**Usefulness of glycated albumin as a biomarker for glucose control and prognostic factor in chronic kidney disease patients on dialysis (CKD-G5D)**

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**Abstract**

In chronic kidney disease patients on dialysis (CKD-G5D) accurate assessment of glycemic control is vital to improve their outcome and survival. The best glycemic marker for glucose control in these patients is still debated because several clinical and pharmacological factors may affect the ability of the available biomarkers to reflect the patient's glycemic status properly.

This review discusses the role of glycated albumin (GA) both as a biomarker for glucose control and as a prognostic factor in CKD-G5D; it also looks at the pros and cons of GA in comparison to the other markers and its usefulness in hemodialysis and peritoneal dialysis.

**Key Words:** Cardiovascular risk, Diabetes, Dialysis, Glycation, Glycated albumin, Hemodialysis, Mortality, Peritoneal dialysis

**Contents**

## 1. Glucose control in chronic kidney disease patients on dialysis

### 1.1 Introduction

The epidemiological data for end-stage renal disease (ESRD) patients in renal replacement therapy (RRT) from the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) registry showed an overall unadjusted incidence rate of 119 and an unadjusted prevalence of 801 per million population in 2015 [1]. The situation is worse in the U.S. where the unadjusted incidence rate and prevalence were respectively 378 and 2,128 per million [2].

Although the prevalence of chronic kidney disease (CKD) in the European population is close to the U.S. figure [3], the higher ESRD risk is related to the prevalence of diabetes mellitus (DM) in the U.S., with 44% of incident and 38% of prevalent cases of DM-related ESRD compared to 23% and 16% in Europe [1].

Besides being a cause, DM may also be a consequence of CKD and its onset may in turn worsen kidney function to the point of ESRD (Figure 1). The high circulating levels of urea may induce DM by affecting insulin secretion and promoting insulin resistance [4, 5]. Although the mortality rates of ESRD patients treated by dialysis (CKD-G5D) have declined in recent years, DM CKD-G5D patients still have poorer survival than non-DM cases, highlighting the importance of glycemic control to reduce their high mortality risk [6].

The most recent Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for DM and CKD recommended a target glycated hemoglobin (HbA1c) of 7% to delay the progression of microvascular complications of DM [7]. Less stringent HbA1c goals (~8%) have been suggested for patients with a history of severe hypoglycemia, limited life expectancy and cardiovascular complications, as proposed by the American Diabetes Association for patients with established macrovascular diseases [8].

In many CKD-G5D patients, glycemic control improves spontaneously with the start of treatment, leading to normal-low blood glucose levels. This phenomenon, known as “burn-out diabetes” may have different causes, such as the decrease in renal and hepatic insulin clearance, decline in renal gluconeogenesis, reduced food intake, protein-energy wasting and hypoglycemic effects of dialysis [9]. As a consequence, drug therapy needs to be modified to reduce the risk of hypoglycemia which - besides hyperglycemia - can negatively affect the outcome of DM patients. Therefore, in DM CKD-G5D good glycemic control remains important to prevent or delay the progression of the vascular

complications, to reduce cardiovascular disease (CVD) morbidity and mortality [10, 11], and to avoid hypoglycemia-related mortality [12, 13].

According to the KDOQI [7], home blood glucose monitoring in combination with HbA1c measurements are suggested for DM management in CKD-G5D. However, questions remain as to how best to control glucose in CKD-G5D because of several factors, such as renal anemia, the use of erythropoiesis-stimulating agents and reduced red cell survival due to hemodialysis (HD), which may affect the ability of the biomarkers employed in clinical practice to properly reflect the patient's glycemic status. This underscores the need for reliable markers for these patients.

### 1.2 Pros and cons of available markers for glucose control

Besides HbA1c and glucose, DM can be managed using additional biomarkers such as fructosamine, glycated albumin (GA) and 1,5-anhydroglucitol (1,5-AG). However, the main guidelines do not mention these and their use for monitoring DM in CKD-G5D seems to suffer some limits that physicians need to know about so as to select the most reliable marker for their patients (Figure 1).

