Glycemic Control as Primary Prevention for Diabetic Kidney Disease

Richard J. MacIsaac, George Jerums, and Elif I. Ekinci

Improving strategies to prevent the development and progression of CKD is a highly desirable outcome for all involved in the care of patients with diabetes. This is because CKD is a major factor contributing to morbidly and mortality in patients with diabetes. Furthermore, diabetes is the leading cause of ESRD in most developed countries. Although tight glucose control is now an established modality for preventing the development and progression of albuminuria, evidence is now accumulating to suggest that it can also ameliorate glomerular filtration rate loss and possibly progression to ESRD. These benefits of intensive glucose control appear to be most pronounced when applied to patients with the early stages of CKD. Recently, medications that belong to the sodium glucose cotransporter-type 2 inhibitor and the glucagon-like peptide-1 receptor analogue classes have been shown to reduce progression of CKD in patients with type 2 diabetes and relatively well-preserved kidney function. Here, we review the evidence from observational and interventional clinical studies that link good glucose control with the primary prevention of diabetic kidney disease with a focus on preventing early glomerular filtration rate loss.

© 2017 by the National Kidney Foundation, Inc. All rights reserved.

Key Words: Glucose, Diabetes, Chronic, Kidney, Disease

INTRODUCTION

Preventing the development and progression of CKD is a major treatment focus in the care of individuals with diabetes. This is because CKD is a leading factor contributing to increased morbidity and mortality in diabetes. In particular, individuals with diabetes who develop CKD are known to be at a greatly exaggerated risk for developing cardiovascular (CV) disease with a subsequent increased vulnerability for a fatal outcome. Furthermore, it is also known that individuals with diabetes and CKD are at a high risk of developing kidney failure with diabetes being the leading cause of ESRD in most developed countries.[1-4]

Optimizing strategies to prevent the development of CKD in people with diabetes is therefore a highly desirable outcome. Blood pressure (BP) control and the use of medications that inhibit the renin-angiotensin-aldosterone system, which may have effects independent of BP lowering, are an established modality for preventing the development and progression of CKD in diabetes.[2-5] Poor glycemic control has clearly been shown to be a major diver for the development and progression of diabetic kidney disease (DKD).[6] However, glycemic thresholds that signify an exaggerated risk for the development of DKD and the achievement of glycemic targets that safely reduce risk still remain to be fully defined.

Here, we review the results of observational and interventional clinical studies that have examined the effects of glycemia on early markers of kidney health in diabetes. As tight glucose control has clearly been shown to reduce the incidence of microalbuminuria or macroalbuminuria, we have mainly focused on highlighting studies that have related glucose control to early changes in glomerular filtration rate (GFR). Furthermore, we briefly review the potential role of newer glucose-lowering agents, especially the sodium glucose cotransporter-type 2 (SGLT-2) inhibitors and the glucagon-like peptide-1 (GLP-1) receptor agonists in the primary prevention of DKD.

EARLY MARKERS OF DIABETIC KIDNEY DISEASE

Hyperfiltration (HF) has been implicated as an early phase of DKD for approximately 4 decades, but the link between HF and the development of other markers of DKD such as albuminuria or a progressive decline in GFR to subnormal values still remains to be fully established.[7-10] One of the most important determinants of HF is hyperglycemia. One mechanism linking hyperglycemia with the onset of HF most likely involves an increase in sodium reabsorption via the SGLT-2 receptor in the proximal tubule which ultimately results in tubuloglomerular feedback modulating blood flow in the glomerular afferent arteriole.[11,12] HF in type 1 diabetes (T1DM) has been shown to be reversible with insulin therapy and near normalization of blood glucose levels.[13] Kidney hemodynamics can also be influenced by body weight and diet, especially high-protein diets. An elevation in circulating amino acids as a result of a high-protein diet is an established inducer of HF.[14] In the setting of poor glycemic control, it has been previously shown that there is an augmented HF response to amino acids which can be reversed by intensive glucose control in patients with T1DM or type 2 diabetes (T2DM).[15,16]

Over the last decade, there has been considerable interest in the value of monitoring an early accelerated decline in GFR from normal GFR levels in diabetes as a prognostic marker for progression of DKD to hard late clinical

From the Department of Endocrinology & Diabetes, St Vincent's Hospital Melbourne, Australia; Department of Medicine, University of Melbourne, Victoria, Australia; and Endocrine Centre, Austin Health, Victoria, Australia.

Financial Disclosure: The authors do not have any conflicts of interest to declare that relate to the contents of this manuscript. R.J.M. was supported by an Australian Diabetes Society-Servier Diabetes Research Grant. E.I.E. was supported by an RACP JDRF Fellowship, Sir Edward Weary Dunlop Medical Research Foundation Grant, Diabetes Australia Research Program Grant.

Address correspondence to Richard J. MacIsaac, Bsc(HONS), PhD, MBBS, FRACP, Department of Endocrinology & Diabetes, St Vincent's Health, Melbourne & Professorial Fellow, University of Melbourne, 4th Floor, Daly Wing, 35 Victoria Parade, PO Box 2900, Fitzroy, Victoria 3065, Australia. E-mail: r.macisaac@unimelb.edu.au

© 2017 by the National Kidney Foundation, Inc. All rights reserved.

