

In-depth Clinical Review

Glycated albumin is the preferred marker for assessing glycaemic control in advanced chronic kidney disease

Frederiek E. Vos, John B. Schollum and Robert J. Walker

Department of Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand

Correspondence and offprint requests to: Frederiek E. Vos; E-mail: frederiek.vos@southernmb.govt.nz

Abstract

Diabetic nephropathy is the most common aetiology of end-stage kidney disease (ESKD). Strict glycaemic control reduces the development and progression of diabetes-related complications, and there is evidence that improved metabolic control improves outcomes in diabetic subjects with advanced chronic kidney disease (CKD). Glycaemic control in people with kidney disease is complex. Changes in glucose and insulin homeostasis may occur as a consequence of loss of kidney function and dialysis. The reliability of measures of long-term glycaemic control is affected by CKD and the accuracy of glycated haemoglobin (HbA1c) in the setting of CKD and ESKD is questioned. Despite the altered character of diabetes in CKD, current guidelines for diabetes management are not specifically adjusted to this patient group. The validity of indicators of longer term glycaemic control has been the focus of increased recent research. This review discusses the current understanding of commonly used indicators of metabolic control (HbA1c, fructosamine, glycated albumin) in the setting of advanced CKD (Stages 4 and 5, glomerular filtration rate <30 mL/min/1.73m²).

Keywords: chronic kidney disease; glycaemic control; glycated albumin; glycated haemoglobin; fructosamine

Introduction

The global incidence of diabetes mellitus is rising exponentially and diabetic nephropathy is now the predominant cause of chronic kidney disease (CKD) [1]. Diabetic nephropathy causing end-stage kidney disease (ESKD) accounts for 30–50% of all new patients commencing renal replacement therapy (RRT) [2, 3]. The expanding number of people with diabetes, in particular type II, with ESKD represents an enormous public health concern and the immense cost of RRT is a major strain on the health care budget globally [2]. In 2010, US \$26.8 billion was consumed by the ESKD programme (excluding expenditures on drug therapy) by Medicare, which is ~6% of total Medicare budget [2]. A number of important studies have demonstrated the importance of tight metabolic control to reduce the risk of longer term complications, in particular cardiovascular events, which are the main cause

of death in diabetics [4] with normal kidney function as well as in diabetics with ESKD [5–8].

Importance of glycaemic control

The impact of glycaemic control on the micro- and macrovascular complications in the diabetes population without CKD has been extensively studied [6–8]. A number of large-scale studies have demonstrated the beneficial effect of strict glycaemic control, by implementing intensive treatment with the aim to maintain blood glucose concentrations close to normal range, on slowing the development of nephropathy in type I and II diabetes [7–9]. Tight glycaemic control ($\leq 6.5\%$) achieved by intensive treatment with drug therapy in comparison with conventional glycaemic control (mean HbA1c 7.3%) resulted in a reduction of microvascular complications and renal events [10]. Two observational studies demonstrated in early stages of diabetic nephropathy that good glycaemic control (defined as HbA1c <7.5 and $<9\%$, respectively) delayed the onset and progression of albuminuria [11, 12]. In people with type II diabetes, intensified multifactorial treatment, including tight glycaemic regulation aiming to maintain HbA1c values $<6.5\%$, resulted in a reduction of cardiovascular and all-cause mortality [4]. Higher HbA1c values were significantly associated with progression of nephropathy, cardiovascular events and mortality [13, 14]. In severe nephropathy, glycaemic control appears to be less important and other factors such as hypertension are more relevant to the progression of kidney disease [15]. Nevertheless, the effect of glycaemic control on further progression has still been demonstrated [13, 14]. Recently, it has become evident that aggressive glycaemic control may be potential harmful in the non-CKD population. Several randomized trials have demonstrated no beneficial effect of intensive treatment and lowering of HbA1c concentrations on cardiovascular events [10]. Moreover, intensive treatment has been associated with overall higher mortality [16] and increase in hypoglycaemic events [10].