*Glycated hemoglobin (HbA1c)*

HbA1c, as well as fructosamine and GA, are products of glycation, which is the non-enzymatic reaction between reducing sugars and amino groups available in proteins, lipids or nucleotides [14]. HbA1c is the result of the non-enzymatic reaction between glucose and hemoglobin. Being related to the mean life of erythrocytes, HbA1c is a long-term glycemic marker since it retrospectively reflects the mean plasma glucose levels of the previous 120 days. HbA1c does not seem useful in CKD-G5D because of the different factors in these patients which, by influencing hemoglobin synthesis, erythropoiesis and erythrocyte survival, can affect its values regardless of glucose levels. These factors include iron, erythropoietin, folate and B12 deficiency/supplementation, reduced cell survival due to toxic uremia and mechanical damage caused by HD, blood pH and blood transfusion. Accordingly, as the average life of circulating erythrocytes increases or decreases, the existing hemoglobin becomes older or younger and more or less glycosylable, respectively. Consequently, the percentage of HbA1c does not properly reflect the patient's glycemic status [15].

*Fructosamine*

Fructosamine is a generic term referring to all early glycated serum proteins and is an intermediate-term glycemic control indicator (7-14 days) [16]. Some studies describe fructosamine as a more accurate marker than HbA1c because it is not affected by all the factors related to anemia. However, fructosamine assay is not specific and suffers from the lack of reference ranges which may be strongly affected by sex, age, sample population, test method, total proteins, uric acid concentration and unspecific serum reducing activities [17, 18]. Hence, false fructosamine levels may be recorded in case of protein wasting, such as in patients undergoing peritoneal dialysis (PD) with protein loss in the peritoneal dialysate and in CKD-G5D patients with protein-energy wasting. In case of protein loss, fructosamine adjusted for albumin appeared to be a more reliable marker of glycemic control in PD patients [19].

*1,5-Anhydroglucitol (1,5-AG)*

1,5-AG is a non-metabolizable polyol, with urinary excretion and 99% tubular reabsorption, which is inhibited in case of hyperglycemia. Thus, stable blood levels of 1,5-AG are rapidly reduced as the renal threshold for glucosuria is exceeded. 1,5-AG indicates rapid changes in glycemia and reflects day-to-day changes in glucose levels [20]. Unfortunately, 1,5 AG has severe limitations in CKD-G5D patients because of the kidney failure, whereas it does not appear to be influenced by mild or moderate renal dysfunction (CKD stages 1–3) [21].

## 2. Glycated albumin

The utility of GA in different clinical settings has been confirmed in numerous studies. Here we discuss its role as a biomarker for glucose control and a prognostic factor for DM-related complications in CKD-G5D patients. The biochemical features of GA and its clinical applications are described in detail in a recent review [22].

### 2.1 Glycated albumin in comparison to other glycemic indices

Compared to HbA1c, which is a long-term glycemic indicator, GA is a medium-term glycemic marker because it reflects the average life of albumin (about 20 days). This means that, compared to HbA1c, GA can promptly indicate either an improvement or a worsening of the patient's glycemic status.

Therefore it could be useful in all those conditions requiring short-term glycemic control, such as after starting or modifying a drug therapy [23].

GA is currently used in Asian countries, including Japan, for DM screening. GA >15.2% [24] and >15.5% [25] were the cut-offs proposed for DM screening. Normal GA levels were recently recorded also in Caucasian subjects and 15.5% was identified as the healthy upper limit for GA in over 1,300 healthy blood donors aged 18-65 years [26, 27].

The risk of complications associated with DM is undoubtedly a topic of great interest and there is a pressing need for valid biomarkers. Many studies have drawn up algorithms to find the best combination of parameters with the highest predictive value. In terms of cardiovascular risk, postprandial blood glucose may be a higher risk factor than fasting glucose [28]. Since albumin is very sensitive to glycation, GA could also be a valid indicator of postprandial glycemic fluctuations, making it possible to identify changes that are not easily detectable with spot blood glucose monitoring, unless done continuously, or with HbA1c, which is less sensitive to sudden, short-lasting glycemic peaks [29].

The ARIC study showed that GA levels are closely related to the incidence of DM and its microvascular complications, with prognostic value comparable to that of HbA1c [30]. In a sub-population of the DCCT/EDIC study, both GA and HbA1c were similarly associated with nephropathy and retinopathy and these associations were stronger when the two measures were used simultaneously. Only HbA1c was associated with the risk of cardiovascular disease (CVD) [31]. GA, similarly to HbA1c, was further associated with the intimal media thickness, a subclinical atherosclerotic indicator, suggesting its utility for estimating atherosclerotic risk [32]. These data suggest that GA may serve as an additional tool for stratification of the risk associated with DM.

