IN THE NAME OF GOD

Which is the best glycemic marker for glucose control in CKD?

DR.roghayeh akbari

Associated professor of babol university of medical science

INCIDENCE

119 PERMILLION

PREVALENCE

801PERMILLION

INCIDENCE

378 PERMILLION

PREVALENCE

2218PERMILLION


DIABETES


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Strict glycemic control in patients with diabetes

has been established to delay the onset and slow the progression of **diabetic microangiopathy** in the patients with types 1 diabetes and type 2 diabetes in the Diabetes

Recent clinical evidence has suggested the favorable effects of strict glycemic control ***on cardiovascular*** disease, a main cause of death in patients with diabetes

has beneficial effects
on the **prognosis** of patients who have diabetes with chronic kidney disease and undergo regular hemodialysis (HD)

The most recent Kidney Disease Outcomes Quality Initiative (KDOQI)
Clinical Practice Guideline for DM and CKD

target glycated hemoglobin (HbA1c) of 7% to
delay the progression of microvascular complications of DM
BUT

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 disease

- ***Whether intensive control of glucose reduces macrovascular events and all-cause mortality in individuals with type 2 diabetes mellitus?***

Lancet. 2009 May 23;373(9677):1765-72. doi: 10.1016/S0140-6736(09)60697-8.

Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials.

Ray KK[1], Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, Erqou S, Sattar N.

Author information

Abstract

, intensive compared with standard glycaemic control significantly reduces coronary events without an increased risk of death. However, the optimum mechanism, speed, and extent of HbA(1c) reduction might be different in differing populations.

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Lancet. 2010 Feb 6;375(9713):481-9. doi: 10.1016/S0140-6736(09)61969-3. Epub 2010 Jan 26.

Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study.

Currie CJ[1], Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, Zagar T, Poole CD.

Author information

a large-scale UK observational study reported a general U-shaped association of the mean HbA1c level with all-cause mortality and CV events, with the HbA1c threshold at approximately 7.5% and higher or lower levels related to increased risks[36]

www.nature.com/scientificreports

SCIENTIFIC REPORTS

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Glycated Hemoglobin and Outcomes in Patients with Advanced Diabetic Chronic Kidney Disease

did not demonstrate a U-shape association, which seems not in concordance with prior studies.

This discrepancy could be interpreted by the low incidence of hypoglycemia

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Glycated Hemoglobin and Outcomes in Patients with Advanced Diabetic Chronic Kidney Disease

Hba1c

2401

6%

6%-7%

7% -9%

>9%

3year

higher HbA1c correlated with higher eGFR in patients with stage 5 CKD but not in stage 3–4 CKD.

Worse clinical outcomes existed when the HbA1clevel exceeded 6% in stage 3–4 CKD, but the significance was only observed for >9%.

, all-cause mortality and combined CV events with mortality in the group of HbA1c >9%

higher HbA1c level is associated higher risks for clinical outcomes in diabetic patients with stage 3–4 CKD but not in stage 5

WHAT IS the relationship between HbA1c levels and clinical outcomes in advanced CKD???

meta-analysis of 7 randomized controlled trials (RCTs) of intensive glycemic therapy, significant reduction in microalbuminuria and macroalbuminuria but the benefits were inconclusive concerning the effect on clinical renal outcomes, defined by the doublingof the SCr level or ESRD .

WSe on Oh et al. enrolled a 5-year cohort of 799 patients with DM and an eGFR < 60 ml/ min/1.73m$_2$ and reported that patients with a baseline HbA1c of < 6.5% had reduced a risk for ESRD by comparing those with a HbA1c of > 6.5%

Oomichi T et al observational study in which 114 diabetic CKD patients. found poor glycemic control is an independent predictor of survival In people requiring chronic hemodialysis,

WHAT IS the relationship between HbA1c levels and clinical outcomes in advanced CKD???

A population-based cohort study on patients with DM and stage 3–4 CKD revealed that a baseline HbA1c higher than 7% was strongly associated with an increased risk of ESRD

.***magnitude of increased risk with higher HbA1c levels seemed attenuate in patients with stage 4 CKD comparedwith patients with stage 3 CKD***

-

a recent cohort study in Taiwan

Demonstrated that for patients with higher preceding HbA1c levels, the negative effects on eGFR deterioration were stronger at stage 3–4 CKD than stage 1–2 or stage 5,

but the outcomes of ESRD were not reported[20].

