Review Article

Major risks indicators for diabetic kidney disease

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Diabetic nephropathy, which is defined as elevated urine albumin excretion or reduced glomerular filtration rate or both, is a serious complication that occurs in 20–40% of all diabetic patients. There is marked racial/ethnic difference besides international difference in the epidemiology of diabetic nephropathy. Hyperglycemia is a well-known risk factor for diabetic kidney disease, in addition to other risk factors such as male sex, obesity, hypertension, chronic inflammation, dyslipidemia, and some genetic loci and polymorphisms in specific genes. Management of its modifiable risk factors might help in reducing its incidence in the near future.

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Risks for diabetic kidney disease have focused on those associated with loss of renal function, particularly glomerular filtration rate (GFR). Loss of renal function includes many aspects other than GFR. A number of comorbidities result from, or are exacerbated by, damage to the kidney: hypertension, anemia, disordered bone and mineral metabolism, dyslipidemia, and inflammation. These co-morbidities may contribute to further kidney dam-age, as well as to cardiovascular disease (CVD). The latter issue is of particular concern because most people with diabetes who develop CKD will die of CVD rather than reach ESRD[1]. Because diabetes and CKD pose a high risk of mortality and morbidity, the pur-pose of this review is to review major risks indicators. Identification of risks allows for development of improved strategies for detection, intervention, and novel therapeutic approaches.

Predictors of Kidney Disease in Early Diabetes :

Renal Hemodynamics :

Genetic predisposition undoubtedly contributes to the development of kidney disease in diabetes. In addition, early renal functional changes have also been associated with subsequent kidney disease. Glomerular hyperfiltration, a higher than normal GFR, has long been recognized in recent-onset type-1 or -2 diabetes[2,3]. In observational studies of persons with type-1 diabetes, those with higher GFR levels have been described as being more likely to develop micro- or macroalbuminuria many years later[4,5]. In classic physiologic studies, diabetic rats were found to have high GFR owing to increased glomerular perfusion and pressure[6]. Intraglomerular hypertension was shown to play a key role in hyperfiltration and subsequent renal injury in diabetes or with high-protein diets in other experimental models[7]. Furthermore, feeding diabetic rats a high-protein diet greatly exacerbated renal injury and loss of function[8]. Conversely, a low-protein diet protected the kidney even in the setting of continued hyperglycemia[8]. Another important observation from this study was that the diabetic rats exhibited greater sensitivity to the renal hemodynamic effects of dietary protein than the normal rats[8]. These data suggested that interactions between the defining feature of diabetes, hyperglycemia, and dietary protein produce an augmented glomerular hyper filtration response and, consequently, kidney damage.

In human physiologic studies, those with either type-1 or -2 diabetes had an augmented glomerular hyperfiltration response that was greatly increased beyond that of non-diabetic individuals when a mixed amino acid (AA) solution designed to resemble a protein meal was infused intravenously[9]. These data suggested that hyperglycemia was necessary but not sufficient to produce glomerular hyperfiltration in diabetes. Human studies were consistent with the animal models in demonstrating greater sensitivity to renal hemo¬dynamic effects of dietary protein,

Hormonal responses to protein feeding or an AA infusion could be responsible for increasing renal perfusion and GFR.

Individuals with diabetes have enhanced sensitivity to AAs as well as to glucagon, another stimulus that raises GFR. Although glucagon and prostaglandins do not appear to be primary causes of AA-induced renal hemodynamic changes in diabetes, they could produce glomerular hyperfiltration under other conditions, such as more severe hyperglycemia.

Cellular Mechanisms :

AAs could directly injure cells and participate in processes induced by high levels of glucose. The mesangial cell culture model was chosen because it is a key cell in-

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volved in regulation of renal hemodynamics, as well as the profibrotic and proliferative response to injury in diabetes. Increased AAs, alone or in combination with a high glucose level, induced mesangial cell proliferation and fibrosis[10]. In addition, the profibrotic response was mediated by increased expression and activation of transforming growth factor-f3. Because of the remarkable similarities between effects of glucose and AAs on mesangial cells, a common metabolic pathway could be responsible. Advanced glycation end products (AGEs) are formed by nonenzymatic glycation of free amino groups, followed by a complex series of sequential glycation and oxidation reactions. Although previous research has focused on hyperglycemia as the main causal factor, increased availability of free amino groups could also initiate these reactions. If so, then cell signaling pathways associated with AGEs should also be activated and participate in the injury responses. In a series of experiments, it was found that AGE formation was increased by the AA condition, and that the combination condition of AA/High glucose (HG) appeared to produce an even greater amount of AGEs[11]. Preventing AGE formation with aminoguanidine blocked the profibrotic mesangiul cell response. Cell signaling pathways associated with AGEs, oxidative stress, and activation of protein kinase C and mitogen-activated protein kinases extracellular signal-related kinases were increased by the AA, HG, and AA/HG conditions. Their causal roles in the profibrotic response were confirmed by specific inhibition of these processes. These observations provide insight into cellular mechanisms of injury induced by AAs and a potential explanation for increased sensitivity of the diabetic kidney to damage resulting from high dietary protein. Furthermore, AGEs are associated with widespread vascular damage and consumption of foods with increased amounts of AGE-modified proteins increase circulating AGEs and inflammatory markers in diabetic subjects[12]. AA-induced injury could be produced at sites other than the kidney, and that the arterial circulation may be particularly vulnerable. In support of this, a study of persons with type-1 diabetes and early CKD (on average stage 2) showed that a modest reduction of dietary protein decreased the combined end point of death and ESRD[13]. Deaths were predominantly owing to CVD and were decreased as much, or more, than cases of ESRD. Thus, limiting exposure to dietary protein and, consequently, increased levels of AAs, may protect against CVD as well as CKD.