Glycaemic control in CKD

Unlike the previous randomized interventional studies in the general population without established CKD, no data exist in

established diabetic CKD concerning the impact of tight glycaemic control on future morbidity and mortality. Data on the effect of long-term glycaemic control are very limited and whether tight glucose regulation is beneficial and correlates with the risk of death or hospitalization in diabetic patients with ESKD remains controversial [17]. There is some evidence from observational studies that good glycaemic control, using glycated haemoglobin (HbA1c) as a marker, prevents progression of nephropathy, reduces morbidity and improves survival in patients with advanced CKD and in people requiring haemodialysis (HD) [18, 19]. More recently, in diabetic HD patients, Drechsler *et al.* [20] demonstrated in a *post hoc* analysis of the four-dimensional study, a 2-fold increase in risk of sudden death in a group with poor glycaemic control (HbA1c > 8%) compared to a good glycaemic-controlled group (HbA1c ≤ 6%). However, risk of myocardial infarction and mortality (excluding sudden death) did not differ between groups. A single intervention study examined the outcomes in diabetic HD patients by comparing intensified diabetes education and care management with standard care and demonstrated improved glycaemic control and reduction in morbidity in the treatment arm [21].

Studies exploring the impact of glycaemic control on mortality in ESKD are limited and yield somewhat inconsistent results. In a number of studies, glycaemic control has been shown to be predictive of survival among diabetic HD patients with higher mortality rates observed in the group with lower HbA1c values (HbA1c <7.5 and <8.0%, respectively) compared to the poor glycaemic control groups (HbA1c ≥7.5 and >8.0%, respectively) [18, 22]. In a large observational study, unadjusted survival analysis demonstrated paradoxically lower hazard ratios of cardiovascular and all-cause mortality with higher HbA1c values. After adjustment for potential confounders, higher HbA1c concentrations were incrementally associated with increased death risk [19]. In contrast, other studies have revealed no association with HbA1c and 1- or 2.3-year survival in population of dialysis patients [23, 24]. By extending their follow-up period to 3 years, Williams *et al.* [25] demonstrated that only the extremes of glycaemia (HbA1c <5 and >11%, respectively) were associated with reduced survival. The discrepancy among studies may be a result of short-term follow-up and underlying differences in methodology. However, the inaccuracy of HbA1c as long-term marker of glycaemic control may contribute to the inconsistencies observed between studies.

Overall, there is evidence in the general diabetic population implying that tight glycaemic control may reduce the development and progression of diabetic complications and there are suggestive data that metabolic control improves outcomes in the CKD population. Current guidelines recommend achieving and maintaining normoglycaemia by implementing intensive treatment in people with CKD [26]. However, there is suggestive data that in ESKD patients with comorbidities and malnutrition, higher HbA1c target values might be favourable [19].

Glycaemic control in the presence of CKD is complicated by altered glucose and insulin homeostasis. Decrease in renal metabolism and clearance results in a prolonged duration of insulin action [27]. Blood glucose concentrations may decline with progressive nephropathy due to malnutrition and

reduced renal gluconeogenesis [28]. Furthermore, glucose and insulin levels are influenced by the HD procedure by increased clearance [29] and equally, the high-glucose concentrate dialysate used in PD impacts on serum glucose levels substantially [30].

Measuring long-term glycaemic control

Chronic hyperglycaemia results in increased formation of glycated proteins including HbA1c [31] and serum proteins [32, 33], which provide a reflection of long-term glycaemic control over a period of ~4 months and 2–3 weeks, respectively [34].

