Review Article

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Glycaemic Monitoring in Diabetic Kidney Disease – Is HbA1c Reliable?

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Abstract:

Diabetic kidney disease (DKD) is a known complication of diabetes mellitus that increases patients' risks of developing end-stage renal failure requiring dialysis treatment and vulnerability of fatal outcomes resulted from cardiovascular events. Therefore, a good diabetic control among patients with DKD is essential. Nevertheless, monitoring glycaemia in DKD is very challenging. The use of the gold standard glycaemic marker, haemoglobin A1c (HbA1c), is complicated by many hindrances associated with both biochemical and physiological derangements of DKD. Despite the constraints, the Kidney Disease Improving Global Outcome has recommended the use of HbA1c as a reliable glycaemic marker in DKD patients, whose estimated glomerular filtration rate is down to 30 millilitres/minute per 1.73 meter^2. In this article, we discuss the reliability and limitations of HbA1c as an advocated glycaemic marker in DKD. Considering that the reliability of HbA1c is highly dependent on the interpretation of the results, we also highlighted the common potential factors that can affect HbA1c interpretation in patients with DKD. The article also discusses the issues related to the utility of glycated albumin and serum fructosamine as alternative glycaemic biomarkers, and continuous glucose monitoring as a complementary marker to HbA1c in clinical practice. Understanding the HbA1c values and their limitations is important to ensure accurate interpretation of glycaemic status and to achieve optimal diabetic control in patients with DKD.

Keywords: diabetes, CGM, glycaemia, HbA1c, kidney disease

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Introduction

Diabetic kidney disease (DKD) is one of the devastating complications of diabetes mellitus (DM). About 20.0–40.0% of diabetic patients develop this disease, with approximately half of them eventually progressing to end-stage renal failure (ESRF) that requires renal replacement therapy.[1] Patients with DKD are also at great risk of developing cardiovascular disease, which increases the risks of a fatal outcome.

Comprehensive strategies to reduce the risks of kidney disease progression and cardiovascular disease in patients with DKD are essential. One of the bottom-line strategies, recommended by the Kidney Disease Improving Global Outcome (KDIGO), is diabetic control. A good over time diabetic control is required to achieve a glycaemic target that is usually set to prevent various diabetic complications; including DKD.[2]

DKD is characterised by complex biochemical and physiological derangements, making glycaemic monitoring very challenging. Various glycaemic markers have been studied; however, none are considered ideal. In this article, we discuss the value of the commonest glycaemic control tool, which is haemoglobin A1c (HbA1c), and various factors that potentially affect its interpretation in patients with DKD. Issues related to the utility of other alternative markers; including continuous glucose monitoring (CGM), are also highlighted. The information in this article is valuable in helping clinicians and laboratorians to better understand the values and limitations of HbA1c in DKD; thus, ensuring optimal diabetic control in patients with this disease.

The value of HbA1c in DKD

HbA1c was first described by Rahbar and associates in 1968, and since then, it has become the most important tool in the management of DM.[3] An HbA1c value reflects the average blood glucose over the period of 8–12 weeks, based on the prediction of red blood cell (RBC) lifespans. The levels correlate well with the average blood glucose obtained by CGM measured over a 12-week period in diabetic subjects.[4]

Although, it has been advocated as the gold standard glycaemic biomarker, the value of HbA1c is compromised in patients with DKD. In diabetic patients with kidney failure, HbA1c results may not accurately reflect the patients' current glycaemic status.[5] When the average blood glucose is supposed to be 126 mg/dl at HbA1c level of 7.0%; a study conducted in type 2 diabetic subjects with kidney disease found that the average blood glucose was higher; for example,144 mg/dl at the corresponding HbA1c level. This implies that HbA1c were relatively lower; thus, underestimating as well as inaccurately reflecting glycaemia in patients with DKD.[6,7]

Another factor contributing to compromised values of HbA1c in DKD is the tests inability to detect hypoglycaemic episodes, and reflect glycaemic variability. In patients with DKD, assessment of these conditions is important, as they are associated with high reactive oxygen species that may confer higher risk for developing macrovascular and microvascular diabetic complications.[8] As the HbA1c measures the amount of glycated Hb in RBCs that areknown to have an average lifespan of 12-weeks, the test cannot readily assess the occurrence of acute glycaemic changes; nor glycaemic variations at a specific time.

Various biochemical and physiological derangements related to kidney failure are also important factors that contribute to compromised values of HbA1c in DKD (Table 1). The common conditions that lead to misleading glycaemic interpretation; thus, affecting the value of HbA1c in DKD are discussed in detail within the subsequent heading of this article.

