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NDT Perspectives

Are there better alternatives than haemoglobin A1c to estimate glycaemic control in the chronic kidney disease population?

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ABSTRACT

Background. Although measurement of haemoglobin A1c has become the cornerstone for diagnosing diabetes mellitus in routine clinical practice, the role of this biomarker in reflecting long-term glycaemic control in patients with chronic kidney disease has been questioned.

Methods. Consensus review paper based on narrative literature review.

Results. As a different association between glycaemic control and morbidity/mortality might be observed in patients with and without renal insufficiency, the European Renal Best Practice, the official guideline body of the European Renal Association-European Dialysis and Transplant Association, presents the current knowledge and evidence of the use of alternative glycaemic markers (glycated albumin, fructosamine, 1,5-anhydroglucitol and continuous glucose monitoring).

Conclusion. Although reference values of HbA1C might be different in patients with chronic kidney disease, it still remains the cornerstone as follow-up of longer term glycaemic control, as most clinical trials have used it as reference.

Keywords: diabetes, chronic kidney disease, glycaemic control, guideline

INTRODUCTION

Diabetes mellitus is the leading cause of chronic kidney disease (CKD) and is associated with an excessive (cardiovascular) morbidity and mortality [1]. Diabetic nephropathy is diagnosed in 20–40% of patients with type 1 or type 2 diabetes [2] and accounts for 30–50% of end-stage renal disease (ESRD) cases [3]. Although hyperglycaemia is the biochemical hallmark of diabetes, haemoglobin A1c (HbA1c) measurement has slowly become the cornerstone for diagnosing diabetes mellitus since its introduction in routine clinical practice in 1976 [4, 5]. For the diagnosis of diabetes, the normal range cut-off point is 48 mmol/mol (6.5%) [6]. However, some authors suggest that population-specific optimum cut-off points may be necessary in the future as an HbA1c-based diagnosis has substantially different consequences for diabetes prevalence across ethnic groups and populations [7, 8]. Differences in intracellular–extracellular glucose balance, differences in red cell survival (e.g. haemolytic anaemia) and non-glycaemic genetic determinants of haemoglobin glycation are possible contributing factors of the racial and ethnic differences. For that reason, reliance on HbA1c as the sole criterion for the diagnosis of diabetes in non-Caucasians could lead to misclassification [8]. In addition to its recent role as a diagnostic marker, HbA1c is used in the

assessment of the degree of metabolic control in diabetic patients and in risk prediction of vascular complications. Although one measurement gives information for the diagnosis of diabetes, HbA1c is mainly considered as a longitudinal parameter, allowing guidance of treatment in the longer term [9].

There are many advantages of using HbA1c rather than blood glucose for screening and diagnosing diabetes: less sensitivity to pre-analytical variables, lower within-subject biological variability, little/no diurnal variations and little/no influence from acute stress [10]. In contrast, the underlying challenge of HbA1c remains 2-fold: (i) accurately reflect the mean plasma glucose levels within a longer time span, taking into account different parameters such as age, ethnicity, geography, pregnancy and underlying disease [11] and (ii) accurately relate the degree of glycaemic control to important outcomes, such as death and diabetes associated morbidity.

There is conflicting evidence regarding the role of HbA1c in reflecting long-term glycaemic control in CKD patients [10, 12, 13]. In addition, the association between glycaemic control and outcome might be different in CKD versus no CKD patients. Given the unique conditions associated with the uraemic environment, there is thus a need to evaluate markers to monitor glycaemic control specifically in the CKD population.

HBA1C: BIOCHEMISTRY, METHODOLOGY AND VARIABILITY

After discovery of the heterogeneity of Hb by the deviating migration speed of sickle cell Hb in an electrical field, five subfractions were identified in 1958 [14]. Hb consists of ∼97% adult Hb (HbA), 2.5% HbA2 and 0.5% fetal Hb (HbF). In healthy individuals, ∼6% of HbA is glycated. Glycated Hb consists of HbA1a, HbA1b and HbA1c [15, 16]. In 1969, Rahbar *et al.* demonstrated elevated fast Hbs in erythrocytes of diabetes patients [17]. Trivelli *et al.* suggested a relationship between fast Hbs, mean blood glucose concentrations and long-term complications in diabetes patients [18].