There are many other differences that point to the utility of GA as a biomarker complementary to HbA1c for glucose monitoring: it is not affected by iron deficiency, Hb variants, erythropoietin, folate and B12 levels - all clinical conditions that can affect hemoglobin synthesis and erythropoiesis and could be present in CKD-G5D patients. The utility of GA for glycemic control in kidney disease and in dialysis is discussed below.

It is also important to recall that GA quantification is different from fructosamine. GA has specific tests for its quantification and, in addition to the gold standard method, which is HPLC, an enzymatic assay standardized against HPLC has been recently developed which is specific, sensitive and reproducible [33, 34]. However, GA cannot be recommended in clinical conditions involving wide variability in albumin metabolism but further studies are need to clarify this issue [22].

## 2.2 Glycated albumin in chronic kidney disease patients on dialysis

The importance of good metabolic control to reduce the risk of micro- and macro-vascular complications of DM has been amply demonstrated [35-38]. This is also true in CKD-G5D patients in whom accurate assessment of glycemic control, both before and after beginning dialysis, is vital to ensure the best possible outcomes and survival [39-43].

The most important studies exploring the link between glycemic control, cardiovascular events and mortality used HbA1c as a marker of glycemic control. As we mentioned, however, HbA1c does not work properly in CKD-G5D patients and glycemic control remains an important issue for them. Therefore there are various questions awaiting answers: 1) Which is the best glycemic marker for glucose control in CKD-G5D? 2) Can HD and PD patients be effectively managed with the same molecules? 3) Which is the best prognostic marker for these patients?

Here we look at the main studies that have explored the role of GA both as a glycemic control marker and as a prognostic factor in CKD-G5D patients.

### 2.2.1 Glycated albumin for glycemic control

HbA1c has been widely used in CKD-G5D patients for glycemic control and to assess the risk of complications and survival. However, as we noted, it suffers some limitations [20, 39, 44]. In HD patients, GA seems more reliable because it is not influenced by the erythrocyte lifespan or erythropoietin and iron therapy, so it could serve as an alternative marker for glycemic control in these patients [15, 39, 45, 46]. Since GA has a mean life of 20 days, it could also be useful for assessing the effects of some medications in a shorter time than HbA1c [47]. However, its efficacy for glycemic control in HD patients has not yet been firmly established because most studies have examined the correlation between GA and the mean of random serum glucose concentrations instead of continuous glucose monitoring [46, 48, 49]. In CKD-G5D patients, continuous glucose monitoring could be a reference method to correctly evaluate glycemic control over a short period (two days) around dialysis. Differently from HbA1c, the results with this method are unaffected by urea, erythrocyte production and lifespan and also indicate glycemic spikes that are additional risk factors for cardiovascular complications and mortality [50-52]. Continuous glucose monitoring, however, presents some limits for routine use and the need for retrospective markers other than HbA1c is compelling.

Vos et al. [48] investigated the accuracy of GA, HbA1c and fructosamine as indicators of glucose control using 48h continuous glucose monitoring in a mixed population composed of DM CKD stages 4-5, HD and PD. They concluded that GA reflected glycemic control more accurately than the other markers, thus supporting its potential as a marker of choice. Meyer reported a similar result, demonstrating the usefulness of GA and continuous glucose monitoring instead of HbA1c in 23 HD patients [49]. Although promising, the type and number of patients included in these studies limit the strength of the results and future investigations are still needed to confirm the observations so far.

If GA seems to provide a more accurate assessment of glycemic control in DM HD patients, its suitability for this purpose in PD is questionable. There are two main factors that must be considered in PD patients: 1) proteinuria and protein loss into the PD fluid may affect the GA level because of reduced exposure of serum albumin to glucose, and 2) the use of different dialytic solutions may permit glycemic spikes during the therapy [53, 54].

In 71 consecutive PD patients (20 with DM and 51 without), Watanabe et al. observed a significant positive correlation of blood glucose levels with HbA1c, but not with GA. GA correlated with blood glucose only in patients with high serum albumin (>3.2 g/dL). It was also significantly correlated with low protein losses in urine and dialysate (<5.9 g/day). The authors concluded that GA can be used as an indicator of glycemic control in PD patients with normal serum albumin and low daily protein losses in urine and dialysate [55], but for a definitive conclusion further studies in larger groups of PD patients, especially those with higher blood glucose, are needed.