"burn-out diabetes

In many CKD-G5D patients, glycemic control improves spontaneously with the start of treatment, leading to normal-low blood glucose levels.

1. *decrease in renal and hepatic insulin clearance,*
2. *decline in renal gluconeogenesis,*
3. *reduced food intake,*
4. *proteinenergy wasting*
5. *hypoglycemic effects of dialysis*

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 and to avoid hypoglycemia-related mortality

HOW?

WICH?

IMPORTANT QUESTION

[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?

How best to control glucose in CKD-G5D

HbA1

glucose

fructosamine

glycated albumin

1,5-anhydroglucitol (1,5-AG).

HbA1

***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* 120-day lifespan of the red blood cell, it correlates best with mean blood glucose over the previous 8 to 12 weeks**

, red cells are freely permeable to glucose. As a result, glucose becomes irreversibly attached to hemoglobin at a rate dependent upon the prevailing blood glucose concentration

Approximately 1 percent of erythrocytes are destroyed every day while an equal number of new ones are formed.

HbA1c does not seem useful in CKD-G5D

HbA1c does not seem useful in CKD-G5D

1. *Hyperinsulinemia in stage 5 CKD.*

2. *glycated hemoglobin formation is reduced in patients with CKD because the fragile red blood cell (RBC) has shortened lifespan by 30%–70%*

3. *carbamylated hemoglobin molecules in the uremic environment become resistant to glycosylation*

4. *Administering erythropoietin stimulating agents (ESAs) in peripheral blood, the proportion of young RBCs, which have a lower rate of glycosylation than do old RBCs, thereby altering glycosylated hemoglobin formation*

How best to control glucose in CKD-G5D

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fructosamine

glycated albumin

1,5-anhydroglucitol (1,5-AG).

FRUCTOSAMINE

is a generic term referring to all early glycated serum proteins

is an intermediate-term glycemic control indicator (7–14 days

it is not affected by all the factors related to anemia.

FRUCTOSAMINE

- lack of reference ranges
- may be strongly affected by sex, age, sample population, test method, total proteins, uric acid concentration and unspecific serum reducing activities

false fructosamine

1. protein wasting in patients undergoing peritoneal dialysis (PD)
2. in CKD-G5D patients with protein-energy wastin.
3. In case of protein loss
4. fructosamine adjusted for albumin appeared to be a more reliable marker of glycemic control in PD patients

How best to control glucose in CKD-G5D

HbA1

glucose

fructosamine

glycated albumin

1,5-anhydroglucitol (1,5-AG).

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.

stable blood levels of 1,5-AG reflects day to day

1,5 AG has severe limitations in CKD-G5D patients because of the kidney failure It does not appear to be influenced by mild or moderate renal dysfunction (CKD stages 1–3)

How best to control glucose in CKD-G5D

HbA1

glucose

fructosamine

glycated albumin

1,5-anhydroglucitol (1,5-AG).

Glycated albumin

a medium-term glycemic marker

because it reflects the average life of albumin (about 20 days)

it could be useful in all those conditions requiring short-term glycemic control, such as after starting modifying a drug therapy

Glycated albumin

Glycated albumin for glycemic control ?

Glycated albumin in chronic kidney disease patients on dialysis ?

Glycated albumin and survival ?

Glycated albumin and cardiovascular outcome?

Glycated albumin and other clinical conditions?

Glycated albumin

Glycated albumin for glycemic control

Glycated albumin in chronic kidney disease patients on dialysis

Glycated albumin and survival

Glycated albumin and cardiovascular outcome

Glycated albumin and other clinical conditions

DM screening

Japan,

for DM screening. GA >15.2% and >15.5%

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 1300 healthy blood donors aged 18–65 years .