Being the major form of all glycohaemoglobin species in human blood, HbA1c has been defined as the result of a non-enzymatic reaction (classical Maillard reaction) of condensation between the aldehydic group of glucose and the N-terminal amino group of the β-chain of HbA0 [*N*-(1-deoxyfructosyl) Hb] [19]. To compensate for intra- and interindividual variation in the total Hb concentration, HbA1c has been expressed as a ratio (HbA1c/total Hb) [20]. Approximately 50% of a given HbA1c value is the result of glucose exposure during the previous 30 days and 40 and 10% is the result of glucose exposure during the previous 31–90 days and 91–120 days respectively. HbA1c is neither considered dysfunctional nor harmful [21].

Different analytic systems have been developed for measurement of HbA1c, either based on difference in charge (ion-exchange chromatography, electrophoresis, capillary electrophoresis and isoelectric focusing) or structural difference (affinity chromatography, immunochemical assays and enzymatic assays). Before the 1980s, methods based on a subtle difference in iso-electric point suffered interferences from other members of the Hb family (e.g. Schiff base, carbamylated Hb and variants) and had to deal with the dominating (20-fold concentration) parent HbA0. New automated high-performance liquid chromatography (HPLC) systems (used in ±60% of the laboratories in Europe) provide reliable results without interference by Schiff base or carbamylated Hb. Immunochemical assays (±35% of users) use antibodies against the β N-terminal glycated tetrapeptide or hexapeptide group or variation of this, but have difficulties in achieving a coefficient of variation of <2% [20]. Finally, new enzymatic tests were developed in the 2000s [22].

Due to the wide range of methods used, each with their own definition of the analyte (e.g. HbA1c, fast Hbs or total Hb) and specificity (e.g. HbF, carbamylated Hb or incomplete separation), standardization became an important topic in the 1990s. Based on the described definition of HbA1c, the International Federation of Clinical Chemistry (IFCC) Working Group on Standardization of HbA1c developed a reference measurement system for HbA1c [19, 23] by implementation of two equivalent reference methods (HPLC/mass spectrometry and HPLC/capillary electrophoresis), characterization of primary and secondary calibrators and organization of an international network of laboratories performing one or both reference procedures. Pure HbA1c and pure HbA0 were isolated from human blood and mixed in well-defined proportions to a certified primary reference material set used to calibrate the primary reference measurement system (PRMS) [24]. The results obtained on routine samples by clinical laboratories using the aligned analytical systems were traceable to the reference measurement system, obtaining standardization of HbA1c measurement. At this moment, the IFCC reference system is the only valid analytic anchor from which all other units in which HbA1c might be expressed are derived. HbA1c results could be reported in both IFCC (mmol/mol) and derived U.S. National Glycohaemoglobin Standardization Program (NGSP) (%) numbers [25, 26]. The NGSP was created to harmonize HbA1c results through the implementation of assay traceability to the ion-exchange HPLC method [27, 28] without providing a stable scientific-based anchor, originally used in the Diabetes Control and Complications Trial [29].

Unfortunately, all the main data of the trials supporting the clinical use of HbA1c have used assays aligned to the U.S. NGSP, resulting in a less specific method as approximately one-third of the chromatographic component denoted as HbA1c is not HbA1c. The conversion of analytical and clinical data from the NGSP system to the IFCC system has become possible by the so-called IFCC-NGSP 'master equation' [NGSP (%) = 0.09148 × IFCC (mmol/mol) + 2.152] [28, 30, 31].

In addition, the use of a bedside HbA1c point-of-care testing (POCT) seems attractive, but at this moment, the reliability and performance level of this approach may be questioned [32–34]. The conclusion of a systematic review and meta-analysis stated that there is insufficient evidence to date for the effectiveness of HbA1c POCT in the management of diabetes [35].

FACTORS INFLUENCING HBA1C VALUES BESIDES GLYCAEMIA

Erythropoiesis and red cell lifespan heterogeneity

The formation of HbA1c is mainly dependent on the interaction (intensity and duration) between blood glucose concentrations and red blood cells (RBCs). On average, erythrocytes survive 117 days in men and 106 days in women. At any given time, a blood sample contains erythrocytes of different ages with a predominance of younger elements and with different degrees of exposure to hyperglycaemia [36]. An unexplained discordance between HbA1c and other measures of glycaemic control can be partly the result of differences in red cell lifespan [37]. Larger longitudinal studies should be carried out to confirm if the observed variation in RBC survival might lead to inappropriate clinical decision-making [38] (Table 1).