Glycated haemoglobin

HbA1c is a widely utilized and well-validated marker for the assessment of glycaemic control that is used routinely in the management of diabetes [35]. HbA1c is produced by the non-enzymatic reaction of glucose with the N-terminal amino group of the beta-chain of haemoglobin forming a Schiff base (reaction between a free primary amine on the haemoglobin molecule with the carbonyl group of glucose) which subsequently undergoes an Amadori re-arrangement resulting in a stable ketoamines [31]. HbA1c concentrations are directly proportional to the ambient blood glucose concentration. As HbA1c is formed during the lifespan of red blood cells (RBCs), older RBCs contain a higher proportion of modified haemoglobin [36]. HbA1c represents a weighted average of blood glucose concentrations during the preceding 4 months [37]. Good correlations exist between plasma glucose concentrations and HbA1c measurements in populations with type I and II diabetes and normal kidney function, and average blood glucose values can be estimated based on HbA1c values and vice versa [35, 38], signifying the utility of HbA1c as a measure of metabolic regulation of diabetes. HbA1c is currently accepted as the most informative biomarker of glycaemic control in subjects with diabetes and is highly prognostic for long-term diabetes-related complications [7, 8, 39].

While HbA1c has proven to be a reliable and prognostic marker in the general diabetic population, it may not be valid in patients with diabetes and CKD. Whether HbA1c corresponds to the same mean glucose concentrations in people with ESKD is debated [40, 41]. Several features, present in CKD, have a significant impact on HbA1c concentrations and values may be falsely low or high. Besides glucose, HbA1c is influenced by other factors including the lifespan of the RBCs, recombinant human erythropoietin (rHuEpo), the uraemic environment and blood transfusions [42–44]. In patients with CKD, and particularly those on HD, the RBC lifespan is significantly reduced with 20–50% [43, 44]. The subsequent increased rate of haemoglobin turnover leads to decreased exposure time to ambient glucose that in turn lowers the extent of non-enzymatic binding of glucose to haemoglobin. This results in reduced value for HbA1c. Thus, in subjects with CKD and a shortened RBC lifespan [45], lower HbA1c levels are observed than would be expected from measured glucose control.

CKD is associated with erythropoietin deficiency and a normochromic normocytic anaemia. It is now standard

clinical practice to correct the anaemia of CKD with rHuEpo. Observational studies have shown that treatment with rHuEpo is significantly associated with lower HbA1c values [46, 47]. Exogenous erythropoietin increases the proportion of immature RBCs in the circulation that have a shorter glycaemic exposure time for glycosylation to occur [46]. In addition, the rate of glycation of young cells is reportedly lower than that of old cells [36], which also contributes to the reduction in measured HbA1c values. Clearly, HbA1c is affected by disorders of RBC turnover and therefore may not properly represent glycaemic control under these conditions.

Iron deficiency elevates the level of HbA1c independently of glucose and haemoglobin levels [48]. However, once treatment is initiated with iron supplementation, HbA1c concentrations decrease significantly as a result of the production of immature cells [49]. An increased amount of carbamylated haemoglobin is formed under uraemic conditions. This acquired form of haemoglobin interferes with some HbA1c assays (only charge-dependent assays), predominantly by incomplete separation of the carbamylated haemoglobin fraction, resulting in an overestimation of HbA1c values [50, 51]. The interference is significant when urea levels exceed 30 mmol/L [52]. In addition, other haemoglobin modifications occur due to various middle molecules that accumulate in CKD such as advanced glycation end-products, which may bind to haemoglobin and causing more potential interference [53].

The interfering and confounding factors, associated with kidney disease and its treatment, may lead to erroneous HbA1c values. Despite these considerations, current international guidelines for diabetes care in CKD recommend that 'target HbA1c for people with diabetes should be <7.0%, irrespective of the presence or absence of CKD' [26].

Glycated proteins Other glycated plasma proteins include fructosamine and glycated albumin (GA) which are also formed non-enzymatically when proteins react with glucose in a similar manner to the formation of HbA1c [32, 33]. However, the turnover of plasma proteins is much shorter than haemoglobin (half-life ~2–3 weeks), thus the degree of glycated plasma proteins provide an index of glycaemia over a shorter period of time. Measurements of glycated serum proteins show a good correlation with HbA1c and plasma glucose concentrations in diabetic subjects without renal disease and therefore have been suggested as alternative methods to assess metabolic control in diabetes [54, 55].