Kobayashi et al. compared 20 PD and 20 HD patients in terms of postprandial plasma glucose, HbA1c, GA and serum albumin for six months, and estimated protein loss in PD by measuring protein concentrations in peritoneal dialysate and by 24h urine collection [56]. Although plasma glucose and HbA1c did not differ significantly between the groups, GA (17.8% versus 20.8%) and GA/HbA1c (2.95% versus 3.45%) were significantly lower in PD patients, suggesting that GA measurements might significantly underestimate blood glucose and that dialysate protein loss could affect GA levels. However, multiple regression analysis identified GA as the only independent factor associated with postprandial plasma glucose. Further, GA was not significantly associated with protein loss because albumin synthesis in the liver made up for the loss in the urine and PD fluid. Therefore, GA might well prove useful for checking glycemic control in PD patients who have no albumin loss, but the factors affecting its decrease have not been clarified.

The type of dialytic solution used in PD is another important issue, in DM and non-DM patients. In PD, the high-glucose solution used to create an osmotic gradient for ultrafiltration may contribute to

hyperglycemia which, in turn, has adverse effects on the patient's survival by promoting cardiometabolic complications [53]. Thus, the solutions may themselves constitute a risk factor for these patients, reinforcing the need for a reliable marker for glycemic control in PD, particularly DM. Anyway, the real-time glycemic effects of different dialysates are hard to demonstrate with conventional glucometers and the most appropriate glycemic control parameter remains to be established. Since GA reflects glycemic spikes well [22], it could be useful for checking the glycemic effects of dialysates.

Lee SY et al. [19] employed continuous glucose monitoring for 25 DM PD patients and correlated it with other glycemic control parameters such as fructosamine, albumin-corrected fructosamine, HbA1c and GA. Glucose levels rose approximately 4-5% in the first hour after exchanging conventional glucose-based dialysates, but not with icodextrin [57, 58], and continuous glucose monitoring effectively reflected the glycemic effects of the different solutions. In addition, HbA1c and albumin-corrected fructosamine, but not GA, were good indicators of glycemic control in PD patients. The authors discussed the GA data, while affirming that they were not sure whether the results were in fact related to the method applied. However, the effects of protein and albumin loss on GA levels were not considered. Additional studies are therefore still needed to clarify this in both DM and non-DM PD patients.

### 2.2.2 Glycated albumin and survival

The five-year cumulative mortality rate among DM patients under dialysis is >70%, with CVDs the leading causes of death [59]. Okada et al. [60] examined the relations between GA and survival in 78 type 2 DM HD patients. The mean follow-up was 35 ± 16 months. The mean GA at enrollment was 23.6 ± 5.1%. A 1% increase in GA was not significantly associated with all-cause mortality. The Kaplan-Meier survival curve suggested no difference in mortality between patients in the higher (GA ≥23%) or the lower (GA <23%) GA group. Similarly, mean HbA1c at the beginning and while on dialysis did not predict mortality. The authors concluded that hyperglycemia may have a small direct influence on survival and that, as previously reported [61, 62], mortality in ESRD is mainly driven by advanced atherosclerosis and other cardiovascular risk factors. In fact, as described in more detail in the next section, GA levels were associated with CVD but not with any increase in CVD mortality, as observed in other studies [18, 45, 63-66].

Isshiki et al. [64] reported different findings in a prospective, longitudinal, observational study on 90 DM patients who had been receiving HD for at least six months. The mean follow-up was 36.0 months. GA and other markers of glycemic control (HbA1c and serum glucose) were measured monthly over a three-month period and their mean values were used as baselines. GA was a significant predictor of all-cause mortality [hazard ratio (HR) for a 1% increase in GA was 1.143 (95% confidence interval, CI: 1.011-1.292)]. The cut-off predicting mortality was 25%, with a cumulative survival rate higher in patients with GA ≤25%.

Shafi et al. [18] measured GA at baseline in 503 HD patients in the CHOICE study [67], a national prospective cohort study with a median follow-up of 3.5 years. In the subgroup of DM HD patients, GA was associated with all-cause mortality [adjusted HR per GA doubling was 1.40 (95% CI 1.09-1.80)], independently of potential confounding factors. Besides GA, the study described a prognostic role for HbA1c too [adjusted HR per HbA1c doubling was 2.30 (95% CI 0.71-7.41)], although only in the small subgroup of patients with available HbA1c the direction and magnitude of the association between GA and mortality were similar to the primary analysis [adjusted HR per GA doubling was 2.53 (95% CI 1.13-4.50)]. Others studies [10, 63, 64, 68, 69] were unable to confirm this association between HbA1c and mortality, possibly because of all the *in-vivo* pre-analytical aspects that affect the ability of HbA1c to reflect the glycemic status of dialysis patients properly.