Glycated albumin

Glycated albumin for glycemic control yes

Glycated albumin in chronic kidney disease patients on dialysis

Glycated albumin and survival

Glycated albumin and cardiovascular outcome

Glycated albumin and other clinical conditions

GA

OXFORD JOURNALS NDT Plus

NDT Plus. 2011 Dec; 4(6): 368–375.
doi: 10.1093/ndtplus/sfr140
PMCID: PMC4421676
PMID: 25984197

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

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Vos et al.investigated the accuracy of GA, HbA1c and fructosamine as indicators of glucose control using 48 h 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
23 HD patients

Can HD and PD patients be effectively managed with GA ?

Can HD and PD patients be effectively managed with GA ?

(1) proteinuria and protein loss into the PD fluid may affect the GA level because of reduced exposure of serum albumin to glucose,

(2) the use of different dialytic solutions may permit glycemic spikes during the therapy

Can HD and PD patients be effectively managed with GA?

For PD patients, protein loss from effluent about 5 to 15 g daily with little variation

However, both glycated and non glycated protein will exist in effluent with similar ratio as in blood.

It was also significantly correlated with low protein losses in urine and dialysate (<5.9 g/day).

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 dialysat

Glycated albumin

Glycated albumin for glycemic control yes

Glycated albumin in chronic kidney disease patients on dialysis yes

Glycated albumin and survival ?

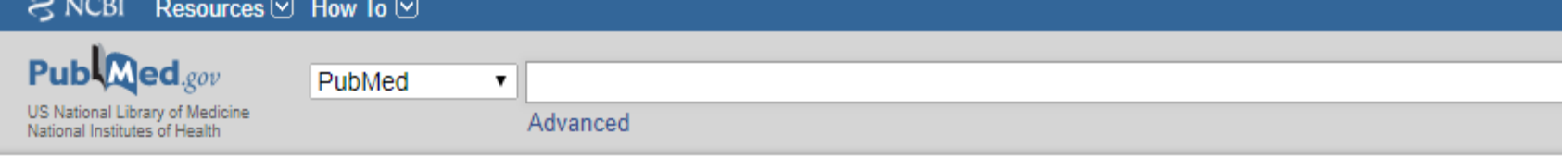
Glycated albumin and cardiovascular outcome?

Glycated albumin and other clinical conditions?

Glycated albumin and survival

The five-year cumulative mortality rate among DM patients under dialysis is >70%, with CVD the leading causes of death

Okada et al. [60] examined the relations between GA and survival in 78 type 2 DM HD patients. The mean follow-up was 35 ± 16months. no difference in mortality between patients in the higher (GA _23%) or the lower (GA <23%)



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Nephrology (Carlton). 2008 Jun;13(4):278-83. doi: 10.1111/j.1440-1797.2007.00864.x.

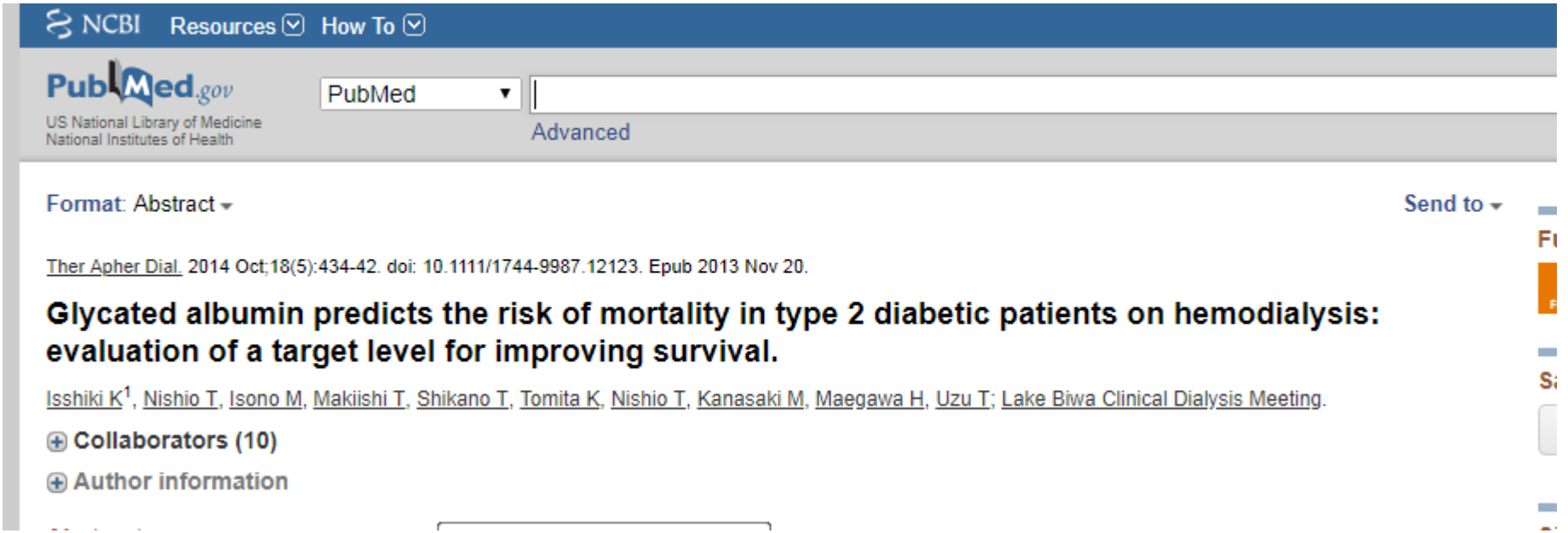
Glycated albumin levels predict long-term survival in diabetic patients undergoing haemodialysis.