A decreased erythropoiesis, due to iron or vitamin B12 deficiency or aplastic anaemia, leads to an increase in the number of circulating aged red cells and accordingly in a progressive rise in HbA1c not related to glycaemic control [39]. Iron deficiency anaemia causes an increase in HbA1c of up to 2%, which can be reversed with iron supplementation [40]. On the contrary, a decrease in HbA1c is observed after administration of erythropoietin, iron and vitamin B12 and in the case of haemolytic anaemia/reticulocytosis. Due to a reduced red cell survival, younger erythrocytes have less time exposure to ambient glycaemia and thus less glycation [41, 42].

Table 1. Comparison of the different glycaemic markers in diabetic patients with chronic renal failure

Marker	Advantages	Disadvantages
HbA1c	Marker of long-term glycaemic concentrations. Excellent standardization of HbA1c assays. Universally available PRMS. Scientific evidence on association with outcomes from several trials. In comparison with blood glucose, less sensitivity to pre-analytical variables, lower within-subject biological variability, little/no diurnal variations, little/no influence from acute stress and little/no influence from common drugs which are known to influence glucose metabolism. Excellent separation of the HbA1c fraction from other haemoglobin adducts and with no interference from carbamylated haemoglobin due to technological advances in HbA1c measurement.	Falsely increased values with iron deficiency, vitamin B12 deficiency, decreased erythropoiesis, alcoholism, chronic renal failure, decreased erythrocyte pH, increased erythrocyte lifespan, splenectomy, hyperbilirubinaemia, carbamylated haemoglobin, alcoholism, intake of large doses of aspirin, chronic opiate use. Falsely decreased values have been reported after administration of erythropoietin, iron or vitamin B12; with reticulocytosis, chronic liver disease, ingestion of aspirin, vitamin C, vitamin E, certain haemoglobinopathies, increased erythrocyte pH, a decreased erythrocyte lifespan, haemoglobinopathies, splenomegaly, rheumatoid arthritis, drugs such as antiretrovirals, ribavirin and dapsone, hypertriglyceridaemia. Variable changes have been seen in patients with HbF, haemoglobinopathies, methaemoglobin, genetic determinants.
Glycated albumin	Measure of short-term glycaemic control (2–3 weeks). Not influenced by gender, erythrocyte lifespan, erythropoietin therapy or serum albumin concentration. Significant association with markers of vascular injury.	Values can be influenced by lipaemia, hyperbilirubinaemia, haemolysis, increased uric acid, uraemia, intake of high doses of aspirin, low serum protein concentrations/nutritional status, age, albuminuria, cirrhosis, thyroid dysfunction and smoking. Concentration is inversely influenced by body mass index, body fat mass and visceral adipose tissue. Different reference ranges depending on the applied method. Limited data, especially on the impact of using it as a target. Expensive, time-consuming, not widely available. Contradictory results concerning the correlation between fructosamine and mean glucose concentrations in patients with renal failure. Values can be influenced by nephrotic syndrome, thyroid dysfunction, glucocorticoid administration, liver cirrhosis, icterus. Concentration in uraemic patients may be influenced by a number of variables other than glycaemia, including hypoalbuminaemia, hyperuricaemia.
Fructosamine	Correlates with average glucose levels in the previous 10–14 days. Simple, automated analysis.	
1,5Anhydroglucitol	Reflects day-to-day changes in glucose levels. Retained metabolic inertness, steady-state levels in all tissues and negligible influence of sampling conditions such as collection time, body weight, age, sex and food intake of the subjects.	Within-subject variation is higher than that for HbA1c. Poorer performance in identifying cases of undiagnosed diabetes in comparison to other glycaemic markers. Influenced by traditional Chinese herbal drugs. Limitations for use in subjects with renal tubular acidosis, advanced or ESRD. Not widely available, limited data on its clinical everyday value.
Continuous glucose measurement	Theoretically the most ideal marker for glycaemic control. Allows examination of short-term glycaemic changes around the time of dialysis.	Exhaustion of the sensor, limited data.

Abnormally high HbA1c values have been reported in patients after a splenectomy due to an increased circulating erythrocyte lifespan. Splenomegaly, acute or chronic major blood loss, glucose-6-phosphate dehydrogenase deficiency, intensive physical activity (especially in marathon runners), rheumatoid arthritis or drugs (antiretrovirals and ribavirin) could falsely reduce the level of HbA1c even in the presence of high ambient plasma glucose [39].

