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STATE OF THE ART REVIEWS

Early stage of vascular disease and diabetic kidney disease: an under-recognized entity

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Abstract

Early stage of vascular disease and diabetic kidney disease (DKD stages 1 and 2) has been under-recognized, under common practice worldwide. The lack of sensitive diagnostic marker leads to late diagnosis and a progression of underlying vascular disease associated with chronic renal ischemia, which eventually intensifies the magnitude of DKD damage. Treatment at this late stage fails to correct the renal ischemia, or restore renal function, due to the altered vascular homeostasis associated with an impaired nitric oxide production. In contrast to the above information, early recognition of vascular disease and DKD with sensitive diagnostic markers would be able to implement an effective prevention of progression of vascular disease and DKD. Treatment at early stage under environment favorable for adequate vascular homeostasis is able to correct the renal ischemia and improve the renal function.

Keywords

Diabetic kidney disease, diagnostic markers, renal function, renal ischemia, vascular disease, vascular homeostasis

History

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Introduction

Under common practice, diagnosis of vascular disease associated with diabetes mellitus is under-recognized due to the lack of sensitive diagnostic marker such as hemodynamic study, or vascular biomarker and mostly relies on the presence of clinical end-organ damage. To support this view, intrarenal hemodynamic study using a double-isotope technique such as ^{131}I labeled with ortho-iodohippuric acid to determine renal plasma flow, and ^{99m}Technitium labeled with diethylene triamine pentaacetic acid to determine glomerular filtration rate, has been repeatedly studied in a wide range of clinical severity of diabetes mellitus type 2 such as during normoalbuminuria microalbuminuria, and macroalbuminuria. In this regard, evidence of renal microvascular disease has been documented as early as during normoalbuminuria namely the reduction in peritubular capillary flow, renal plasma flow, an abnormally elevated intraglomerular hydrostatic pressure (PG), an increased renal arteriolar resistance, a normal or mildly altered glomerular filtration rate, which indicate the presence of renal ischemia in early stage of diabetic kidney disease (DKD).[1–6] Furthermore, biomarkers of endothelial injury has also been demonstrated such as an abnormally elevated circulating endothelial cells in early stage type 2 DKD.[2,7,8] In contrast, such information of renal microvascular disease in early stage of DKD would be unable to obtain under general practice due to the unavailability of the diagnostic instrument. In addition to the renal hemodynamic study, renal microvascular disease can be assessed by an invasive renal histopathology such as endothelial factor VIII staining in renal microcirculation.[9,10]

With respect to the issue of DKD, the recognition of DKD is generally relied on the presence of microalbuminuria and the value of serum creatinine concentration >1 mg/dL.[9] In this regard, such conceptual view is inappropriate and recognizes only late stage of DKD (stage 3), but is unable to sort out early stage DKD. Much evidence renders support that the value of serum creatinine >1 mg/dL is equivalent to the level of creatinine clearance <60 mL/min/1.73 m^2, or DKD stage 3.[11–15] During the stage of microalbuminuria the level of glomerular filtration rate, or creatinine clearance is usually approaching DKD stage 3. This view is supported by the intrarenal hemodynamic study which reveals a greater reduction in peritubular capillary flow and renal plasma flow, in conjunction with a greater increased renal arteriolar resistance and intraglomerular hydrostatic pressure in type 2 DKD associated with microalbuminuria.[1–3] Further study in microalbuminuric type 2 DKD reveals a greater reduction in renal perfusion as the renal disease severity progresses.[14] This finding implies that the severity of renal microvascular disease associated with the magnitude of renal ischemia inversely correlates with the severity of renal disease progression.[16–22] What is the cause-and-effect relationship between renal microvascular disease associated with renal ischemia and renal disease damage remaining a crucial issue to be elucidated. In this regard, recent study has addressed to

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Table 1. Demonstrates five stages of diabetic kidney disease (DKD).

	Renal function	Biomarkers
DKD stage 1	CCr 90–120 ml/min/1.73 m^2 (hyperfiltration)	FE Mg, RPF, (CCr) (normoalbuminuria)
DKD stage 2	CCr 60–89 ml/min/1.73 m^2	FEMg, RPF, CCr (normalbuminuria)
DKD stage 3	CCr 30–59 ml/min/1.73 m^2	Microalbuminuria
DKD stage 4	CCr 15–29 ml/min/1.73 m^2	Macroalbuminuria
DKD stage 5	CCr < 15 ml/min/1.73 m^2	End-stage renal disease

CCr, creatinine clearance; FEMg, fractional excretion of magnesium; RPF, renal plasma flow.

this issue that renal microvascular disease associated with the reduction in renal plasma flow or the peritubular capillary flow occurs before the development of tubulointerstitial disease in mild form of idiopathic steroid-sensitive nephrotic syndrome. In steroid-resistant type, there is a greater reduction in renal plasma, or peritubular capillary flow, which would be able to induce a mild degree of tubulointerstitial fibrosis. Furthermore, a greater reduction in renal perfusion induces a higher degree of tubulointerstitial fibrosis as indicated in case of treatment resistant nephrosis associated with focal segmental glomerulosclerosis.[23]

