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The clinical usefulness of glycated albumin in patients with diabetes and chronic kidney disease: Progress and challenges

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ABSTRACT

Prolonged hyperglycemia leads to a non-enzymatic glycation of proteins, and produces Amadori products, such as glycated albumin (GA) and glycated hemoglobin (HbA1c). The utility of HbA1c in the setting of chronic kidney disease (CKD) may be problematic since altered lifespan of red blood cells, use of iron and/or erythropoietin therapy, uremia and so on. Therefore, as an alternative marker, GA has been suggested as a more reliable and sensitive glycemic index in patients with CKD. In addition to the mean plasma glucose concentration, GA also reflects postprandial plasma glucose and glycemic excursion. Besides, with a half-life of approximately 2–3 weeks, GA may reflect the status of blood glucose more rapidly than HbA1c. GA is also an early precursor of advanced glycation end products (AGEs), which cause alterations in various cellular proteins and organelles. Thus, high GA levels may correlate with adverse outcomes of patients with CKD. In this review, the clinical usefulness of GA was discussed, including a comparison of GA with HbA1c, the utility and limitations of GA as a glycemic index, its potential role in pathogenesis of diabetic nephropathy and the correlations between GA levels and outcomes, specifically in patients with diabetes and CKD.

1. Introduction

Chronic kidney disease (CKD) is a growing global health problem and diabetes mellitus (DM) is the leading cause of CKD. One study found that patients with diabetes (type 1 or 2) were 7 times more likely to have clinically substantial CKD than those without diabetes.[1] Diabetes has become the primary cause of new cases of end-stage renal disease (ESRD).[2] In the meantime, the decline in renal function impairs the clearance and metabolism of renal glucose and insulin. Besides, renal failure causes related changes in insulin signaling, glucose transport and metabolism. All of these factors also make diabetes more prevalent in the CKD patients.

Good glycemic control is associated with a better clinical outcome of patients with diabetes and chronic kidney disease.[3–5] At present, we often use fasting plasma glucose (FPG), 2 h postprandial plasma glucose (2 h PG) and random plasma glucose to measure the actual glucose levels. However, these indices often affected by short-term lifestyle changes, and show significantly variability within individuals. So glycated proteins are frequently used to provide an index of glycemic control over a period of time. Hemoglobin A1c (HbA1c), which reflects average glucose levels (AG) over the 120 days preceding the test, is widely used as a gold standard index for glycemic control in clinical practice. However, the utility of HbA1c in the setting of CKD has been questioned since CKD is accompanied by several factors such as anemia, altered erythrocyte turn-over and erythropoietin treatment.[6–8] Therefore, serum glycated albumin (GA), as an alternative marker, has been suggested as a more reliable and sensitive glycemic index than HbA1c in diabetic patients with CKD,[9–12] since it is not influenced by anemia and associated treatments. Fructosamine is a generic term that refers to all glycated serum proteins including GA in blood serum and GA measures specifically the glycation product of albumin. The clinical assays for glycated albumin typically express their results in terms of the ratio of the amount of glycated albumin versus the total amount of albumin that is present. This feature means that these methods are not generally affected by changes in the overall concentration of albumin.[13,14]

Recently, some studies have found that GA was a good predictor of adverse outcomes of diabetic patients with CKD,[15–23] and this may

Abbreviations: CKD, chronic kidney disease; DM, diabetes mellitus; T2DM, type 2 diabetes mellitus; ESRD, end-stage renal disease; FPG, fasting plasma glucose; 2 h PG, 2 h postprandial plasma glucose; HbA1c, hemoglobin A1c; AG, average glucose levels; GA, glycated albumin; AGEs, advanced glycation end-products; RAGEs, AGE receptors; ROS, reactive oxygen species; Ang II, angiotensin II; DN, diabetic nephropathy; R, correlation coefficient; SMBG, self-monitoring of blood glucose; CGMS, continuous glucose monitoring systems; eGFR, estimated glomerular filtration rate; adjGA, serum albumin-adjusted GA; PKC, protein kinase C; TGF-β, transforming growth factor-β; VEGF, endothelial growth factor; ROC, receiver-operating characteristic curve; AUC, areas under the curve; HR, hazard ratio.

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because GA is involved in many pathologic processes. GA is the major form of circulating Amadori-type glycated proteins and it is an early precursor of advanced glycation end products (AGEs),[24] which bind to AGE receptors (RAGEs) opening the floodgate of deleterious downstream signals including increased reactive oxygen species (ROS) production, inflammatory cell activation, inappropriate increase of angiotensin II (Ang II), and release of growth factors.[25,26] For example, some latest studies showed the potential role of GA in pathogenesis and predicting diabetic nephropathy (DN) in patients with DM.[27] Then by observing the degree of increase in GA, measures can be taken to prevent DN before evolving structural damage is clinically apparent.

This review summarizes current knowledge about the clinical usefulness of glycated albumin in patients with diabetes and CKD and we will mainly discuss: (1) Albumin: biochemical and glycation aspects; (2) GA as a marker for glycemic control; (3) GA may function as a pathogenic protein and predictor of DN in diabetes; and (4) GA as a prognosis indicator in patients with CKD.