Altered Hb

In the presence of haemoglobinopathies (e.g. sickle cell anaemia and thalassaemias), the correct interpretation of the measured HbA1c can be difficult. Besides the normal phenomenon (glycation of adult HbA0 to form HbA1c), other glycated products derived from HbC (African populations), HbD (Indian populations), HbE (Asian populations) or HbS (sickle cell disease) are formed in addition to or instead of HbA1c [39]. In the past, persistence of HbF leads to an overestimation of the HbA1c levels due to co-migration or co-elution with the HbA1c fraction [43–45]. However, no interference of HbF with the IFCC Reference Method has been reported, which can be explained by the absence of β chains in HbF. Only the HbA terminal hexapeptides are measured with the IFCC Reference Method [46]. Besides the genetic Hb variants, chemical alterations could also influence HbA1c results. By increasing methaemoglobin levels and decreasing erythrocyte survival, dapsone can artefactually lower HbA1c [47].

Glycation

In the Third National Health and Nutrition Examination Survey, alcohol consumption was associated with lower HbA1c levels among 1024 adults with diabetes [48]. Those findings were confirmed in a large follow-up study of 38 564 adult patients with type 1 or 2 diabetes (Kaiser Permanente Northern California members, 1994–1997). Increasing levels of alcohol consumption predicted lower HbA1c values through a nadir at a consumption of 2–2.9 drinks/day [49]. pH levels within the erythrocyte can increase (low erythrocyte pH) or decrease (high erythrocyte pH) HbA1c. In chronic renal failure, lipid peroxidation of Hb may increase Hb glycation [50]. Chronic ingestion of aspirin and high doses of antioxidants (e.g. vitamins C and E) can lower HbA1c due to inhibition of Hb glycation [51]. It is unclear whether these phenomena could lead to a different appreciation of HbA1c in clinical practice.

Assays

Decreased HbA1c values have been reported in lipaemic blood samples. Due to a turbidity effect of triglyceride which increases the absorbance of the total Hb and unbound Hb fractions, some assays reported a decreased calculated percentage of glycated Hb [52]. Some other well-documented causes, depending on the assay used, for elevated HbA1c include hyperbilirubinaemia, carbamylated Hb and chronic opiate use [39].

HBA1C AS A MARKER OF GLYCAEMIC CONTROL IN CKD PATIENTS

In contrast to plasma glucose, HbA1c represents non-enzymatic glycosylation, which depends on the glucose concentration in the intra-erythrocyte compartment [53]. Although multiple studies found a good (positive) correlation between HbA1c and glucose concentrations in diabetic non-CKD patients [54] and CKD patients [55], the variable relationship between HbA1c and estimated average glucose (eAG) remains a potential source of concern [56], which can be partly explained by the within-subject variability in degree of Hb glycation. This 'glycation gap' is for ∼70% genetically predetermined [57]. In addition, measurement of glucose has also been a major concern due to point and trend accuracy, sensitivity and specificity, device stability, calibration, lag time and traceability to the highest standard.

Falsely decreased HbA1c values

HbA1c readings can be falsely low in patients on either form of dialysis (haemodialysis or peritoneal dialysis), questioning the accuracy of the HbA1c assay in diabetic patients with severely reduced renal function [58]. Besides the average glucose concentrations, HbA1c is also determined by lifespan of RBCs [59, 60], the use of recombinant human erythropoietin [61], intravenous iron replacement treatment [62], the uraemic environment itself, blood pH and blood transfusions. Iron replacement therapy and erythropoietin-stimulating agents result in a fall in HbA1c, independent of glycaemic changes [58, 62]. Some caution in the interpretation of HbA1c alone with regard to glycaemia management is thus warranted.

Falsely increased HbA1c values

The production of carbamylated Hb depends on the duration and severity of renal failure. Carbamylated Hb is formed by non-enzymatic condensation of cyanate with the N-terminal valine of Hb [63]. Carbamylation is a physiologic process that can alter protein structure and function, inducing significant pathophysiological perturbations [64]. Previous studies described a clinically relevant overestimation of glycated Hb by chromatography, but not by immunochemical measurement, which can be attributed predominantly to incomplete separation of the carbamylated Hb fraction and the HbA1c fraction [65, 66]. Technological advances in HbA1c measurement (e.g. newer ion-exchange HPLC assay methods, specific immunoassays or affinity chromatography) showed however an improved separation of the HbA1c fraction from other Hb adducts with no interference from carbamylated Hb [67, 68], thus allowing a correction for carbamylated Hb interference by simply subtracting carbamylated Hb from the measured HbA1c value.