The degree of compromised values of HbA1c are higher in more advanced stages of DKD. Although, the findings from many published studies have shown that HbA1c results are reliable in mild to moderate stages of chronic kidney disease (CKD) (stage 1 to 3, or estimated glomerular filtration rate (eGFR) levels between 90 to 30

millilitre/minute (ml/min) per 1.73 meter^2 (m^2), the reliability of the test becomes compromised in more advanced stages of CKD (stage 4 to 5, or eGFR <30 ml/min per 1.73 m^2).[10] In patients treated with dialysis, the reliability is further compromised, due to the presence of more pronounced blood glucose variability[10] in addition to DKD-associated biochemical and physiological abnormalities.[11,12]

Table 1 Factors compromising the clinical value of haemoglobin A1c in diabetic kidney disease

HbA1c limitation factor
Inability to detect hypoglycaemic episodes
Inability to reflect glycaemic variability
Underestimation of glycaemia
DKD-associated biochemical and physiological abnormalities
Uraemia
Anaemia
Blood transfusion
Blood loss
Erythropoietin stimulating agent
Hypertriglyceridemia
Haemolysis
Hyperbilirubinemia

HbA1c=haemoglobin A1c, DKD=diabetic kidney disease

Despite having compromised reliability, HbA1c still remains considered as the best available glycaemic marker for patients with advanced stage DKD, and those on dialysis. A study conducted in diabetic subjects with eGFR <60 mL/min/1.73 m^2 reported that GA and serum frcutosamine were no less variable than HbA1c when compared to CGM glucose levels.[13] Another study, conducted in an older diabetic population with various CKD stages, also reported similar findings. Therefore, this suggests that HbA1c may not need to be necessarily replaced with alternative markers.[14] In other studies, when correlated to CGM, HbA1c was shown to be more superior than other markers.[6,7] Therefore, as recently as 2020, the KDIGO clinical practice guidelines have advocated HbA1c as a reliable biomarker for monitoring glycaemic control in patients with DKD; including those in stage 4 and 5. HbA1c targets should be individualized and flexible, according to an individual's risk, life expectancy, disease or therapy burden as well as the patient's preferences.[15]

Although, recommended as a useful and reliable marker, the use of HbA1c in DKD; especially for those on dialysis, should consider all the limitations and potential factors that may impact the results: especially when extreme values or discordances with symptoms are encountered. Lack of awareness of the limitations and misleading effects of HbA1c results may cause inaccurate glycaemic status interpretation; and thus, suboptimal diabetic control in certain circumstances.

Biochemical and physiological abnormalities invalidating HbA1c results in patients with DKD

1. Uraemia

A high urea concentration increases the formation of carbamylated Hb (cHb), through the non-enzymatic condensation of cyanate in the urea molecules with the N-terminal valine of the globin chain, subsequently altering the structure and function of the Hb.[16] This chemically modified Hb derivative interferes with the HbA1c measurement on methods based on electrical charges; such as, electrophoresis and chromatography. However, with current technology advancements, cHb interference is probably not a major issue anymore. However, other consequences of hyperuraemia; such as, inhibition of erythropoiesis, reduction of RBC lifespans, alteration of the Hb glycosylation process, and uraemic acidosis, are not avertible; even by the most sophisticated measurement techniques. Consequently, the results obtained may not accurately reflect the glycaemic status in patients with DKD; especially those on haemodialysis (HD).[17-19]

2. Anaemia

Anaemia is a common feature of DKD; especially in those undergoing dialysis treatment.[20] The causes include: relative erythropoietin (EPO) deficiency, functional and absolute iron deficiency, folate and B12 deficiency, shortened RBC survival, and uraemic-induced inhibition of erythropoiesis.[18] Despite the various causes of anaemia, the majority of the studies have focused on the effects of iron deficiency anaemia (IDA) on HbA1c levels. They found that IDA spuriously increased HbA1c, with a subsequent level reduction seen after iron supplementation.[21,22] The exact mechanism is not clear, but it might be related to delayed clearance of old circulating RBCs in response to the reduction of reticulocytes production in the bone marrow. This is a counterbalance mechanism to allow the body to maintain a stable, total RBC population at a point of time.[23] Another postulated mechanism is the increased tendency of the globin chain for glycosylation, due to the changes in the quaternary structure of Hb, and increased glycolytic fraction, due to decreased Hb concentration.[24]

3. Blood transfusion

Blood transfusions are required in cases with ineffective erythropoietin stimulating agent (ESA) treatment, ESA resistance, and bone marrow failure.[25] The effects of blood transfusions on HbA1c are conflicting among studies. In an earlier study, in 1986, HbA1c was found to increase in diabetic recipients after a blood transfusion on several occasions. It was thought that exposure of Hb to dextrose in blood storage medium led to increased Hb glycation in the donated blood; thus, increasing the HbA1c level in the diabetic recipients.[26] However, a later study revealed a contradicting finding. The HbA1c levels were shown to decrease in a majority of recipients receiving at least one pack of RBCs, suggesting the lowering effects of blood transfusions on HbA1c levels. Theoretically, the donated RBCs contain a typical, or lower amount of pre-formed glycated Hb. Consequently, this produces a "dilutional effect" in diabetic recipients; thus, lowering their HbA1c levels. This effect is more pronounced in subjects with a higher pre-transfusion HbA1c level, and in those who receive a high volume of blood transfusions.[27]

