

Vascular response to vasodilator treatment in microalbuminuric diabetic kidney disease

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Abstract

Under common practice, the conventional diagnostic marker such as microalbuminuria determination does not recognized early stage of diabetic kidney disease (normoalbuminuria, chronic kidney disease stage 1, 2); due to the insensitiveness of the available marker. Treatment at later stage (microalbuminuria) simply slows the renal disease progression, but is rather difficult to restore the renal perfusion. Intrarenal hemodynamic study in these patients revealed an impaired renal perfusion and abnormally elevated renal arteriolar resistances. Treatment with vasodilators such as angiotensin converting enzyme inhibitor and angiotensin receptor blocker fails to correct the renal ischemia. Recent study on vascular homeostasis revealed a defective mechanism associated with an impaired nitric oxide production which would explain the therapeutic resistance to vasodilator treatment in microalbuminuric diabetic kidney disease. This study implies that the appropriate therapeutic strategy should be implemented at earlier stage

before the appearance of microalbuminuria.

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Key words: Microalbuminuria; Diabetic kidney disease; Renal hemodynamics; Fractional excretion of magnesium; Renal function

Core tip: This manuscript demonstrates the therapeutic resistance to vasodilator treatment in restoring the renal functions in microalbuminuric diabetic nephropathy. It is supported by the intrarenal hemodynamic study which reveals a decline in renal plasma flow, peritubular capillary flow and glomerular filtration rate following vasodilator treatment. The above finding concerns with the recent study on vascular homeostasis which reveals a defective angiogenesis associated with an impaired nitric oxide production, which explains the therapeutic resistance to vasodilator and clinical failure in restoring renal perfusion in late stage diabetic nephropathy.

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INTRODUCTION

Diabetic kidney disease has been the public health threat which is the most common cause of end-stage renal failure^[1-3]. Under common practice, it is recognized when there is presence of microalbuminuria (albumin/creatinine ratio is greater than 30 microgram/milligram creatinine^[4-6]). In this regard, microalbuminuria cannot recognize early stage diabetic kidney disease (normoalbuminuria). Such practice would allow these early stage

Table 1 Renal function and intrarenal hemodynamic study in microalbuminuric type 2 diabetic kidney disease

	Healthy Subject	Initial value in Microalbuminuric patients	P value
Renal function			
Microalbumin/creatinine ratio, $\mu\text{g}/\text{mg}$	< 30	170 \pm 193	0.010
Creatinine clearance, mL/min per 1.73 m^2	117 \pm 13	73 \pm 28	0.001
Fractional excretion of magnesium, %	1.6 \pm 2.2	4.1 \pm 1	0.050
Mean arterial pressure, mmHg	79	99 \pm 5	0.001
Renal hemodynamics			
Renal plasma flow, mL/min per 1.73 m^2	585 \pm 30	505 \pm 120	NS
Peritubular capillary flow, mL/min per 1.73 m^2	479 \pm 26	423 \pm 120	NS
Glomerular filtration rate, mL/min per 1.73 m^2	116 \pm 14	82 \pm 6	0.010
Afferent arteriolar resistance, dyne.s.cm^{-5}	2331 \pm 108	2841 \pm 299	0.050
Efferent arteriolar resistance, dyne.s.cm^{-5}	3012 \pm 130	4045 \pm 1168	NS

NS: Not significant.

diabetic kidney disease patients to progress without therapeutic interruption. Intrarenal hemodynamic study in this stage reveals reduction in renal perfusion indicating renal ischemia^[7-10]. Treatment with vasodilators such as angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) during microalbuminuria or macroalbuminuria simply slows the renal disease progression determined by creatinine clearance, but is unable to restore all of the renal abnormalities^[11-13]. This information concurs with the progressive increment in number of diabetic kidney disease patients entering end-stage renal disease. Recent study on vascular homeostasis in these patients revealed a defective angiogenesis namely vascular endothelial growth factor receptor 1, angiotensin 1 leading to impairing the nitric oxide production as well as impairing the vascular repair. In addition, the abnormally elevated level of antiangiogenic factors namely vascular endothelial growth factor receptor 2, and angiotensin 2 would induce the progression of renal microvascular disease and the progressive reduction in renal perfusion^[14-18]. The altered vascular homeostasis observed in late stage diabetic kidney disease is believed to be the crucial mechanism of renal disease progression. In contrast to the altered vascular homeostasis observed in late stage diabetic kidney disease, the study on vascular homeostasis in early stage associated with normoalbuminuria has recently been demonstrated to be normal or mildly impaired values of both angiogenic and antiangiogenic factors^[19].