1548-5595/$36.00

https://doi.org/10.1053/j.ackd.2017.11.003

end points, such as the development of ESRD. This early decline in GFR has been defined as a rate of kidney function loss greater than that ascribed to aging alone and occurs before a GFR threshold of 60 mL/min/1.73 m^2 (CKD Stage 3) is reached and which is also distinct from resolution of HF.[17] However, caution is required in interpreting this parameter when GFR is estimated from creatinine-based equations. There are uncertainties associated with GFR estimating equations at any level of GFR, but the issue of significant underestimation of directly measured GFR values in the normal to HF range, especially in the setting of diabetes, has been well documented.[18,19]

The presence of albuminuria is not only recognized as an early marker of DKD but also to signify an increased risk for the development of CV disease.[20] While a transition from normoalbuminuria to microalbuminuria and subsequently to macroalbuminuria occurs in the majority of patients with diabetes who develop ESRD, the limitations of following serial trends in albuminuria have been well described. These include the entities of normoalbuminuric kidney insufficiency, the inherent variability of albuminuria, spontaneous regression rather than progression of microalbuminuria, and the fact that an early decline in GFR, as mentioned above, can occur during the phase of normoalbuminuria.[21]

GLYCEMIC THRESHOLDS FOR THE DEVELOPMENT OF ALBUMINURIA AND EARLY GLOMERULAR FILTRATION RATE LOSS

Most studies including the Diabetes Control and Complications Trial (DCCT)[22] and the United Kingdom Prospective Diabetes Study[23] have suggested that there is a strong relationship between glucose control in both T1DM and T2DM, respectively, and the risk of the development of diabetic microvascular complications without a clear-cut HbA1c threshold.[22,23] A recent observational analysis of the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial that involved 12,537 people with T2DM or prediabetes followed for 6.2 years suggested that the risk for adverse kidney outcomes rises progressively from the lowest (<5.7% [33.8 mmol/mol]) to the highest quintile (7.4% [57.4 mmol/mol]) of HbA1c levels observed during the study. In this study, the hazard ratio (HR) for kidney failure was 1.54 (95% CI: 1.24-1.91, $P = 0.001$) per 1% higher baseline HbA1c.[24] In contrast, an observational analysis from the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study, involving subjects with T2DM, suggests that within the range of HbA1c studied (5.5%-10.5% [37-91 mol/mol]), there was evidence of a glucose threshold for the development of DKD.[25] In this study, HbA1c levels below 6.5% (48 mmol/mol) were not associated with a significant increase in the risk risks for the development of eye or kidney complications including macroalbuminuria, doubling of serum creatinine levels, need for kidney-replacement therapy, or death due to kidney disease. Therefore, substantiating whether a glycemic threshold for the onset of DKD exists still requires further work.

CLINICAL SUMMARY

- Intensive glucose control prevents the development and progression of albuminuria.
- Intensive glucose control most likely prevents glomerular filtration rate loss.
- The kidney benefits of intensive glucose control are most pronounced when applied to patients with early-stage CKD.
- Some members of the SGLT-2 inhibitor and glucagon-like peptide-1 receptor analogue class of glucose-lowering medications reduce progression of CKD in patients with type 2 diabetes.

GLUCOSE CONTROL AND EARLY GLOMERULAR FILTRATION RATE LOSS

In the DCCT, subjects with T1DM, who were mostly free from manifestations of DKD, were randomized to intensive glucose control (HbA1c 7.3% [56 mmol/mol], n = 711) or conventional glucose control (HbA1c 9.1% [76 mmol/mol], n = 730) and studied for 6.5 years and then subsequently followed in an observational fashion in the Epidemiology of Diabetes and Interventions and Complications (EDICs) study which continues today.[26,27] Of note, the approximate 2% difference in HbA1c levels in the intensive compared to conventional glucose control arms of DCCT was no longer apparent during the EDIC study when kidney end points were assessed with Hb1Ac levels being approximately 8.0% (64 mmol/mol) for all subjects.

The above DCCT/EDIC study has revealed that the risk for developing a sustained impairment of eGFR was approximately 50% lower in subjects originally randomized to intensive glucose control in the DCCT compared to conventional glucose control. Interestingly, this effect was not evident until 10 years after the completion of randomization to conventional or intensive glucose control. ESRD developed in only 8 subjects randomized to intensive glucose control compared with 16 subjects randomized to conventional glucose control but due to the low number of subjects that developed ESRD, the difference in this event rate was not statistically significant. In contrast, initial intensive glucose control reduced the risk of impaired GFR or death by 37% (95% CI: 10-55, $P = 0.01$)[26,27] (Table 1).

The ADVANCE study has also examined the effects of intensive glycemic control on GFR loss and progression to ESRD in T2DM. In this study, 11,140 subjects with T2DM were randomized to intensive glucose control or conventional glucose control and followed for a median of 5 years. The time-weighted average HbA1c difference was 0.67% for intensively (mean HbA1c 6.5% [48 mmol/mol] at the end of the study) and conventionally treated subjects (HbA1c 7.3% [56 mmol/mol] at the end of the study). The majority of subjects in the study had normal kidney function with a mean eGFR of 78 mL/min/1.73 m^2, but 19% had a GFR < 60 mL/min/1.73 m^2, 27% had microalbuminuria, and 4% had macroalbuminuria.[28] At the 5-year completion of the ADVANCE study, the

Download English Version:

https://daneshyari.com/en/article/8769608

Download Persian Version:

https://daneshyari.com/article/8769608

Daneshyari.com