4. Blood loss

In patients with DKD, the risk of acute and chronic blood loss is increased due to multiple factors; such as, uraemic-associated bleeding diathesis, use of medications that affects haemostasis, co-morbid conditions predisposed to bleeding as well as haemodialysis itself.[28] The effects of blood loss on HbA1c in patients with DKD have not been extensively studied. In non-diabetic adults, acute blood loss has been shown to reduce HbA1c.[29] HbA1c that was measured post blood donation in diabetic subjects was also shown to be reduced.[30-32] In theory, when some amounts of blood are evacuated; either during a blood donation or from acute blood loss, a compatible percentage of HbA1c will be also be lost. The bone marrow will try to compensate for the RBCs loss by increasing the production of new RBCs, which are devoid of Hb. As the glycation of Hb is a slow process, the increasing number of immature erythrocytes in circulation, therefore "dilute" the HbA1c levels at least for 2 months after blood loss.[31]

5. ESA

ESA is initiated in patients whose Hb is less than 10 grams per decilitre when the Hb continues to fall, despite adequate iron therapy.[33] EPO is one of the ESAs that stimulates proerythroblasts in bone marrow to further proliferate and develop into erythroblast, reticulocytes, and subsequently mature RBCs. A few studies have shown that the use of EPO in DKD patients for the treatment of anaemia resulted in a significant change in the level of the HbA1c; independent of glycaemia. The effects of EPO on HbA1c are mediated through its effects on erythroid lineage, causing the acceleration of RBCs maturation that subsequently

reduces its lifespan. Besides this, the formation of new RBCs through erythropoiesis alters the existing proportion of young to old RBCs; regardless of the glycaemic level. Similar the "dilutional effect"; such as seen after blood loss occurs, results in reduced HbA1c levels. The effects are more noticeable when the EPO dosage is adjusted, due to the fluctuation of erythropoiesis.[34]

An adjustment factor to estimate the patient's glycaemic control, using haematocrit (Hct) value in anaemic patients receiving EPO treatment, has been proposed: HbA1c x 1.14 (if Hct >30.0%) or HbA1c x 1.19 (if Hct <30.0% and treated with low dosages of EPO), or HbA1c x 1.38 (if Hct <30.0% and treated with high dosages of EPO).[35] Nonetheless, an extensive validation of the equation is required before it can be used routinely in clinical practice.

6. Hypertriglyceridemia

Triglyceride (TG) levels are often used to elevate kidney disease; especially for those on HD, due to raised levels of apoB, decreased activity of lipoprotein lipase (LPL) and hepatic lipase enzymes as well as reduced apoB-riched lipoproteins catabolism; such as, very low-density lipoprotein and intermediate-density lipoprotein. Besides this, the prolonged use of heparin during HD may cause depletion of LPL; reducing the TG-rich lipoproteins catabolism leading to high blood TG.[36]

The effect of TG on HbA1c is conflicting. Falko et al. demonstrated that TG led to spurious elevation of HbA1c in a diabetic patient.[37] On the contrary, Garrib et al. reported false low HbA1c in diabetic patients with hypertriglyceridemia.[38] A recent, prospective study, which examined the effects of TG on analytical measurement of HbA1c using high performance liquid chromatography method, found that TG was not an important factor to be considered in the interpretation of HbA1c.[39] Although, TG does not interfere with the HbA1c measurement method, whether or not it affects the glycation of Hb requires further research.

7. Haemolysis

The presence of oxidative stress, such as uraemic condition, leads to the development of chronic haemolysis. Haemodialysis-induced-haemolysis may also occur in patients receiving haemodialysis treatment as a result of mechanical, technical, or dialysate factors.[40] Haemolysis leads to shortened RBC lifespans; thus, falsely reducing the HbA1c values. Besides this, the breakdown of RBCs during haemolysis releases free Hb that is subsequently metabolized to bilirubin, leading to hyperbilirubinemia. Bilirubin, through its property as an anti-oxidant, inhibits oxidative stress that subsequently inhibits glycation of glucose to the carbonyl intermediate in the early Maillard reaction.[41,42] It also decreases insulin resistance, while increasing the activity of glucose transporter for cellular glucose uptake.[43] Moreover, haem oxygenase-1 is involved in the conversion of Hb to bilirubin, following haemolysis. This enhances the insulin sensitivity and glucose metabolism, leading to a lower Hb glycation rate and HbA1c result.[44]

