Restoration of Renal Function in Diabetes Mellitus: Is It Plausible ?

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Abstract

The present therapeutic strategy fails to improve renal function in diabetes mellitus, which commonly leads to end-stage renal failure. It is noted that treatment is generally initiated at a late stage due to the lack of sensitivity of available diagnostic markers such as serum creatinine or microalbuminuria. We plan to study the mechanism of vascular repair in order to explain such therapeutic failure in diabetes mellitus.

The study indicates that the mechanism of vascular repair is markedly defective in the late stage chronic kidney disease associated with diabetes mellitus. A defective angiogenic factor namely vascular endothelial growth factor (VEGF) receptor 1 induces an abnormal activation through the antiangiogenic pathway (VEGF → VEGF receptor 2) preventing enhancement of nitric oxide production. In contrast, adequate angiogenic factors namely VEGF, VEGF receptor 1 observed in the early stage diabetic nephropathy (normal serum creatinine, normoalbuminuria, a slightly impaired creatinine clearance, an abnormally elevated fractional excretion of magnesium reflecting chronic kidney disease), would activate through the classical pathway (VEGF → VEGF receptor 1), inducing coupling of endothelial nitric oxide synthase, and enhancing nitric oxide production. In accordance with the preceding information treatment at the early stage of diabetic nephropathy can restore renal perfusion and function.

Key words: diabetic nephropathy, vascular repair, renal perfusion, renal function, fractional excretion of magnesium, vasodilators

There is a general consensus that treatment of diabetic nephropathy under common practice fails to restore renal function. It is noted that such diabetic patients are associated with altered serum creatinine concentrations, or the presence of proteinuria which reflects a rather late stage of chronic kidney disease (creatinine clearance less than 60 ml/min/1.73m^2). This is due to the lack of sensitivity of the available diagnostic markers such as serum creatinine or microalbuminuria, which become abnormal only when renal function impairment is approaching the 50 percent level.[1] Since renal microvascular disease is believed to be the crucial determinant inducing chronic renal ischemia and renal disease progression, the therapeutic target should be the administration of vasodilators to improve renal perfusion and function.[2] Surprisingly renal microvascular disease does not seem to respond to vasodilators in this late stage of diabetic nephropathy. We then decide to explore this issue further by studying the mechanism of vascular repair in order to explain why there is no response to vasodilators in these patients.

Mechanism of vascular repair in the late stage of diabetic nephropathy (creatinine clearance less than 60 ml/min/1.73m^2)

A defective mechanism of vascular repair was observed in these patients with the late stage of chronic kidney disease.[3] A defective angiogenic or classical pathway (VEGF → VEGF receptor 1) due to an impaired VEGF receptor 1 would trigger an abnormal activation of VEGF through the alternative (antiangiogenic) pathway (VEGF → VEGF receptor 2), which would be unable to induce coupling of endothelial nitric oxide synthase, and therefore unable to enhance nitric oxide production. This would explain the unresponsiveness of renal microvessels to vasodilators, and thus, the inability to induce vasodilation, and the failure to enhance renal perfusion and function in late stage diabetic nephropathy.

Mechanism of vascular repair observed in the early stage of diabetic nephropathy (normal serum creatinine, normoalbuminuria, a mildly impaired creatinine clearance, an abnormally elevated fractional excretion of magnesium reflecting chronic kidney disease)

In contrast to the above finding documented in the late stage diabetic nephropathy, the mechanism of vascular repair appears to be normal at an early stage of diabetic nephropathy.[4] In this regard, a normal status of angiogenic factors namely VEGF, VEGF receptor 1, would allow normal activation through the classical pathway, which would be able to induce coupling of endothelial nitric oxide

synthase, and therefore enhance nitric oxide production. Enhanced nitric oxide production would facilitate the renal microvessels response to vasodilators, and therefore increase renal perfusion and eventually enhance renal function.

An appropriate therapeutic strategy to restore renal perfusion and function in early stage of diabetic nephropathy

In accordance with the preceding information, the normal status of mechanism of vascular repair observed in early stage of diabetic nephropathy would be suitable for the process of enhancing renal perfusion and renal regeneration. A correction of renal ischemia would inhibit the degenerative process, and allow the regenerative arm of vascular homeostasis to take place. Improved renal perfusion would induce the reparative process of the nephronal structure.[5-7] This view is supported by (1) the improvement in the fractional excretion of magnesium — an index reflecting the suppression in the magnitude of tubulointerstitial fibrosis following treatment with vasodilators. (ii) the improvement in creatinine clearance. This successful restoration of renal perfusion and function implies that an effective preventive strategy to minimize end-stage renal failure could be accomplished under this new conceptual view of early treatment in diabetes mellitus.

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References

[1] Futrakul N, Sila-asna M, Futrakul P, 2007. A therapeutic strategy towards restore renal function in chronic kidney disease. *Asian Biomed,* 1:33-44.

[2] Futrakul N, Yenrudi S, Sensirivatana R, Sensirivatana R, Watana D, Laohapaibul A, Watanapenphaibul K, Futrakul S, 2000. Peritubular capillary flow determinestubulointerstitial disease in idiopathic nephritic syndrome. *Ren Fail,* 22:329-335.

[3] Futrakul N, Butthep P, Futrakul P, 2009. Altered vascular homeostasis in type 2 diabetic nephropathy. *Ren Fail*, 31:207-310.

[4] Futrakul N, Futrakul P, 2010. An adequate vascular repair in normooalbuminuria type 2 diabetic nephropathy. *Asian Biomed 2010*; 4:153-157.

[5] Futrakul N, Butthep P, Futrakul P, Sitprija V, 2007. Improvement of renal function in type 2 diabetic nephropathy. *Ren Fail*, 29:155-158.

[6] Ritt M, Ott C, Raff SC, Schneider MP, Schuster I, Hilgers KF, Schlaich MP, Schneder RE, 2009. Renal vascular endothelial funciton in hypertensive patients with type 2 diabetes mellitus. *Am J Kidney Dis*, 53:281-289.

[7] Futrakul N, Futrakul P, 2010. Improved vascular repair is relevant to enhanced renal function with vasodilators in early stage of chronic kidney disease. *Asian Biomed*, 4:153-157.