Kidney Disease as a Window to the Circulation :

Development of kidney disease in diabetes reflects processes operative at distant sites that have a major impact on risks of adverse outcomes. Albuminuria is the earliest clinical indicator of CKD in diabetes. However, albuminuria also increases risk of CVD events and death independent of traditional risk factors[14]. Although this relationship is particularly apparent in diabetes", albuminuria also appears to increase CVD risk in other groups, including those with essential hypertension and the general population[15]. In a study of persons undergoing elective coronary angiography, there was a direct correlation between albuminuria levels and severity of coronary artery disease[16]. This relationship was most pronounced in the subset of individuals with type-2 dia¬betes. Importantly, the levels of albuminuria that correlated with coronary artery disease were largely below the traditional threshold for defining microalbuminuria (albumin-to-creatinine ratio <30 mg/g). This concept is also supported by data from the Heart Outcomes Prevention Evaluation (HOPE) study that showed that risk of major CVD events in high-risk patients, with and without diabetes, increases at levels of albuminuria far below the traditional threshold for microalbuminuria[17]. Therefore, elevated levels of albuminuria defined by predicting progression of kidney disease may be higher than those that predict clinically important CVD.

As for most CVD risk factors, the relationship to CKD appears to be continuous. Risk of major CVD events increases even further as albuminuria progresses to clinical albuminuria (albumin-to-creatinine ratio >300 mg/g) or overt proteinuria (dipstick-positive, protein-to-creatinine ratio >500 mg/g). Risks for strokes and coronary events are amplified afact, most people with CKD will die-of CVD and not reach ESRD. People with both diabetes and decreased GFR are at especially high risk of cardiac death[19].

The strong influence of kidney disease on CVD is likely to be multifactorial. There are several possible explanations: vascular disease expressed at the level of the kidney reflects greater severity; persons with CKD have a greater burden of traditional risk factors including diabetes; CKD produces nontraditional risk factors[20]. It is important to recognize that these possibilities are not mutually exclusive. Endothelial injury, a key component of the atherosclerotic process, occurs in the glomerular microcirculation and in the circulation at large. Albuminuria is believed to be an excellent marker of this process. In persons with known coronary heart disease, defined by a previous myocardial infarction, albuminuria correlated directly with the transvascular escape rate of albumin[21]. Even in apparently healthy persons, increased levels of albuminuria are associated with endothelial dysfunction, as determined by impaired flow-associated dilation of the brachial artery[22]. Thus, albuminuria can be considered an indicator of endothelial injury in the kidney as well as at distant sites in the circulation.

Persons with type-2 diabetes and albuminuria have a particularly high risk of CVD. A seminal question is whether or not reduction of albuminuria predicts improved risk status. In secondary analyses of the Reduction in Endpoints in Noninsulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial, lowering albuminuria was associated with reduced risk of renal and cardiovascular events[23]. This has been interpreted to mean that albuminuria should be a therapeutic target in type 2 diabetes. However, a limitation of this interpretation is that those who were responsive to treatment with the angiotensin receptor blocker may have had less severe disease. Nevertheless, the hypothesis that albuminuria should be a therapeutic target is an important one worthy of prospective testing. Other important questions are embedded in this hypothesis: Do albuminuria-reducing treatments other than angiotensin receptor blockers improve outcomes? Do treatments without an effect on albuminuria improve outcomes?

In summary, indicators of CKD in diabetes, albuminuria, and decreased GFR, reflect damage to the kidney that predicts a broad spectrum of adverse outcomes in multiple vascular target organs.

Conclusions :

Risks for diabetic kidney disease have traditionally focused on those associated with loss of renal function, particularly GFR. Loss of renal function also encompasses many aspects other than GFR: hypertension, anemia, disordered bone, and mineral metabo¬lism, dyslipidemia, and inflammation, among others. Many of these disturbances are more prevalent, occur' earlier, and are more severe in diabetes than in other forms of CKD. Furthermore, they may contribute to further kidney damage, as well as to CVD. The latter issue is of particular concern because most people with diabetes who develop CKD will die of CVD rather than reach ESRD. Predictors of early kidney disease, focusing on renal hemodynamic disturbances produced by diabetes and nutritional influences (excess dietary protein), were discussed. Evidence for a direct effect of dietary protein, acting through increased AAs, to induce mesangial cell injury was also presented. Finally, the concept that indicators of CKD, albuminuria, and decreased GFR, reflect widespread circulatory disease was reviewed.

Development of kidney disease in diabetes heralds a number of adverse outcomes.

An understanding of major risks indicators should facilitate future research designed to elucidate basic mechanisms of disease at one end of the spectrum, whereas improving design of clinical trials on the other. Indeed, identification of major risks indicators is a critical component of translational research, the bench-to-bedside paradigm.

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