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A Review on Biomarkers for Early Diagnosis of Diabetic Kidney Disease

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Abstract:

Introduction
To assess the potential of galectin-3 and growth differentiation factor-15 (GDF-15) biomarkers for the early detection of diabetic kidney disease (DKD).

Methodology
This was a cross-sectional study conducted over a period of 1.2 years. Patients were stratified based on estimated glomerular filtration rate (eGFR) and albuminuria level. The receiver operating characteristic (ROC) curve was plotted to assess the diagnostic potential of biomarkers.

Conclusion
In DKD patients the galectin-3 and GDF-15 levels were inversely related to the eGFR which was further confirmed by the ROC curve demonstrating the potential of galectin-3 and GDF-15 as a biomarker.

Keywords: Diabetic kidney disease, Biomarkers, Detection, Diagnosis

INTRODUCTION

Diabetic kidney disease is a type of kidney disease caused by diabetes. Diabetes is the leading cause of kidney disease. About 1 out of 3 adults with diabetes has kidney disease.

The main job of the kidneys is to filter wastes and extra water out of your blood to make urine. Your kidneys also help control blood pressure and make hormones that your body needs to stay healthy.

Cause : High blood glucose, also called blood sugar, can damage the blood vessels in your kidneys. When the blood vessels are damaged, they don't work as well. Many people with diabetes also develop high blood pressure, which can also damage your kidneys.

Biomarkers in Use

It is well established that the best predictor of future ESRD is the current GFR and past GFR trajectory. Thus, GFR is the most common prognostic biomarker being used for predicting ESRD in both clinical practice and in trials. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) equations, both based on serum creatinine, are commonly used to estimate GFR. The difference in accuracy for staging between CKD-EPI and MDRD is slight, with 69% vs 65% overall accuracy for given stages being found in one study.

Serum cystatin C-based eGFR has been proposed as advantageous since, unlike creatinine, it is not related to muscle mass. Equations based on cystatin C overestimated directly measured GFR, while equations based on serum creatinine underestimated GFR in a large study.

Others have found that creatinine agrees more closely than cystatin C with directly measured GFR.

In those with and without diabetes, cystatin C predicts CVD mortality and ESRD better than eGFR does.

However, this may be because factors other than renal function that affect ESRD risk, including diabetes, might also affect serum cystatin C levels, rather than because cystatin C-based eGFR is more accurately measuring GFR itself.

Albuminuria: strongly predicts progression of DKD but it lacks specificity and sensitivity for ESRD and progressive decline in eGFR. In type 2 diabetes a large proportion of those who have renal disease progression are normoalbuminuric.

It has been shown that the coexistence of albuminuria makes DKD rather than non-diabetic CKD more likely in people with type 2 diabetes.

However, even in type 1 diabetes, where non-diabetic CKD is much less common, albuminuria was reported to have a poor positive predictive value for DKD as only about a third of those with microalbuminuria had progressive renal function decline. Albumin excretion also had low sensitivity, as only about half of those with progressive renal function decline were albuminuric.

Clearly, in evaluating the predictive performance of novel biomarkers, investigators should adjust for baseline eGFR and albuminuria. Historical eGFR data are not always routinely available. Nonetheless, it is important where possible to evaluate whether biomarkers improve prediction on top of historical eGFR.

In reality, despite all the attempts to develop novel prognostic biomarkers, few current trials use biomarkers other than albuminuria or eGFR as stratification variables or entry criteria. An exception is the PRIORITY trial, in which the CKD273 panel is being used to risk stratify people into a spironolactone vs placebo arm.

Biomarkers as surrogates of drug response is not the focus of this review but we note that there are also few trials using surrogate biomarkers as endpoints.

One ongoing trial is using urinary proteomic panels as a surrogate outcome measure

Another study includes urinary NGAL and KIM-1 as secondary outcome measures, and another is using *N*-acyl-β-D-glucosidase, B2M and cystatin C .

The SYSKID consortium have argued that past trials have shown that albuminuria/eGFR are insufficient to predict the individual's response to renoprotective treatments in DKD, and that biomarkers more closely representing molecular mechanisms involved in disease progression and being targeted by therapies are needed

Recently, Pena et al found that urinary metabolites previously shown to be at lower levels in those with DKD than without, decreased in the placebo arm of a trial but remained stable in the arm treated with the endothelin A receptor blocker atrasentan over a short, 12 week trial . Further such studies of changes in biomarkers over time and in response to treatment are needed.

Future perspective:

In summary, despite the large number of reports in the literature, at present there are few validated biomarkers that have been clearly shown to substantially increase prediction of DKD-related phenotypes beyond known predictors. Few studies have attempted to estimate the marginal improvement in prediction beyond historical eGFR readings that can be expressed as the within-person slope or weighted average past eGFR, as we did in the SUMMIT study [25]. This is an important omission given the increasing availability of electronic healthcare records and potential for applying algorithms to such longitudinal clinical data more easily than measuring biomarkers. Even where some consistency in findings is observed, the extent of publication bias is unknown. Most importantly, biomarkers other than ACR and eGFR are not being routinely used to risk stratify individuals into trials or in clinical practice, despite considerable research investment into DKD biomarkers in recent years.

If this field is to be advanced, there is a need for a concerted effort to

(1) generate and share data on the correlation between existing candidate biomarkers and biomarkers generated from available discovery platforms;

(2) generate replication and validation sample and data sets that allow the best panel from available data to be defined;

(3) harness the predictive information that exists in clinical records in the era of electronic health record data. Future discoveries should then be evaluated for their marginal prediction on top of clinical data and validated biomarkers.

Conclusion

Galectin-3 and GDF-15 levels were inversely correlated with eGFR. The level of the biomarkers significantly elevated as the kidney function worsens. The findings of this study suggest that galectin-3 and GDF-15 could be a potential and reliable biomarker for the early detection of DKD. Further, multination, multicenter, and multiethnic studies are warranted to make the evidence more robust.

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