Fukuoka K[1], Nakao K, Morimoto H, Nakao A, Takatori Y, Arimoto K, Taki M, Wada J, Makino H.

Author information

Glycated albumin and survival

poor glycemic control (GA 29%) before starting haemodialysis is associated with increased cardiovascular morbidity and shortened survival in diabetic patients with ESRD but not in the case with HbA1c



Isshiki et al. [64] longitudinal, observational study on 90 DM patients who had been receiving HD for at least six months. The mean follow-up was 36.0. GA was a significant predictor of all cause mortality [hazard ratio (HR) for a 1% increase iGAthe cut-off predicting mortality was 25%, with a cumulative survival

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Diabetes Care. 2013 Jun;36(6):1522-33. doi: 10.2337/dc12-1896. Epub 2012 Dec 18.

Serum fructosamine and glycated albumin and risk of mortality and clinical outcomes in hemodialysis patients.

Shafi T[1], Sozio SM, Plantinga LC, Jaar BG, Kim ET, Parekh RS, Steffes MW, Powe NR, Coresh J, Selvin E.

Author information

Abstract

Shafi et al. 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

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Clin J Am Soc Nephrol. 2011 Jul;6(7):1635-43. doi: 10.2215/CJN.11491210. Epub 2011 May 19.

Glycated albumin and risk of death and hospitalizations in diabetic dialysis patients.

Freedman BI[1], Andries L, Shihabi ZK, Rocco MV, Byers JR, Cardona CY, Pickard MA, Henderson DL, Sadler MV, Courchene LM, Jordan JR, Balderston SS, Graham AD, Mauck VL, Russell GB, Bleyer AJ.

Freedman et al. 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.

Glycated albumin

Glycated albumin for glycemic control yes

Glycated albumin in chronic kidney disease patients on dialysis yes

Glycated albumin and survival yes

Glycated albumin and cardiovascular outcome?

Glycated albumin and other clinical conditions?

Glycated albumin and cardiovascular outcome

Patients on dialysis have an increased risk of CVD and this risk is further increased in the presence of DM.

Yamada et al. [73] explored in DM HD patients the association between GA and HbA1c and peripheral vascular calcification, Multiple regression analyses suggested that both HD duration and GA, but not HbA1c, were associated with vascular calcification