2. Albumin: biochemical and glycation aspects

Albumin is the most abundant circulating protein, accounting for 50–60% of total plasma proteins. It comprises a single polypeptide chain of 585 amino acids with abundance of lysine (59) and arginine (24) residues and contains 35 cysteine residues, 34 of which form 17 disulfide bridges, important for the overall tertiary structure of the protein.[28–31] One of the main processes affecting the structure of albumin is glycation, a nonenzymatic chemical reaction between reducing sugars or their degradation products and free amino groups of proteins.[32,33] This results in the production of early and advanced glycation end-products (AGEs). The formation of glycated products is quite complex but, according to a more simplified view, it is often described as a chemical process that proceeds through three main stages: initial, intermediate and late.[29] In the initial stage, the free amino group of protein and the aldehyde group of glucose form the Schiff base, which produces a substance called aldimine.[34] This reaction is relatively quick and reversible. Then, this aldimine becomes ketoamine by the Amadori rearrangement reaction, leading to the production of stable Amadori product, that is, glycated protein.[35] This reaction progresses slowly and is almost irreversible. And in the last stage, Amadori products undergo a series of reactions involving multiple dehydration, fragmentation, and oxidative modification via highly reactive dicarbonyl intermediates to form irreversible advanced glycation end products (AGEs).[36–39] HbA1c is a glycated protein in which glucose binds with N-terminal valine residue in the β chain of hemoglobin nonenzymatically.[35] However, large number of lysine and arginine residues are involved in the formation of GA, especially lysine 525 is the main target site of glycation.[29,40] The difference between HbA1c and GA in the glycation site may lead to major consequences since the deglycating enzyme fructosamine 3 kinase does not recognize HbA1c as a substrate (in contrast to GA).[41–43] Therefore, GA might be much more representative for the glycation damage caused to target organs (such as coronary arteries, cardiovascular system, kidney, eye and nervous system).[29]

CKD and diabetes mellitus are two diseases that accelerate protein molecular ageing through carbamylation and glycation reactions, characterized by the binding of urea-derived isocyanic acid and of sugars on proteins, respectively. These two reactions target the same protein amino groups and, thus, compete with each other.[44] The protein carbamylation depends on the duration and severity of renal failure and it is an unavoidable consequence of excess urea.[45,46] Carbamylated Hb (carbHb) is formed by non-enzymatic condensation of cyanate with the N-terminal valine of Hb.[47] Previous reports have suggested that HbA1c methods may have interference from carbHb that would be expected to falsely increase HbA1c results,[48–50] but many of these methods are no longer in use. Technological advances in HbA1c measurement (e.g. newer ion-exchange HPLC assay methods, specific immunoassays or affinity chromatography) showed improved separation of the HbA1c fraction from other hemoglobin adducts and therefore did not show interference from carbHb.[51,52] Fructosamine and GA may also be impacted by the competition between glycation and carbamylation, such as homocitrulline which derives from isocyanic acid binding to the ε-amino group of lysine residues.[53] But nowadays improved new measurement methods can provide more robust results. When interpreting results from different laboratories, the differences in methods of measurement should be taken into account.

3. GA as a marker of glycemic control

3.1. Average glucose level

Both HbA1c and GA are spontaneously glycated over their circulating lifespan, and thus are the biomarkers for time-averaged blood glucose concentrations. But the shorter half-life makes GA a much more dynamic marker for glycemic control that can be used to assess the efficacy of diabetes medication therapy and short-term changes in glycemic control. In the setting of CKD, many studies considered GA may more accurately in reflecting the recent average glucose level.[7,54–68] Data relating the linkage observed between average blood glucose and these two biomarkers in patients with diabetes and CKD are summarized in Table 1, and the correlation coefficient (R) is used to assess the correlations. From these studies, we find there is a significant correlation between mean glucose concentration and GA. Especially in CKD stage 4 and 5 including patients receiving dialysis, GA is superior to HbA1c in assessing blood glucose control. These have been demonstrated by our previous meta-analysis which include 24 studies.[69] However, when interpreting the results of different studies, we should notice the differences in the nation of population and measurements of GA. The Lucica GA-L assay is an accurate and most used in the test of determination of GA, but consensus on international standards and external quality assessment programs of GA has not yet fixed. So in the future, international standardization is clearly required for use for both clinical practice and research.

GA seems to be a better marker in reflecting the accuracy of glycemic control when compared with HbA1c in patients with CKD, thus we compared HbA1c, GA and fructosamine and the results were listed in Table 2. Considering the limited data, the absence of studies on the results of interventions based on GA and its expensive and laborious methodology, it might be premature to abandon HbA1c in favor of GA. Therefore, we suggest monitoring HbA1c every 3 months and GA could be used as additional tools, rather than replacing HbA1c. Since GA level is falsely low in the condition of marked proteinuria in patients with CKD, some studies suggested that serum albumin-adjusted GA (adjGA) could be a good indicator of glycemic control and glycemic excursion in these patients.[56,63,70] Considering the number of studies concerning adjGA is limited, more large-scale prospective studies should be conducted to verify the usefulness of adjGA in the future.

3.2. Glycemic excursion and postprandial hyperglycemia

GA is also a sensitive indicator of glycemic excursion and postprandial glucose level in patients with diabetes.[71–77] Glycemic excursion is very common to diabetic patients with CKD, in part because of renal failure-related changes in insulin signaling, glucose transport and metabolism, favoring both hyperglycemic peaks and hypoglycemia. Additionally, the decline in renal function impairs the clearance and metabolism of anti-diabetic agents and insulin. Independently of chronic hyperglycemia represented by mean glucose levels, glycemic excursion additionally contributes to the risk of diabetic complications such as cardiovascular disease. What's more, it is reported that even when HbA1c and fasting glucose level is within normal ranges, postprandial hyperglycemia is associated with a two-fold increase in the

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