RENAL FUNCTION IN MICROALBUMINURIC DIABETIC KIDNEY DISEASE

In microalbuminuric diabetic kidney disease, recognition of its status can be made through the conventional marker such as microalbuminuria (Table 1). In addition, fractional excretion of magnesium (FE Mg) appears to

be more sensitive than the conventional markers and becomes abnormally elevated even in the stage of normoalbuminuria and recognizes chronic kidney disease (CKD) stage 1 and early stage 2^[20]. FE Mg has been earlier demonstrated to correlate directly with the magnitude of tubulointerstitial fibrosis reflecting the presence of diabetic kidney disease^[21,22]. It is noted that this group of diabetic kidney disease is associated with systemic hypertension. Creatinine clearance or estimated glomerular filtration rate is also a sensitive diagnostic marker for early stage diabetic kidney disease.

INTRARENAL HEMODYNAMIC STUDY IN MICROALBUMINURIC DIABETIC KIDNEY DISEASE

Altered renal hemodynamics has already been documented in normoalbuminuric diabetic kidney disease^[20,23]. In microalbuminuric stage, renal plasma flow, peritubular capillary flow and glomerular filtration rate were depleted, whereas afferent and efferent arteriolar resistances were abnormally elevated. As indicated in Table 1, efferent arteriolar resistance was greater than the resistance of afferent arteriole - a phenomenon indicating a preferential constriction of the efferent arteriole. This phenomenon in turn, would induce intraglomerular hyperfiltration and therefore increase glomerular filtration rate. Subsequently, there is a greater degree of reduction in peritubular capillary flow. A longitudinal study on intrarenal hemodynamics along the clinical course of diabetic kidney disease has revealed a greater increase in degree of efferent arteriolar resistance indicating a further reduction in peritubular capillary flow as the disease severity progresses^[18]. This finding implies that the sustained and progressive elevation of efferent arteriolar resistance would be capable of inducing a chronic renal ischemia to the tubulointerstitial structure, which is the crucial determinant of renal disease progression in diabetic kidney disease.

THERAPEUTIC RESPONSE TO VASODILATORS IN MICROALBUMINURIC DIABETIC KIDNEY DISEASE

It has been a general consensus that treatment of diabetic kidney disease with vasodilators, under common practice, does not cover all of the diabetic kidney disease patients, but infact excludes the group of early stage diabetic kidney disease (normoalbuminuria). Such practice would stabilize temporarily the renal function, or simply slow the renal disease progression, which is due to the defective angiogenesis and an impaired nitric oxide production induced by a variety of circulating toxins namely oxidative stress lipid, cytokines and glycation end-products^[18,19]. The preceding information of altered vascular homeostasis concurs with the therapeutic resistance to vasodilators, as well as the progression of renal disease toward end-

Table 2 Follow-up value of intrarenal hemodynamic study in microalbuminuric diabetic kidney disease

	Pre-treatment	Post-treatment	P value
Renal function			
Creatinine clearance, mL/min per 1.73 m ²	73 ± 28	80 ± 37	NS
Fractional excretion of magnesium, %	4.1 ± 1	4.2 ± 2	NS
Microalbumin/creatinine ratio, µg/mg	170 ± 193	109 ± 148	NS
Mean arterial pressure, mmHg	99 ± 5	85 ± 14	< 0.05
Hemodynamics			
Renal plasma flow, mL/min per 1.73 m ²	505 ± 120	416 ± 9	NS
Peritubular capillary flow, mL/min per 1.73 m ²	423 ± 120	350 ± 13	NS
Glomerular filtration rate, mL/min per 1.73 m ²	82 ± 6	75 ± 9	NS
Afferent arteriolar resistance, dyne.s.cm ⁻⁵	2842 ± 299	3359 ± 1587	NS
Efferent arteriolar resistance, dyne.s.cm ⁻⁵	4045 ± 1168	4093 ± 53	NS

NS: Not significant.

stage renal disease in late stage diabetic kidney disease.

Recently, we had performed intrarenal hemodynamic study during pre-treatment and post-treatment period with vasodilators containing ACEI Enalapril 10-20 mg/d, ARB Telmisartan 40-80 mg/d ± calcium channel blocker in 29 microalbuminuric diabetic kidney disease patients. Following vasodilator treatment, progressive reductions in renal plasma flow, peritubular capillary flow and glomerular filtration rate were noted. In addition, a progressive increase in both afferent and efferent arteriolar resistances was also noted (Table 2). Such progressive change in intrarenal hemodynamics confirms the therapeutic resistance to vasodilators, and is in accordance with the altered vascular homeostasis observed in microalbuminuric diabetic kidney disease^[17,18].

The preceding information of intrarenal hemodynamics observed in microalbuminuric diabetic kidney disease renders support that it would be appropriate to change the conceptual view of therapeutic strategy towards an early treatment of diabetic kidney disease during normoalbuminuria. Recent study of treatment with vasodilators during normoalbuminuric diabetic kidney disease has successfully restore renal perfusion and function indicating such therapeutic strategy at this early stage is under environment favourable for vascular repair and renal regeneration^[8,18-23].

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