Other studies confirmed the prognostic role of GA. Freedman et al. [63] ran a longitudinal observational study with a median follow-up of 2.25 years on 444 DM CKD-G5 (401 HD and 43 PD). GA was associated with the risk of death [adjusted HR per 5% GA increase was 1.14 (95% CI 1.01-1.28)] and in the best-fit model increasing GA levels, but not HbA1c and random serum glucose concentrations, were predictive of survival.

Fukuoka et al. [45] evaluated the outcomes of 98 DM HD patients during a follow-up of 47.7 months. GA was quantified at the first dialysis and patients were divided into two groups according to GA levels (<29% and ≥29%). As GA levels are about three times HbA1c, the authors used this cut-off because of previous reports suggesting that HbA1c >10% before the start of HD was a predictor of survival [70]. The one-, three- and five-year cumulative survival rates were significantly higher in the low GA group (88.8%, 75.6% and 54.6%) than the higher one (77.3%, 54.1% and 42.2%). After multivariate adjustment, high GA levels were an independent predictor of survival [HR per increment of one unit was 2.211 (95% CI 1.195-4.092)] whereas HbA1c was not [HR per increment of one unit was 0.929 (95% CI 0.734-1.175)].

The preliminary results of the GIDE study (Glycemic indices in dialysis evaluation) [65], an ongoing observational prospective study designed to compare multiple markers of glycemic control for predicting complications in more than 3000 DM CKD-G5 patients, confirmed that HbA1c levels were independent of glycemic control and open to alternative markers, such as GA.

Similar results have been reported by Chen et al. [66] who tested whether the relationship between high GA and mortality observed in previous studies could be confirmed in a large sample. GA was measured in 1053 patients in the 4D clinical trial (The German Diabetes and Dialysis Study), a prospective randomized controlled trial which examined the effect of atorvastatin on cardiovascular events and survival in DM patients under HD during a mean follow-up of 3.96 years [71]. GA and HbA1c were measured at 0, 6 and 12 months. Multivariable-adjusted Cox-proportional hazard analysis indicated a significantly higher mortality risk in patients with GA in the 4th quartile (>21%) compared to the 1st (GA ≤14.5%) (reference) [HR was 1.32 (95% CI 1.01-1.73)]. When the same analysis was done on HbA1c, a discontinuous relationship was seen between HbA1c and mortality. The risk increased in the 3rd HbA1c quartile (>17.5% and ≤21%) [HR was 1.36 (95% CI 1.04-1.77)] but not in the 4th [HR was 1.27 (95% CI 0.96-1.67)] compared to the 1st (≤5.8%) (reference). Furthermore, time-dependent analyses using repeated GA and HbA1c values found a higher risk with repeated GA values in the 4th quartile [HR was 1.39 (95% CI 1.05-1.85)], but not HbA1c [HR was 0.87 (95% CI 0.70-1.08)]. Instead, the risk was lower for patients in the 2nd (>5.8% and ≤6.6%) and 3rd HbA1c quartiles (>6.6% and ≤7.4%). The study by Chen is to date the largest confirming a relationship between GA and mortality, and the U-shaped relationship between HbA1c and mortality previously observed in other studies [42, 65, 72]. These last provided evidence of: 1) the existence of additional factors that can confound the relationship between HbA1c and survival; 2) the need for reliable markers for glycemic control in dialysis patients.

The findings discussed here suggest GA is a better tool for DM management in these patients, although reference intervals have still to be validated for clinical purposes.

### 2.2.3 Glycated albumin and cardiovascular outcome

Patients on dialysis have an increased risk of CVDs and this risk is further increased in the presence of DM. Most of the studies previously discussed, in addition to the association between GA and all-cause mortality, also examined CVD and CVD-related mortality.