Therapeutic resistance to vasodilator treatment in type 2 DKD under common practice

Due to the lack of sensitive vascular marker for recognition of early vascular disease, and for screening of early stage of DKD, treatment is generally implemented at a rather late stage (DKD stage 3), and fails to correct the renal ischemia or restore renal function; but instead simply slow the renal disease progression toward end-stage renal disease dependent to renal replacement therapy.[14,22] Recent study on vascular response to vasodilator treatment in microalbuminuric DKD patients (DKD stage 3) reveals a progressive decline in peritubular capillary flow and glomerular filtration rate in microalbuminuric DKD.[23] This finding of therapeutic resistance in late stage DKD concurs with the report of other investigators who have demonstrated the progression of renal function impairment toward end-stage renal disease.[23–28] Repeated intrarenal hemodynamic studies along the clinical course of late stage DKD have consistently observed the progressive decline in renal plasma flow and peritubular capillary flow compatible with the progressive decline in renal function.[2,14] To explain the therapeutic resistance to vasodilator treatment in the late stage DKD patients, recent study on vascular homeostasis has addressed to this special issue. Vascular homeostasis reveals a defective angiogenesis associated with an impaired nitric oxide production, an inability to repair the vascular repair. The lack of nitric oxide production fails to induce the blood vessel to respond to vasodilator, and thus fail to relax the blood vessel and unable to correct the renal ischemia.[29–32] In addition, the late stage DKD patients also show an abnormally elevated level of antiangiogenic factors such as angiopoietin 2, vascular endothelial growth factor receptor-2, which induces a progressive renal microvascular disease and a progressive reduction in renal perfusion determined by intrarenal hemodynamic study.[14] Therefore, treatment implemented at late stage DKD under common practice fails to restore renal function, but simply slow the renal disease progression toward renal replacement therapy.

Is there a possibility to sustainably prevent the progression of vascular disease and avoidance of kidney damage in clinical practice?

Accumulative evidence renders support that there has been a progressive increment in the number of DKD patients entering end-stage renal disease dependent to renal replacement therapy due to therapeutic failure in restoring renal function at the late stage DKD. To overcome this clinically unfortunate event, it is necessary to change the conceptual view of therapeutic and preventive strategy to early treat the vascular disease and target on DKD patients at the early stage, inasmuch as vascular disease has been recognized as early as DKD stage 1 (hyperfiltration) (Table 1). In this regard, we have recently demonstrated that altered vascular indices namely nitric oxide, endothelin-1, angiotensin converting enzyme and endostatin are present in this early DKD stage associated with a rather normal or hyperfunction of creatinine clearance. At this very early stage, elevation of both nitric oxide and endothelin-1 implies the early stage of vascular disease associated with a vascular compensation. In addition, vascular disease of both macro- and micro-subtypes has been illustrated in early stage of DKD during normoalbuminuria. In type 2 diabetes mellitus, macrovascular disease indices namely an increased arterial stiffness and an increase in estimated age of artery have been noted by cardio-ankle vascular index method.[32] Under common clinical practice, most of the diabetic patients at this early DKD stage have been under-recognized and the vascular disease has been left unnoticed, and allowed the disease to progress, as well as induce kidney damage further to an advanced stage that would eventually be caught up by the conventionally available biomarkers.

With respect to the new conceptual view of preventive and therapeutic strategy, an early vascular disease and DKD stages 1 and 2 can be recognized by sensitive markers such as creatinine clearance, fractional excretion of magnesium (FE Mg). With respect to FE Mg, it has been demonstrated that FE Mg correlates directly with the degree of tubulointerstitial fibrosis,[33,34] and inversely correlates with creatinine clearance.[8]

The preceding information renders support that an appropriate therapeutic strategy should be implemented at an early stage of DKD. To support this alternative conceptual view, recent study on vascular homeostasis in both diabetic at early stage during normoalbuminuria and non-DKD with mildly impaired renal function reveals a rather normal angiogenic as well as antiangiogenic factors; indicating that such normal vascular homeostasis would be able to be adequately functional with an adequate nitric oxide production, and thus

respond to vasodilator treatment.[35,36] In fact, vasodilator treatment of both diabetic and non-DKD at this early stage, could improve renal perfusion as well as restore the renal function.[2,3,37–41] An ability to correct renal ischemia and restore renal function would effectively prevent the progression of vascular disease as well as the entering of end-stage renal disease. Recently, we have an interesting observation to demonstrate a reversal of altered vascular homeostasis toward normal in early stage of chronic kidney disease under treatment, implying that a primary prevention of vascular disease as well as the development of target organ damage is likely plausible in the near future.[36,37,40,41]

To further support this concept of early detection and prevention of vascular disease and DKD, the Bhumirajanagarindra Kidney Institute under The Royal Patronage and the Ministry of Public Health of Thailand have set up a policy to extend this pilot study which is presently on – going in several provinces in the country.

Declaration of interest

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