Fructosamine Fructosamine originally introduced as a general term for glycated proteins includes all serum glycated proteins that have become stable ketoamines and have the ability to act as reducing agents in alkaline solution which is then measured by a reduction colouring reaction with nitro blue tetrazolium [32]. Only half of the reducing activity measured is due to specific non-enzymatic glycation of proteins, the remaining non-specific activity varies between subjects [56]. Although fructosamine is not affected by disorders of haemoglobin metabolism, it is affected by disorders in protein turnover. Fructosamine originates from non-enzymatic glycation of mainly albumin (~90%) and various proteins and therefore strongly depends on the concentration of each protein [32, 57].

Considerable debate remains whether fructosamine measurements should be corrected for albumin or total protein concentration [58]. Evidence for the positive correlations between fructosamine and albumin or total protein concentrations is conflicting, though correction for proteins is routinely recommended [59]. However, if serum fructosamine concentrations are simply divided by the serum albumin (or total protein) concentration, the value is high when albumin is low and vice versa. Several arguments against correction of fructosamine concentrations exist. The rate-limiting step in the glycation reaction is glucose and not the protein concentration, as there is an excess of serum proteins and reactive lysine groups [60]. Imprecision of total protein determinations and changes in serum composition (dysproteinaemias) may severely affect fructosamine and lead to inaccurate results [61]. The majority of total protein consists of albumin but also includes various other proteins with different concentrations, turnover rate and reactivity with glucose. Correcting for total protein or albumin may therefore not be justified as it may not fully or accurately compensate for the altered metabolism of proteins and their compositions and their reaction with serum glucose concentrations [57]. Moreover, fructosamine is influenced by the concentration of low-molecular-weight substances (i.e. urea and uric acid) [35].

Glycated albumin Similar to fructosamine, GA provides a short-term index of glycaemic control and is not influenced by albumin concentration, as the glycation component is calculated as a ratio of total albumin concentration [33, 58]. In addition, GA is not affected by RBC lifespan or rHuEpo administration [40, 41] and other limitations affecting HbA1c and fructosamine values. In diabetic subjects, GA has strong correlations with glucose and provides a reliable index of glycaemic control over the preceding 2–3 weeks [34]. GA concentrations increase and decrease more rapidly with fluctuations in overall glucose compared to HbA1c, allowing rapid changes to be detected at an earlier stage [62]. It has been revealed that increased levels of GA are linked to both the presence and severity of cardiovascular disease and impaired kidney function [63]. Observations of the biological properties of GA have been related to the pathogenesis of diabetic vascular complications [64]. As such, GA is perhaps a more reliable measure of glycaemic control as well as a predictor of developing vascular complications, in people with diabetes and nephropathy.

Limitations of HbA1c and glycated proteins as measures of metabolic control in diabetes in the setting of CKD are listed in Table 1.

Glycaemic control in CKD

Numerous studies have attempted to evaluate the clinical performance and correlation of blood glucose with long-term glycaemic markers in subjects with CKD and ESKD. These studies employ different statistical approaches, hampering the comparison between studies. Many studies have assessed the strength of the correlation either by Pearson's correlation coefficient or multiple regression analysis. Other studies report the GA to HbA1c ratio. Data relating the linkage observed

between average blood glucose and HbA1c, fructosamine and GA are summarized in Tables 2 and 3.