Debate on the pros and cons of using HbA1c in CKD patients

The relationship between HbA1c and glucose is in advanced CKD more complex because of a wide variability in Hb, poor nutritional status and inflammation [69]. In addition, these underlying comorbidities might also hamper

the prognostic value of HbA1c. Current guidelines recommend HbA1c as the preferred biomarker of glycaemic control in CKD patients with a target of <53 mmol/mol (7.0%) to prevent or delay progression of the microvascular complications of diabetes, including diabetic nephropathy [70]. However, these guidelines mostly focus on early stages of CKD. In diabetic patients with advanced CKD, it is suggested that aiming at a too intensive glycaemic control [HbA1c level <48 mmol/mol (6.5%)] may be associated with increased mortality [71]. Similar to diabetes patients without CKD [72], observational cohort studies of diabetic patients with advanced CKD, peritoneal dialysis or haemodialysis demonstrate a U- or J-shaped curve of HbA1c versus mortality [71, 73, 74]. However, after adjustment for potential confounding factors (demographics, dialysis vintage, dose, comorbidity, anaemia and surrogates of malnutrition and inflammation), patients with an HbA1c ≥ 86 mmol/mol (10%) had all-cause and cardiovascular death a hazard ratio of 1.41 (95% CI: 1.25–1.60) in comparison to an HbA1c in the 31–42 mmol/mol (5–6%) range ($P < 0.001$) [75]. Similarly, the hazard ratio for cardiovascular death was significantly increased to 1.73 (95% CI: 1.44–2.08). In addition, an inferior survival was reported in diabetic haemodialysis and peritoneal dialysis patients with extremes of glycaemia [76]. The association between high HbA1c values [≥64 mmol/mol (8%)] and all-cause mortality was particularly robust in individuals with higher Hb levels (>11 g/dL) [74]. Subgroup analyses showed that the HbA1c threshold for higher all-cause mortality was lower [HbA1c ≥ 53 mmol/mol (7%)] in Caucasians, men and patients with albumin level of >3.8 g/dL. These findings may illustrate the possible interaction of factors related to protein-energy wasting, inflammation and anaemia with indices of glycaemic control [77]. In a large-scale and contemporary cohort of 54 757 diabetic maintenance haemodialysis patients, a time-averaged HbA1c of >64 mmol/mol (8%) or time-averaged serum glucose of >200 mg/dL appeared to be associated with a higher all-cause and cardiovascular mortality [74]. Other small studies have reported that a poor glycaemic control is a predictor of cardiovascular morbidity and mortality for type 2 diabetics with advanced CKD [78, 79]. In 2872 kidney transplant recipients, poor glycaemic control [HbA1c > 64 mmol/mol (8%)] during the preceding haemodialysis period appeared to be associated with higher all-cause and cardiovascular mortality [80]. A recent meta-analysis, investigating the relationship between HbA1c and risk of death in diabetic haemodialysis patients, showed that the HbA1c level remains a useful clinical tool in predicting mortality risk. In this study consisting of nine observational studies [12, 74, 76, 81–86] and one secondary analysis [87] of a randomized trial ($n = 83\,684$ participants), baseline HbA1c levels of >69 mmol/mol (8.5%) were associated with a 29% increase in the adjusted risk of death compared with the reference group with HbA1c levels of 48–57 mmol/mol (6.5–7.4%). Mean HbA1c levels <36 mmol/mol (5.4%) were associated with a small, but non-significant increase in mortality, which could be explained by the heterogeneity of this subgroup. There was a similar association between mean HbA1c level and mortality risk in both incident and prevalent patients. Based on their findings, the authors proposed an HbA1c target of <69 mmol/mol (8.5%) in diabetic haemodialysis patients [88].

Other observational studies do not confirm the link between HbA1c values and survival in ESRD patients [75, 84, 89–91]. In a cohort study of 24 875 haemodialysis patients with type 1 or 2 diabetes mellitus, only a weak correlation with mean random glucose values and HbA1c and no correlation between HbA1c and subsequent 12-month mortality risk was observed [89]. This study was criticized however for a short follow-up period, non-time-dependent survival models and lack of stratified analyses [92]. Also in peritoneal dialysis patients, baseline and time-averaged follow-up HbA1c did not correlate with patient and peritoneal dialysis technique survival [90]. Of note, the study only included 91 patients, which may have been far too few to reach a statistical significance.