Among the 78 type 2 DM patients under dialysis studied by Okada [60], 15 died from CVD and 23 cases of CVD developed in 20 patients during the follow-up. A 1% increase in GA was not significantly associated with CV mortality [HR 0.88 (95% CI 0.75-1.03)] or development of CVD [HR 1.09 (95% CI 0.96-1.24)]. Similarly, the mean HbA1c value at the beginning of dialysis and on dialysis did not predict CV mortality or CVD. However, 15 patients who developed CVD belonged to the higher GA group (39 patients with GA ≥23%), only five to the lower one (39 with GA <23%). The higher GA group, but not HbA1c, had a significantly higher rate of CVD than the lower group [HR 3.25 (95% CI 1.04-10.19)]. Thus, GA seemed not to be related to mortality and CVD mortality, but with the development of CVD.

Yamada et al. [73] explored in DM HD patients the association between GA and HbA1c and peripheral vascular calcification, which is highly prevalent in CKD-G5 patients and enhances cardiovascular and other causes of mortality. Glycemic control in this study was rather good: GA was 24.5±8.4% and HbA1c 5.9±1.3%. Vascular calcification was present in 65.3% of these DM HD patients. Multiple regression analyses suggested that both HD duration and GA, but not HbA1c, were associated with vascular calcification. HbA1c became statistically significant when a weekly erythropoietin dose was added to the statistical model. This confirms that GA provides a better measure of glycemic control in DM HD patients, and HbA1c suffers some limits.

Fukuoka [45] suggested the role of GA as a predictor of long-term survival in DM HD patients. Considering the causes of death, a Cox proportional hazard model indicated that high GA (≥29%) was a significant predictor of CVD compared to the lower GA group [HR 2.971 (95% CI 1.064-8.298)].

Similar results were reported by Shafi [18] in their 503 HD patients in the CHOICE study [67]. They recorded 302 CVD events, 208 of them in the DM sub-group. There were 159 deaths due to CVD, of which 109 in the DM sub-group. GA was associated with a linear increase in risk of first CVD events (p for change in slope at the median = 0.95) and CVD mortality (p = 0.47).

Isshiki et al. [64] also confirmed the role of GA as a predictor of cardiovascular mortality in DM HD patients. Eleven patients of the 90 enrolled in the study died. All the patients who died because of CVD had poor glycemic control, according to the median GA level. Kaplan-Meier analyses indicated that CVD mortality was greater in patients with high GA (>25%) than low (≤25%).

### 2.2.4 Glycated albumin and other clinical conditions

Some studies also examined the potential association of GA with other specific causes of mortality, in addition to CVDs, and to hospital admission rates. Increasing GA levels were associated with hospitalization in the 17 days after quantification [18], whereas HbA1c and blood glucose were not. During the observation time (median follow-up 2.25 years), 86.71% of 444 DM HD patients had at least one hospital admission with a median number of 10.55 days of hospitalization per year (25-75th percentiles 4.15-49.46 days). Hospitalization rates per quintile of GA differed significantly between the lowest and the highest quintiles (5.90% *vs.*9.67%).

In the study by Isshiki [64], the non-cardiovascular causes of death among DM HD patients were infection, renal bleeding, cerebral bleeding, malignancy and multiple organ failure. The rates of non-cardiovascular mortality were the same in the group with high (>25%) and low GA (≤25%).

The main non-cardiovascular causes of death in the study by Fukuoka [45] were infectious diseases, malignant diseases and others. Low (<29%) and high (≥29%) GA groups did not differ in the incidence of these events. Considering infections, a Cox proportional hazard model indicated that high GA was not a predictor of death compared to low GA [HR 1.478 (95% CI 0.467-4.681)] nor was a 1% increase in GA [HR 0.983 (95% CI 0.933-1.035)]. This study seems to reinforce the utility of GA as a marker for glycemic control in patients under dialysis and points to its potential as a prognostic marker for mortality, mainly for cardiovascular causes, and hospitalization.

## Conclusions

We have conducted a novel review on GA as a biomarker for glucose control and a prognostic factor in CKD-G5D. In CKD-G5D patients, accurate glycemic measurements before and after beginning dialysis are vital to improve outcomes and survival. According to the KDOQI, blood glucose monitoring in combination with HbA1c is suggested for DM management in CKD-G5D, even if HbA1c suffers limits in ESRD patients. No other biomarker, such as GA, is mentioned in the main guidelines, although several studies confirm the utility of GA in different clinical settings.

GA can promptly indicate improvement or worsening of patients' glycemic status. In HD and PD patients, GA reflects glycemic control more accurately than the other markers. In HD patients, GA seems to give a more accurate picture of glycemic control than in PD patients, where its use is still debated. Therefore, further studies in larger groups of PD patients are needed. Besides the potential as

a biomarker for glucose control, GA can be a useful predictor of survival and of cardiovascular mortality in DM HD patients.
Research on GA is still in the early stages, but we believe it merits further studies to clarify its potential role for management in CKD-G5D.