Apart from one study [74], all studies describe a significant and positive relationship between HbA1c and mean glucose in diabetic subjects with advanced CKD (dialysis dependent, CKD Stages 4 and 5 or a combination of both groups), and the degree of correlation appears reasonable (r values ranging from 0.5 to 0.7). Several studies in HD and also peritoneal

dialysis (PD) patients describe the correlations between HbA1c and glucose as weak [40, 70, 72]. Regardless of the positive and significant relationship observed in these studies, data consistently demonstrate HbA1c values to be lower in diabetic subjects with ESKD than values measured in individuals without nephropathy, irrespective of glucose concentrations. Furthermore, it has been concluded that HbA1c underestimates true glycaemic control in the presence of CKD Stages 3–5 and dialysis-dependent patients [40, 72, 73, 74]. Indeed, as listed in Table 3, the ratio GA to HbA1c is consistently increased in dialysis and pre-dialysis patients, further confirming the notion that HbA1c underestimates and inaccurately reflects long-term glycaemia in this population.

There are contradictory data regarding whether a positive and significant relationship exists between fructosamine and mean glucose in ESKD (Table 2). Most reported coefficients of correlation between fructosamine and blood glucose concentrations have been too low to allow fructosamine to be implemented as a reliable marker in diabetes management [65, 67]. In addition, the literature is conflicting on whether fructosamine concentrations relative to glucose tend to be falsely high or low in dialysis patients compared to diabetic subjects with normal kidney function [66, 69, 72].

Table 1. Limitations of markers of glycaemic control in CKD^a

	Falsely decreased	Falsely increased
HbA1c	Shortened RBC survival rHuEpo therapy Iron supplements Haemolytic anaemia RBC transfusion Vitamins C and E	Carbamylated haemoglobin Uraemic acidosis Iron deficiency Hypertriglyceridaemia High-dose aspirin
Glycated plasma proteins	Low serum protein concentrations	Uraemia Increased uric acid High dose of aspirin

^aRBC, red blood cell survival.

Table 2. Overview of studies correlating different markers of glycaemic control with mean/median glucose in diabetic patients with established CKD^a

Study	CKD status	<i>n</i>	No. of glucose measures/study duration	HbA1c	Fr	GA
Bilo <i>et al.</i> [65]	PD	13	8/4 weeks	$r = 0.71, P < 0.005$	$r = 0.68, P < 0.01$	NA
Nunoi <i>et al.</i> [66]	HD	14	96/3 weeks	$r = 0.70, P < 0.001$	$r = 0.37, P = \text{n.s.}$	NA
Ichikawa <i>et al.</i> [67]	HD	31	12/4 weeks	$r = 0.67, P < 0.001$	$r = 0.46, P < 0.01$	$r = 0.59, P < 0.001$
Morgan <i>et al.</i> [68]	HD, PD, pre-dialysis	14	6/6 weeks	$r = 0.57, P = 0.01$	$r = -0.1, P = \text{n.s.}$	
Joy <i>et al.</i> [69]	HD	23	14/1 week	$r = 0.58, P < 0.05$	$r = 0.35, P = \text{n.s.}$	
Chujo <i>et al.</i> [70]	HD, pre-dialysis	37	7/1 day	$r = 0.42, P < 0.01$		$r = 0.50, P < 0.001$
		49	7/1 day	$r = 0.47, P < 0.0005$	$r = 0.56, P < 0.0001$	
Inaba <i>et al.</i> [40]	HD	538	3/8 weeks	$r = 0.54, P < 0.001$		$r = 0.52, P < 0.001$
Nagayama <i>et al.</i> [71]	HD	23	1 (fasting)/1 day	$r = 0.67, P < 0.0004$		$r = 0.66, P < 0.0006$
Riveline <i>et al.</i> [72]	HD	19	CGM/4 days	$r = 0.47, P = 0.04$	$r = -0.04, P = \text{n.s.}$	
Chen <i>et al.</i> [73]	CKD 3 and 4	30	168/12 weeks	$r = 0.81, P < 0.001$	$r = 0.59, P < 0.001$	
Vos <i>et al.</i> [74]	HD, PD, CKD 4 and 5	25	CGM/2 days	$r = 0.38, P = \text{n.s.}$	$r = 0.56, P < 0.01$	$r = 0.54, P < 0.01$

^aHbA1c, fructosamine and GA are compared with plasma blood glucose concentrations and the strength of the correlation is expressed as r value (P-value). n , number of subjects; Fr, fructosamine; n.s., not significant; NA, not applicable.