Despite the evidence showing an association between HbA1c and outcomes, several trials did not show a benefit of targeting lower HbA1c values [93], probably because the potential advantages (prevention from diabetes associated comorbidity) might not outweigh the disadvantages (risk of hypoglycaemia) in advanced CKD patients. Physicians are encouraged to individualize glycaemic targets based on potential risks and benefits in diabetic ESRD patients [76, 77, 94].

ARE THERE BETTER ALTERNATIVE MARKERS OF GLYCAEMIC CONTROL?

Glycated albumin

Glycated albumin is gaining interest as a potential marker of glycaemic control [95]. Glycated albumin is a ketoamine formed from a non-enzymatic oxidation of albumin by glucose [96]. As the half-life of albumin is ∼15 days, glycated albumin is a measure of short-term glycaemic control (2–3 weeks) [97] and as such, it could act as an intermediate-term index of glycaemic control (Table 1).

Analytical methods. Boronate-affinity chromatography (followed by tandem mass spectrometric detection), ion-exchange chromatography, HPLC, immunoassay-related techniques (e.g. enzyme-linked immunosorbent assays or radio-immunoassays), Raman spectroscopy, refractive index measurements, capillary electrophoresis and other electrophoretic and enzymatic assays (e.g. ketoamine oxidase) can be used for measuring the glycated albumin concentration. This involves calculation of the glycated albumin peak area to the total albumin peak area [95, 98, 99]. A method for conversion between HbA1c and glycated albumin using a measurement error model has been published [100].

Measurement of glycated albumin is not influenced by gender, erythrocyte lifespan and erythropoietin therapy; for serum albumin concentration, conflicting results are reported [58, 101–103]. However, results can be impacted by age, nutritional status [104], albuminuria, cirrhosis, thyroid dysfunction and smoking. Glycated albumin is inversely influenced by body mass index, body fat mass and visceral adipose tissue [105, 106]. Accelerated albumin catabolism accompanied by chronic micro-inflammation, which occurs for example in the

wasting syndrome in many patients with advanced CKD, could explain this phenomenon [107]. Slightly higher reference ranges have been reported in African Americans in comparison with European Americans [108].

Glycated albumin versus HbA1c. It has been suggested that the relationship between HbA1c and serum glucose concentration is altered as the GFR declines in diabetic subjects with advanced CKD, whereas the glycated albumin assay is not impacted by Stage 3 (after transplantation) or Stage 4 CKD [109]. However, this study had several important limitations. In patients with diabetic nephropathy (CKD Stage 3 or 4) and overt proteinuria, glycated albumin values may be lower relative to plasma glucose levels as a result of an increased turnover in albumin metabolism [96]. As albuminuria typically falls with decreasing glomerular filtration rates, this effect might be mitigated in dialysis patients [110].

A better correlation between glycated albumin and glycaemic status (measured by casual plasma glucose or average blood glucose level) has been reported in patients on haemodialysis or peritoneal dialysis in comparison to HbA1c [58, 102, 109, 111, 112]. Opponents argue that ESRD is characterized by an abnormal albumin homeostasis and that the serum albumin threshold at which risk of death increases varies by dialysis modality [113–115]. In hypoalbuminaemia, plasma protein glycation is increased [116]. However, glycated albumin seems to reflect the percentage of albumin that is glycated regardless of the total serum albumin concentration [110], although further large-scale studies with dialysis patients are needed to substantiate this observation.

Glycated albumin apparently has a better association with different parameters of microvascular (kidney disease, retinopathy) and macrovascular disease (pulse wave velocity) as compared with HbA1c [103, 117–119] and also with mortality [82, 120, 121]. New prospective studies are necessary to provide evidence that improving glycaemic control ameliorates glycated albumin and decreases mortality, micro- and macroangiopathy.

Glycated albumin appears to be superior in accuracy as a marker of glycaemic control compared with HbA1c in patients with diabetic nephropathy [122]. However, given the limited data, the absence of interventional outcome studies based on glycated albumin and the expensive and laborious methodology, it seems premature to abandon HbA1c in favour of glycated albumin [91, 123].

Fructosamine

Fructosamine (1-amino-1-deoxy-D-fructose) represents a clinically accessible measure of non-enzymatic glycation of proteins in the same compartment as plasma glucose and should integrate plasma glucose fluctuations [53]. It is formed when the carbonyl group of glucose reacts with an amino group of circulating serum proteins and is a measure of serum ketoamines.