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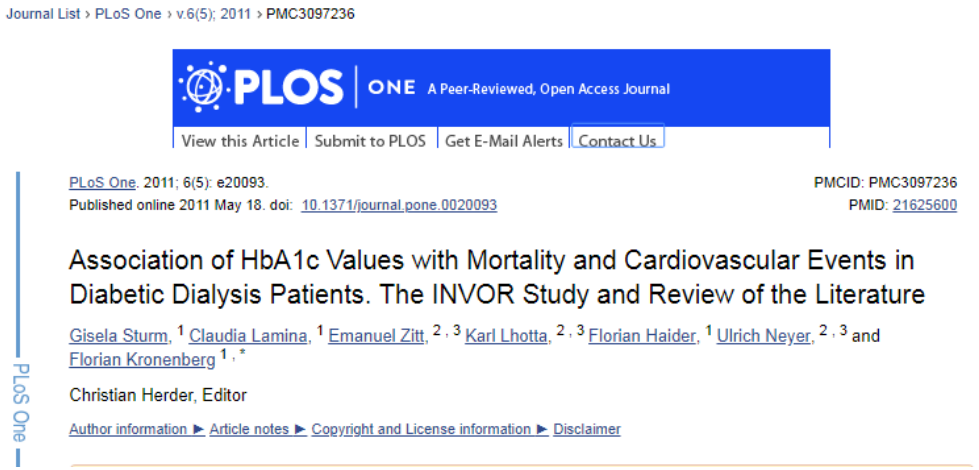
poor glycemic control (GA 29%) before starting haemodialysis is associated with increased cardiovascular morbidity and shortened survival in diabetic patients with ESRD but not in the case with HbA1c

HbA_{1c} over a period of more than seven years. Besides the methodological advantages data indicate a significant inverse association ***between HbA_{1c} levels and all-cause mortality***. However, **for CVD events no significant association could be found**



Glycated albumin and cardiovascular outcome CHOICE STUDY

Glycated albumin

Glycated albumin for glycemic control yes

Glycated albumin in chronic kidney disease patients on dialysis yes

Glycated albumin and survival yes

Glycated albumin and cardiovascular outcome yes

Glycated albumin and other clinical conditions?

Glycated albumin and other clinical conditions

hospital admission rates

non-cardiovascular causes of death DM HD

- ***patients infection,***
- ***renal bleeding,***
- ***cerebral bleeding,***
- ***malignancy***
- ***multiple organ failure***

hospital admission rates

of 444 DM HD patients had at least one hospital admission with a median number of 10.55 days of per year (25–75th percentiles 4.15–49.46 days).

Increasing GA levels were associated with hospitalization in the 17 days after

whereas HbA1c and blood glucose were not

non-cardiovascular causes of death DM HD

In the study by Isshiki , The rates of noncardiovascular mortality were the same in the group with high (>25%) and lowGA (25%).

by Fukuoka were infectious diseases, malignant diseases and others. Low (<29%) and high (29%) GA groups did not differ in the incidence of main non-cardiovascular causes

utility of GA in patients under dialysis as a prognostic marker for mortality, mainly for cardiovascular causes, and hospitalization

Glycated albumin

Glycated albumin for glycemic control yes

Glycated albumin in chronic kidney disease patients on dialysis yes

Glycated albumin and survival yes

Glycated albumin and cardiovascular outcome yes

Glycated albumin and other clinical conditions?

IMPORTANT QUESTION

[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?

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Conclusions

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.

GA can promptly indicate improvement or worsening of patients' glycemic status. In HD and PD patients, GA reflects glycemic control more accurately than other markers

GA can be a useful predictor of survival and of cardiovascular mortality in DM HD patient

In HD patients, GA seems to give a more accurate picture of glycemic control than in PD patients,

