metabolites. Similarly, insulin metabolism is also altered, since part of its metabolization and excretion is carried out by the renal system. A restricted diet, either by prescription or even due to uremia, reduces hepatic gluconeogenesis, thus contributing to the occurrence of hypoglycemic episodes observed at higher frequency in this population [25].

6. Conclusions

The relationship between diabetes mellitus (DM) and diabetic kidney disease (DKD) is more complex than just the predisposition of a diabetic patient to develop kidney disease and the negative impact on morbidity and mortality of patients with kidney disease and DM. Recently, the kidney has been recognized as being directly involved in the pathogenesis of DM because of its ability to regulate glucose reabsorption as well as determine insulin half-life and resistance. Additionally, it is now clear that glomerular filtration provides a safe and effective target for many hypoglycemic drugs. Thus, understanding the renal physiology and pathophysiology of DKD has become essential for all specialties treating diabetic patients. Spreading this knowledge and outlining the evidence will be important to initiate breakthrough research and encourage proper treatment of this patient group. Regardless of insulin being considered the best option for glycemic control in patients with renal impairment, its prescription must follow certain guidelines, such as: (1) individualization of therapy; (2) frequent reassessment or dose adjustment based on glomerular filtration rate; (3) basal-bolus regimens using intermediate- or long-acting insulin for stable blood glucose in the post-absorptive state, plus short-acting insulin to control carbohydrate metabolism and postprandial glycemia; and

(4) blood glucose monitoring with frequent insulin therapy adjustments based on individual response. Few studies have reported specific information on the differential action profiles, half-life, metabolism, and clearance of different insulin types adjusted for different chronic kidney disease (CKD) stages. Such studies would enable more effective therapeutic regimens, minimizing hypoglycemia risk, which is potentially more harmful in this population. Therefore, treatment should be individualized based on factors like complications, associated diseases, disease management ability, CKD stage and duration, and prior glycemic control. Additionally, a multidisciplinary team of nephrologists, endocrinologists, nutritionists, and nurses should participate. This approach has proven effective for achieving optimal individual glycemic values, reducing kidney disease progression and other DM2 complications, and improving quality of life for patients with DKD.

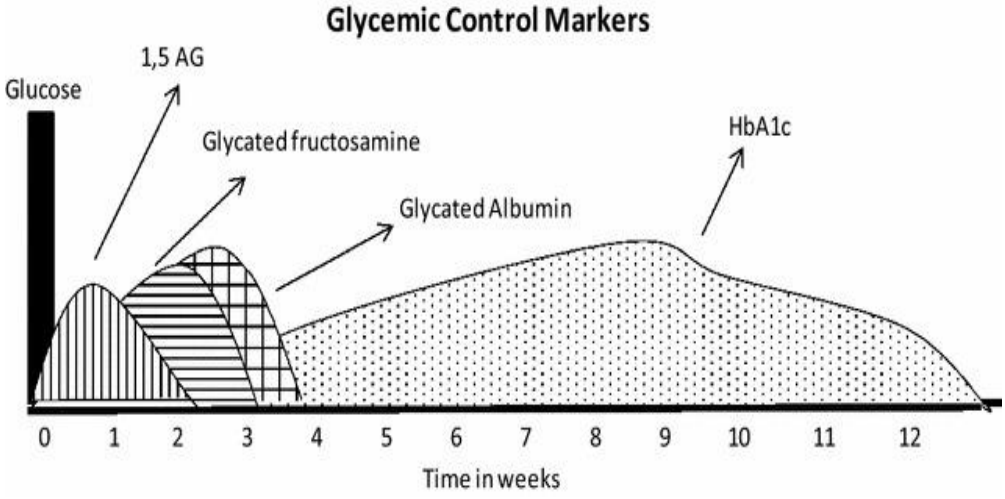

Fig (1) Correlation between each marker and the time of hyperglycemia that each indicates

7. References

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