Analytical methods. Several assays have been designed to quantify fructosamine: boronate-affinity chromatography, phenylhydrazine procedure, furosine procedure, colorimetric methods and enzymatic methods [124–126]. The fructosamine level correlates best with average glucose levels in the previous 10–14 days [127]. Being a measure of total glycated serum proteins with glycated albumin accounting for ∼90% of these proteins, fructosamine concentrations may be influenced by serum protein concentrations and profile of different proteins [128]. Simply correcting for total protein may not accurately compensate for variations in protein half-life and reaction to serum glucose concentrations [129]. In addition, fructosamine is influenced by the concentration of bilirubin and low-molecular-weight substances (e.g. urea and uric acid) coexisting in the plasma [130]. Fructosamine is not altered by disorders of Hb metabolism, but is affected by disorders in protein turnover, such as dysproteinaemias [131]. Serum fructosamine concentration may also be determined by some reducing activities caused by unknown factors other than glycated proteins [132]. Reference values depend upon age, gender, sample population and applied test method.

Fructosamine versus HbA1c. Contradictory results have been reported with respect to the correlation between fructosamine and mean glucose concentrations in patients with renal failure [55, 56, 133–136]. The relationship between the fructosamine level and glycaemic control was good in type 2 diabetic patients with CKD Stages 3–4. However, calculation of eAG from fructosamine level may underestimate mean blood glucose levels in those patients [56].

Consistent discordances between HbA1c and fructosamine have been reported, which has been called the previous mentioned 'glycation' gap, defined as actual HbA1c minus HbA1c predicted from fructosamine [53, 137]. In a study of 23 diabetic haemodialysis patients, HbA1c appeared to correlate most accurately with measured blood glucose, whereas fructosamine and glycated plasma proteins correlated poorly with glycaemic control [55]. Fructosamine is considered a reliable marker of medium-term integrated blood glucose in diabetics on maintenance haemodialysis by some [133], but not by others [135, 136]. In a study of 100 diabetic haemodialysis patients with a follow-up of 3 years, albumin corrected fructosamine was as reliable as HbA1c for glycaemic control in diabetic patients on haemodialysis and might be advantageous for patients with serum glucose in a desirable therapeutic range (<8.3 mmol/L). The value of fructosamine as a glycaemic index in CAPD diabetic patients has also been demonstrated [138, 139].

In a cohort study of 9704 white women (>65 years of age), elevated serum fructosamine levels were found to be associated with cardiovascular mortality [140]. In contrast to HbA1c, albumin corrected fructosamine correlated with morbidity (hospitalizations and infections) in diabetic haemodialysis patients [141]. Again, the relatively small sample size needs to be taken into account and the prognostic role of fructosamine in dialysis patients has to be further investigated [96].

1,5-Anhydroglucitol

1,5-Anhydroglucitol (1,5-AG) is a non-metabolizable glucose analogue found in plasma after ingestion. It is characterized by urinary excretion, filtration via the glomeruli at a

rate of 5–10 g/L each day and very high tubular reabsorption (>99%), which is inhibited by glucose during periods of hyperglycaemia [142, 143]. As a consequence, 1,5-AG levels in blood respond within 24 h [144] and repetition of hyperglycaemic episodes decreases dramatically the normal steady-state concentration. The 1,5-AG values reflect hyperglycaemic exposure over approximately a 1-week period [145]. Measurement of 1,5-AG could play a role in diabetes monitoring as an adjunct to continuous monitoring of plasma glucose and HbA1c measurement, especially as a unique short-term marker for excursions of hyperglycaemia beyond the glucosuric threshold [146].

Analytical methods. Several methods for 1,5-AG measurement have been evaluated: gas chromatography, gas chromatography/mass spectrometry [147], liquid chromatography/mass spectrometry [148] and enzymatic methods [149]. The 1,5-AG measurement has several advantages: retained metabolic inertness, steady-state levels in all tissues, no influence of anaemia, haemoglobinopathy or liver disease and negligible influence of sampling conditions such as collection time, body weight, age and gender [150, 151]. Serum 1,5-AG levels are influenced by the intake of traditional Chinese herbal drugs [152] and dairy products [153].