The value of alternative glycaemic bio-markers in DKD

Glycated albumin (GA) and serum fructosamine are the two common, alternative biomarkers for HbA1c, for providing information on glycaemic control in DKD. GA is ketamine, formed through non-enzymatic glycation of albumin with reducing sugars, such as glucose.[45] It reflects glycaemic status of the preceding 2-3 weeks, based on albumins short half-life, and shows a strong correlation with complications of DKD.[46] As the level is independent of the Hb amount, the RBCs lifespan, iron, and EPO treatment, GA is thought to have some advantages over HbA1c in DKD.[47] Most studies have reported that GA is better than HbA1c in reflecting glycaemia in DKD; especially in stage 4 and 5, including those on dialysis.[9,48] As GA is a protein derivative, increased urinary protein loss and malnutrition in chronic kidney disease and dialysis may lower GA levels, leading

to an underestimation of glycaemia. Other factors; such as, acidosis and hyperosmolality, may reduce albumin glycation, causing false low GA levels. Conversely, hypoosmolality and hyperphosphatemia, which are also common in DKD, may accelerate albumin glycation; thus, increasing the GA level; regardless of glycaemia.[46]

Though demonstrating superior accuracy in reflecting glycaemia, as compared to HbA1c in DKD in some studies, its performance data at different stages of kidney disease in comparison to HbA1c is still insufficient. In addition to that, non-standardized measurement methods and lack of uniform reference ranges also restrict the wider use of this biomarker.[49] Based on the current limitations, local or international guidelines neither recommend the routine use of GA, nor as a replacement of HbA1c for monitoring glycaemia in patients with DKD at present.

While GA represents glycated albumin, serum fructosamine represents all glycated blood proteins. It measures short-term glycaemia, and it is similarly affected by factors affecting GA. Since, serum fructosamine is less extensively studied than GA and HbA1c, the data on its performance in DKD is still sparse. Besides this, the relationship between serum fructosamine and disease outcomes; such as, those developed for HbA1c and GA, is not well-established in DKD. As with GA, the lack of any standardized method measurement has also further contributed to the limited use of serum fructosamine in patients with DKD.[46]

The value of CGM in DKD

CGM utilizes sensors implanted in the subcutaneous tissue to measure the interstitial glucose concentration at pre-determined time intervals within a specific duration. The accuracy of the device has been proven satisfactory when compared with the serum glucose levels. [50] Therefore, CGM is considered as useful diabetic technology, which complements HbA1c, in providing a better assessment of glycaemia in conditions when the reliability of HbA1c is compromised; such as patients with advanced DKD: including those on dialysis.[51]

The data obtained from CGM is useful for determination of CGM metrics. One of the important GCM metric is GMI, or previously known as estimated A1c (eA1c). A GMI value corresponds to HbA1c in %; thus, serving as a proxy for long-term glycaemia in the previous 3 months. A recent study concluded that 14 day CGM data provided a good estimate of glucose metric for a 3-month period, and was considered sufficient for generation of a CGM-derived mean glucose used for the estimation of GMI.[52] The value is estimated from a formula; for example, GMI [%] = 3.31 + 0.02392 × [mean glucose in milligram per decilitre].[53] Another CGM metric of clinically importance, is time in range. Time in range is a glycaemic control metric that provides more actionable information than HbA1c. It allows for the identification of hypo- and hyperglycaemia, and assessment of glycaemic variability in patients with insulin-requiring diabetes as well as for those at risk of hypoglycaemia. It includes the determination of time in target range (TIR), time below range (TBR) and time above range (TAR). The values are expressed as the percentage of CGM readings, and/or average hours and minutes spent in each range.[54]

Although, reports validating the usage of CGM in DKD are still lacking, it may be considered most ideal for patients with advanced DKD; especially those on dialysis, for whom reliability of HbA1c is compromised. In fact, KDIGO has recently recommended the use of GMI for assessment of glycaemia in patients with advanced DKD; including those on dialysis. Despite of gaining importance in glycaemic management of DKD, routine use of CGM is currently restricted, due to a lack of clinical consensus and high device costs. Moreover, more research is required to

investigate the interferences and pitfalls of the device, so as to ensure the results reliability and optimal use in patients with advanced DKD; particularly those treated with dialysis.

Conclusion

HbA1c is a more reliable marker than GA and serum fructosamine for monitoring glycaemia in DKD, with eGFR down to 30 ml/min/1.73 m^2. However, the reliability of its use is highly dependent on the knowledge and awareness of the limitations and factors affecting its result interpretation. In patients whose HbA1c is discordant with the symptoms, or in the presence of confounding factors, CGM can be used as a complementary tool to better index the patients' glycaemic status; thus, ensuring more accurate glycaemic monitoring and management in patients with DKD.

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Conflict of interest

There are no potential conflicts of interest to declare.

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