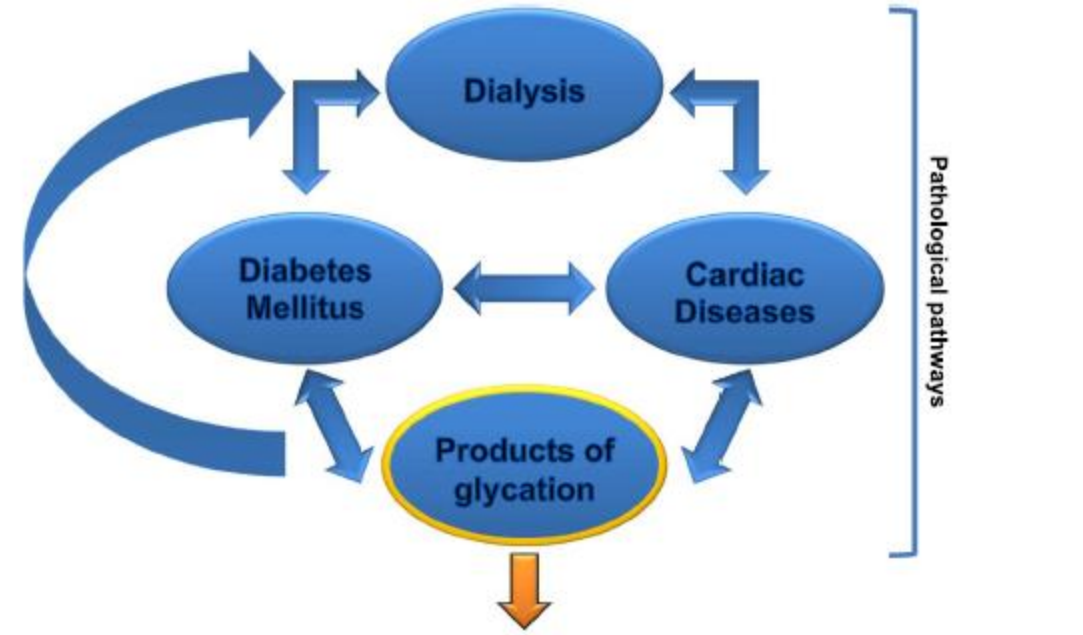
Research on GA is still in the early stages, but we believe it merits further studies to clarify its potential role for management in CKD-G5D