Table 3. Overview of studies reporting GA/HbA1c ratios^a

Study	CKD status	<i>n</i> (CKD)	No. of glucose measures/study duration	GA/HbA1c CKD	GA/HbA1c, controls	P-value
Inaba <i>et al.</i> [40]	HD	538	3/8 weeks	3.81	2.93	<0.001
Peacock <i>et al.</i> [41]	HD	258	1 (random)/1 day	2.72	2.07	0.0001
Nagayama <i>et al.</i> [71]	HD	23	1 (fasting)/1 day	3.58	3.0 ^b	Not stated
Freedman <i>et al.</i> [75]	CKD 4	70	1 (random)/1 day	2.95	2.30	<0.0001
Freedman <i>et al.</i> [76]	HD	415	1 (random)/1 day	2.93	2.2	<0.05
	PD	55		2.70		<0.05
Vos <i>et al.</i> [74]	HD, PD, CKD 4&5	25	CGM/2 days	2.5	2.2	<0.05

^a n , number of subjects with CKD.

^bValue based on reports in the literature [62].

More recently, the accuracy of GA compared to HbA1c as indicators of long-term glycaemic control in pre-dialysis and dialysis patients has been explored in a number of studies. Good correlations among GA and mean blood glucose were demonstrated in subjects with and without CKD Stages 4 and 5, including dialysis-dependent subjects. Furthermore, GA was a better indicator of glycaemic control in patients on dialysis and pre-dialysis subjects [40, 41, 70, 74].

A limited number of studies have explored the correlation of glucose with HbA1c, fructosamine and GA markers in diabetic subjects with less severe stages of CKD (Stages 3 and 4) [73] and in those with Stage 5 CKD not yet receiving dialysis [75]. HbA1c as well as fructosamine underestimate glycaemic control in CKD Stages 3 and 4 [73]. Moreover, the glomerular filtration rate (GFR) was negatively associated with HbA1c concentrations. Therefore, declining GFR has an impact on and alters the relationship of HbA1c with mean glucose, whereas GA values appear to be unaffected by CKD status [75].

A major drawback that limits the clinical utility of the majority of previous studies is the means of assessing mean glucose concentrations. In most studies, the average blood glucose value was determined from very limited and infrequent random glucose measurements. Clearly, this may be an inaccurate quantification of overall glycaemic state. Especially in advanced CKD, the glucose concentrations vary widely during the day and are dependent on caloric intake, activity and treatment, and in the case of ESKD, the influence of the dialysis procedures on insulin and glucose concentrations may be important [77]. These considerations should be taken into account when overall glucose state is measured. Hence, the true relationship between mean blood glucose concentrations and markers of glycaemic control remains poorly understood.

Continuous glucose monitoring (CGM) provides a detailed series of real-time consecutive observations of glucose fluctuations [78]. It is a reliable indicator of real-time blood glucose concentrations in the general population [78, 79] and is not affected by kidney disease [72, 77]. Only two studies have incorporated this method for accurate determination of glycaemia when exploring the correlation between markers of glycaemic control [72, 74]. Utilizing continuous blood glucose monitoring over a 48-h period, there was a strong correlation between mean blood glucose and GA, but no correlation with HbA1c in CKD Stages 4 and 5, including subjects receiving dialysis [74].