## Figures

**Figure 1.**
**Dialysis-related cardio-metabolic diseases and biomarkers.** Diabetes mellitus (DM) and cardiovascular diseases are both risk factors for dialysis and dialysis-related clinical outcomes. Product of glycations, which are produced at high level in DM, have a direct role as pathogenic molecules. Among these, glycated hemoglobin, fructosamine and glycated albumin, which are used as markers for screening DM and monitoring patient outcome, have some pros and cons in CKD-G5D patients.

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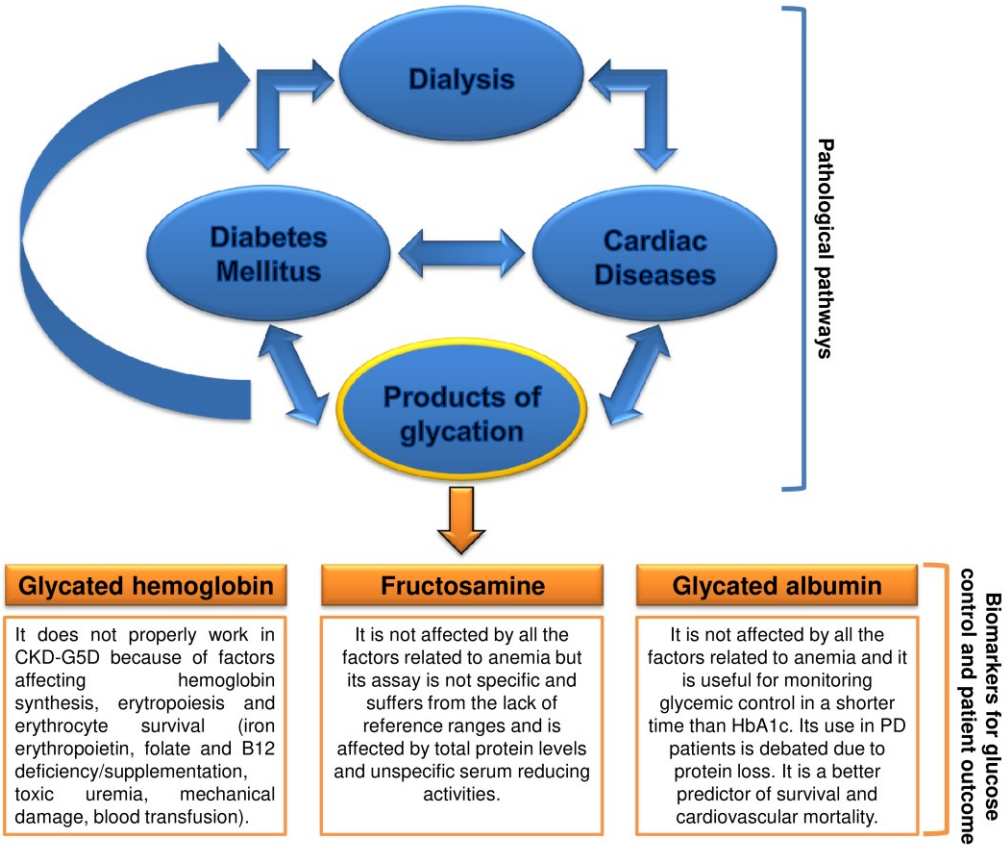
**Figure 1**


Dialysis
Diabetes Mellitus
Cardiac Diseases
Products of glycation
Pathological pathways
Glycated hemoglobin
It does not properly work in CKD-G5D because of factors affecting hemoglobin synthesis, erytropoiesis and erythrocyte survival (iron erythropoietin, folate and B12 deficiency/supplementation, toxic uremia, mechanical damage, blood transfusion).
Fructosamine
It is not affected by all the factors related to anemia but its assay is not specific and suffers from the lack of reference ranges and is affected by total protein levels and unspecific serum reducing activities.
Glycated albumin
It is not affected by all the factors related to anemia and it is useful for monitoring glycemic control in a shorter time than HbA1c. Its use in PD patients is debated due to protein loss. It is a better predictor of survival and cardiovascular mortality.
Biomarkers for glucose control and patient outcome