Thank you for your attention

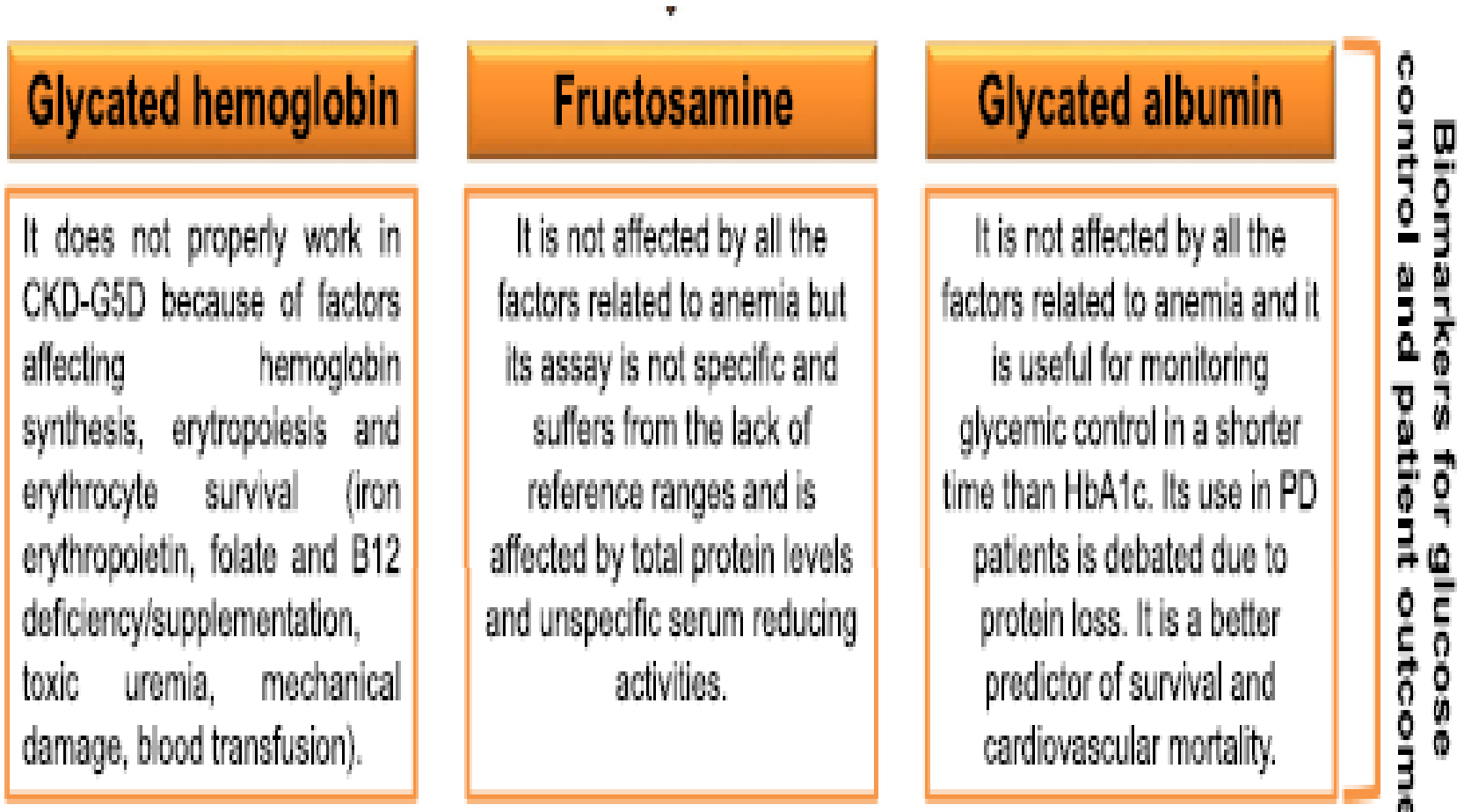
HbA1

UP TO DATE

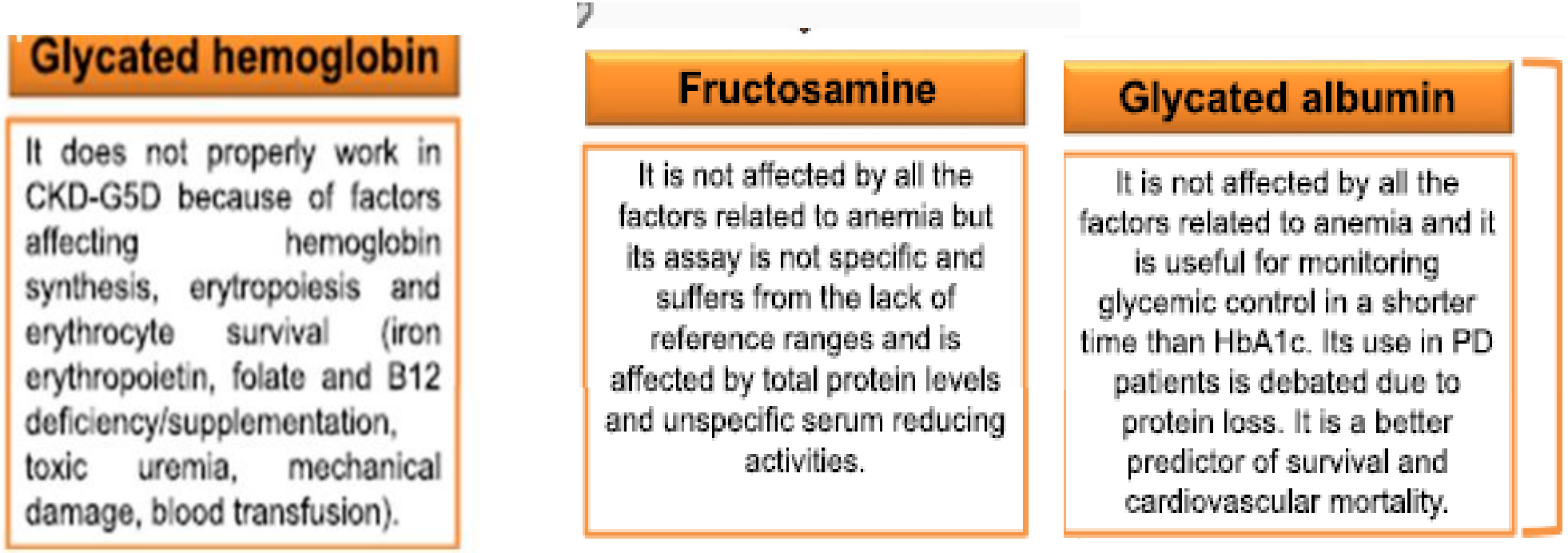
GVDUHBV


Dialysis
Diabetes Mellitus
Cardiac Diseases
Products of glycation
Pathological pathways

GVDUHBV


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

GVDUHBV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