Letter to Editor

Vascular repair is vulnerable to renal regeneration in early stage of diabetic nephropathy

Recent studies on vascular homeostasis in type 2 diabetic patients associated with altered serum creatinine concentration or presence of microalbuminuria have revealed an impaired mechanism of vascular repair, namely defective angiogenic factors, such as VEGF receptor 1, angiopoietin-1 in conjunction with abnormally elevated levels of anti-angiogenic factors such as VEGF receptor 2 and angiopoietin-2 [1]. Such impaired vascular repair explains: 1) reduction in renal perfusion observed in these patients, 2) unresponsiveness to vasodilators that are usually initiated at the late stage of diabetic nephropathy, resulting in therapeutic failure and progressive impairment of renal function towards end-stage renal disease. Under common practices, type 2 diabetic patients have generally been underestimated at the early stage (normal serum creatinine and normo-albuminuria), and usually been left unattended.

To classify this specific issue further, we have recently demonstrated that 18 diabetic patients (10 males and 8 females, age: 45 ± 13 years ranging 25-71 years) associated with normal serum creatinine level and normo-albuminuria have impaired actual creatinine clearance (chronic kidney disease stage 1 and 2) (see **Table 1**).

Evidence of diabetic nephropathy is reflected by an abnormally elevated fractional excretion of magnesium – an index that has previously been demonstrated to directly correlate with the presence

of tubulointerstitial fibrosis [2, 3]. Furthermore, the mechanism of vascular repair in this early stage is not significantly different from the normal controls, and thus appears to be adequately functional. Theoretically, normal angiogenic factors observed would allow the process of activating vascular repair through the classical pathway (VEGF $\rightarrow$ VEGFR1) by which it might induce coupling of endothelial nitric oxide synthase, and eventually enhance nitric oxide production from the arginine substrate [4, 5].

The above view is further supported by clinical trial with multi-drug vasodilators such as enalapril 5-10 mg/D, angiotensin receptor blocker (Micardis) 40-80 mg/D, in addition to the correction of metabolic disorders, which has indeed increased renal plasma flow and peritubular capillary flow in conjunction with the increase in actual creatinine clearance [6, 7]. The reduction in fractional excretion of magnesium following treatment implies that there is likely reduction in the degree of tubulointerstitial fibrosis, or it reflects renal regeneration.

In conclusion, treatment of diabetic nephropathy at the early stage under the environment favorable for renal regeneration would effectively restore renal perfusion and enhance renal function.

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Table 1. Enhanced renal perfusion and function in the early stage of type 2 diabetic patients (normal serum creatinine and normo-albuminuria).

	Pre-treatment	P-value	Post-treatment	Normal
Hemodynamics				
Renal plasma flow (mL/min/1.73m ²)	470 $\pm$ 57	<0.05	539 $\pm$ 45	605 $\pm$ 39
Glomerular filtration rate (mL/min/1.73m ²)	85 $\pm$ 25	<0.05	106 $\pm$ 30	119 $\pm$ 15
Peritubular capillary flow (mL/min/1.73m ²)	382 $\pm$ 62	<0.05	433 $\pm$ 42	485 $\pm$ 39
Serum creatinine (mg/dL)	0.9 $\pm$ 0.1	NS	0.8 $\pm$ 0.2	$\leq$ 1
Creatinine clearance (mL/min/1.73m ²)	94 $\pm$ 22	<0.01	113 $\pm$ 23	120
Fractional excretion of Mg (FE Mg %)	3.4 $\pm$ 1.5	<0.05	2.5 $\pm$ 0.1	1.6 $\pm$ 0.6
Microalbumin/creatinine ratio (μ g/mg)	14 $\pm$ 6	<0.05	11 $\pm$ 4	<30

NS= not significant.

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