1,5-Anhydroglucitol versus HbA1c. As a subanalysis of the Atherosclerosis Risk in Communities study, a cross-sectional comparison of 1,5-AG, fructosamine and glycated albumin with HbA1c and fasting glucose measurements in 1719 participants was conducted. Although a strong correlation was found between 1,5-AG and HbA1c, 1,5-AG performed worse (AUC: 0.74; 95% CI: 0.69–0.78) for identifying cases of undiagnosed diabetes in comparison to the other glycaemic markers [154]. In the same population, fructosamine, glycated albumin and 1,5-AG were strongly associated with future diabetes risk, even after adjustment for HbA1c or fasting glucose [155]. The poorer performance of 1,5-AG in identifying diabetes cases is consistent with the fact that 1,5-AG concentrations are substantially lowered only when circulating glucose concentrations are very high [156]. Of note, 1,5-AG may be useful in the setting of overt hyperglycaemia [154, 155]. It may function as an alternative index for some subtypes of diabetes and as a warning sign of diabetes complications [151].

In patients with CKD, serum 1,5-AG decreases due to a decrease in reabsorption, independently of glucose excretion. Serum and/or urinary 1,5-AG can be a useful marker for renal tubular dysfunction because its reabsorption system is more vulnerable than the glucose reabsorption system [157]. In a recent cross-sectional study of 269 subjects with type 2 diabetes (57 in control, 111 in CKD Stages 1–2, 78 in Stage 3 and 23 in Stages 4–5), 1,5-AG levels did not appear to be influenced by mild or moderate renal dysfunction. This suggests that 1,5-AG could be a reliable glycaemic marker in type 2 diabetes with CKD Stages 1–3. Associations between logarithmic transformed 1,5-AG and HbA1c or fasting plasma glucose were insignificant for CKD Stages 4–5 [158]. Impaired renal function and removal of 1,5-AG by dialysis may contribute to its decreased concentration in patients with ESRD [159]. So 1,5-AG has severe limitations for use in subjects with renal tubular acidosis, uraemia or ESRD [158].

Continuous glucose monitoring system

In patients undergoing dialysis, the use of continuous subcutaneous glucose monitors (CGM) is probably the only method to correctly evaluate glycaemic control. The evaluation of short-term glycaemic undulations around the time of dialysis is possible and results are unaffected by urea, RBC lifespan and RBC production [160]. Using CGM over a 2-day period, significantly higher glucose profiles were reported on the day off dialysis than the day on dialysis [161]. This increased glycaemic variability may represent an adjunctive risk factor for cardiovascular complications [162]. Using the CGM system as reference, mean glucose concentration correlated weakly with HbA1c, but did not correlate at all with fructosamine in haemodialysis patients, in contrast with non-dialysis patients. The CGM system could represent a major advance in assessing glycaemic control in dialysis patients, although future studies should evaluate if this method can be used to indicate necessary adjustments in diabetes treatment or will result in lower mortality rates [163]. In this context, the detection of hypoglycaemic episodes by CGM may be particularly relevant for the prevention of morbidity and mortality in diabetic patients with kidney disease.

CONCLUSION

Due to the availability of relatively inexpensive and routinely measured HbA1c assays and the inconsistent or limited data to prove superiority of other glycaemic markers (glycated albumin, fructosamine, 1,5-AG and continuous glucose monitoring) at this moment, HbA1c is the reference standard for glycaemic monitoring in diabetic patients with CKD (see data extraction table in supplementary data table online). It remains an open question whether and how the HbA1c target should be individualized in patients with advanced CKD, based on age, comorbidity, life expectancy and the presence of risk factors for the occurrence of hypoglycaemia. Continuous subcutaneous glucose monitoring seems to be well suited to correctly evaluate glycaemic control in diabetic patients undergoing dialysis as a 20–40 min time delay can be important. Prospective studies testing pre-specified diabetes control targets based on glycated albumin and continuous glucose measurement remain to be performed in order to determine whether morbidity and mortality would be reduced with intensive glycaemic control using these measurements as reference target.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

The declaration of interest forms of C.D., I.N., W.V.B., R.V. and A.W. can be found on the webpage of ERBP: www.european-renal-best-practice.org; M.S., R.L., J.D. and R.S. declared no interests with regard to this paper. The present text is based upon the information available to the guideline development group at the moment of the preparation of this publication. It has been designed to provide information and assist decision-making, but is not intended to define a standard of care or to improve an exclusive course of treatment. Individual decision-making is essential in the approach to any disease and thus also diabetes and advanced chronic kidney disease. Variations in practice are inevitable when physicians take into account individual patient needs, available resources and limitations specific for a geographic area, country, institution or type of practice. In addition, evidence may change over time as new information becomes available, so that practice may be modified subsequently. Every practitioner using this text is responsible for its application to any particular clinical situation.

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