There are some potential concerns related to albumin turnover that will need to be clarified before GA can be widely endorsed as a marker of glycaemic control in CKD. Increased protein turnover may affect glycation of albumin and result in falsely lower GA levels. Dialysis (HD and PD) may be associated with increased protein losses [80, 81], and this may or may not modify observed GA values in dialysis subjects [76]. Whether GA concentrations reflect glycaemic control accurately in patients with heavy proteinuria remains debatable [82]. There are some data suggesting that the concentration of albumin influences its own half-life, with lower concentrations prolonging the lifespan and vice versa [58]. This implies that an altered lifespan may affect the glycation duration of albumin and thereby influence GA concentration. However, the impact of variations in half-life of albumin and in turn the

proportion of glycation remains unknown and deserves additional exploration. Also, under circumstances where there is an increased amount of albumin redistributed in extravascular compartments (i.e. sepsis) [83], it is unclear what impact this may have on glycation rate and the accuracy of GA measurements.

Summary and conclusions

The consistently observed underestimation of glycaemic control by HbA1c in a number of studies [40, 41, 74, 76] has led to uncertainty regarding the usefulness of HbA1c as an indicator of glycaemic control in CKD. The clinical utility of a biomarker such as HbA1c depends on a constant rate of glycation without substantial interference of plasma levels by the underlying disease independent of the ambient glucose levels. In this instance, HbA1c is restricted by the reduced RBC survival observed in ESKD plus the use of rHuEpo therapy [44]. This is of significance, as renal impairment is highly prevalent in the diabetic population [84]. Hence, due to the reduced validity of the HbA1c assay in pre-dialysis and dialysis subjects, concerns exist regarding the use of this marker to guide glycaemic control along with the potential risk of exposing this population to an increased risk of hyperglycaemic-related complications.

GA lacks these CKD-related limitations and hence may better identify sub-optimal glycaemic control in patients with advanced CKD for whom intensified treatment may offer improved outcomes. In this context, the evidence from the reviewed literature indicates that in the presence of advanced CKD, glycaemic control should be evaluated by means of GA. Of interest, in a recent study, Freedman *et al.* [23] demonstrated elevated GA concentrations, in contrary to HbA1c, to be predictive of mortality and hospitalization in dialysis patients with diabetes [23]. These findings confirm the earlier notion that high GA concentrations ($\geq 29\%$) are associated with cardiovascular death [85].

At present, no clear consensus on optimal concentrations of GA has been reached. There is limited data on the relationship of CGM and GA in the later stages of CKD, although lower values of GA in dialysis groups have been observed compared to pre-dialysis groups, regardless of comparable glucose concentrations (F. E. Vos, J. B. Schollum, C. V. Coulter, P. J. Manning, S. B. Duffull and R. J. Walker, unpublished data). Whether, GA concentrations are consistently lower in dialysis patients needs to be confirmed in upcoming studies. Perhaps, different target values need to be established for glycaemic control in patients on dialysis and with milder stages of CKD.

Further research is warranted to establish a target GA concentration that predicts the best prognosis for patients with diabetes and CKD. In addition, only very limited data are available regarding the accuracy of GA as glycaemic control indicator in less severe stages of CKD, hence the relationship between glucose and GA cannot be extrapolated to milder forms of renal impairment. Future research should focus on the validation of GA as indicator of glycaemic control in different stages of CKD. There is need for diagnostic accuracy studies and a formal systematic review of the accuracy of glycaemic markers in the CKD and ESKD setting. This

should be followed by prospective randomized trials assessing the efficacy and safety of different GA concentrations in ESKD. Furthermore, the role of GA as screening and diagnostic tool is yet to be clarified.

Review criteria

Studies were identified from PubMed electronic reference database using combinations of the following search terms and/or Medical Subject Headings (MeSH): chronic renal insufficiency; renal dialysis, HD, PD; diabetes; haemoglobin A, glycosylated; serum albumin, glycosylated; fructosamine; blood glucose and blood glucose monitoring. The search was limited to papers published in the English language and relevant observational studies designed for the purpose of assessing the relationship between mean glucose and HbA_{1c}, fructosamine or GA in diabetic patients with established CKD were included in this review.

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