

## Diabetic Nephropathy: Current Concept of Therapeutic Strategy Toward Self-Sufficiency

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### Abstract

Diabetic nephropathy (DN) has been regarded as a non-restorative chronic kidney disease (CKD) under current concept of practice. The current definition of CKD and the conventional diagnostic markers such as serum creatinine or microalbuminuria unfortunately limit them to CKD stage 3. Treatment initiated at this late stage fails to restore renal function, but simply slows the renal disease progression toward end-stage renal disease dependant to renal replacement therapy. Recent study on vascular homeostasis in late stage DN reveals (1) defective angiogenic factors associated with an impaired nitric oxide production which explains the therapeutic resistance to vasodilator treatment. (2) abnormally elevated anti-angiogenic factors associated with a progressive reduction in peritubular capillary flow and a progressive decline in renal function.

In contrast to the above observation, DN would become restorative if it would be recognized and treated at an early stage during normoalbuminuria (CKD stages 1,2) under which the vascular homeostasis is adequately functional. ACEI and ARB combination can enhance peritubular capillary flow, correct the chronic renal ischemia and therefore restore renal function. This innovative therapeutic strategy can effectively prevent the end-stage renal disease in DN.

**Keywords:** Diabetic nephropathy; Vascular homeostasis; Chronic renal ischemia; FE Mg; Renal function

### DN Under Current Concept of Practice

Diabetic nephropathy (DN) under current concept of practice has become one of the most public health threats due to therapeutic resistance commonly leading to the progression toward end-stage renal disease. We, therefore attempt to (1) address the crucial issues relevant to such practice failure in restoring the renal function in DN (2) provide an alternative therapeutic strategy of restoring renal function toward self-sufficiency for DN.

There are several conventional handicaps under current practice as follows.

### Insensitive diagnostic markers recognize DN at only late stage CKD

When should we consider a diabetic patient having kidney disease? This is a simple question but the answer is not that simple. Under current conceptual view, a diabetic patient has been considered to have kidney disease when the serum creatinine is greater than 1 mg/dL or there is microalbuminuria (> 30 µg/mg creatinine) present [1,2]. Such conceptual view is definitely underestimated the status of DN, since both diagnostic markers infact recognize only late stage CKD (stage 3), but unable to detect early stage CKD (stages 1,2) Table 1. In this regard, under current practice, the DN patients associated with early stage CKD have been left unattended without any appropriate recommendation, or treatment. Physicians very often [3] misinform their patients associated with early stage CKD to have no kidney disease. This unfortunate group of DN has infact an impaired creatinine clearance, evidence of renal ischemia reflected by a reduction in peritubular capillary flow, and an abnormally elevated level of fractional excretion of magnesium (FE Mg) - an index reflecting the presence of tubulointerstitial fibrosis which is a biomarker indicating the state of chronic kidney disease [3,4]. A correlation between FE Mg and the magnitude of tubulointerstitial fibrosis had been previously reported [5-7]. Such patient has usually escaped recognition of the underlying kidney disease and been allowed the clinical course to progress until the serum creatinine is abnormally elevated, or the microalbuminuria develops.

### Definition of CKD is inappropriately applied to CKD stage 3

The definition of CKD defined by the National Kidney Foundation. K/DOQI Clinical Practice Guidelines is inappropriately applied to only those patients associated with creatinine clearance of less than 60 ml/min/1.73m [2,8]. This would mislead the general practitioners as well as the nephrologists to pay attention only to the late stage CKD patients and in the same time ignore those patients associated with early stage CKD. This conceptual view leads to the initiation of therapeutic strategy of DN generally implemented at a rather late stage CKD. Moreover, this inappropriate definition of CKD leads to the underestimation of

S.No	Conventional handicaps under current practice of DN
1	Insensitive diagnostic markers such as serum creatinine, microalbuminuria detects DN only at late stage CKD (CKD stage 3)
2	Definition of CKD inappropriately limits to CKD stage 3.
3	Therapeutic targets are multiple and indecisive to correct the chronic renal ischemia which is the crucial mechanism of renal disease progressive.
4	Treatment of DN at late stage CKD is resistant to vasodilators, which is due to altered vascular homeostasis associated with an impaired nitric oxide production.

**Table 1:** Conventional handicaps responsible for therapeutic failure in DN under current practice.

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the total prevalence of CKD, as well as to the lack of preventive strategy of renal disease progression for early stage DN patients.

### Indecisive therapeutic target under common practice

Under common practice, therapeutic targets of DN are not unanimous and yet indecisive such as hypertension [9], proteinuria [10] and target at late CKD patients [11-13]. Treatment to control hypertension, with vasodilators, to minimize proteinuria and to slow the renal disease progression are in general partially effective. With respect to controlling hypertension, vasodilator treatment is usually recommended to those hypertensive patients but exclude the other under normotension. However, such therapeutic approach has not been supported by the intrarenal hemodynamic study in DN patients. The intrarenal hemodynamic study demonstrates a dissociation between systemic circulation and renal microcirculation that an altered renal hemodynamics is usually substantiated in DN patients irrespective of the associated status of blood pressure [4,14]. In normotensive DN patients, the altered hemodynamics is characterized by a reduction in peritubular capillary flow and an abnormally elevated renal arteriolar resistance [15]. Such state of renal ischemia is demonstrated in normotensive and normoalbuminuric DN patients. Under common practice, this specific group of early DN patients receive no vasodilator treatment to correct the state of renal ischemia which is spontaneously progressive as the clinical course of DN progresses. With respect to the issue of minimizing proteinuria as another therapeutic target, the magnitude of proteinuria does not predict renal function. Such controlling of hypertension and suppression of proteinuria under common practice usually lead to therapeutic resistance in restoring renal function in DN [14,15]. This implies that the preceding therapeutic targets are not relevant to the crucial mechanism that determines renal disease progression. In this regard, accumulating evidence renders support that renal microvascular disease associated with chronic renal ischemia is the crucial mechanism of renal disease progression. A correlation between renal microvascular disease reflected by a reduction in peritubular capillary flow and the degree of tubulointerstitial fibrosis has recently been demonstrated [16-19]. In this essence, the reduction in peritubular capillary flow precedes the development of tubulointerstitial fibrosis. The magnitude of peritubular capillary flow reduction also correlates with the severity of tubulointerstitial fibrosis indicating its cause-and-effect relationship [3,20]. Therefore, an appropriate therapeutic target for DN is to correct the chronic renal ischemia with vasodilators.

### Treatment of DN at late stage CKD is resistant to vasodilators

Treatment of both diabetic and non-diabetic CKD patients with vasodilators at late stage CKD fails to enhance renal perfusion or corrects the renal ischemia and therefore is unable to restore renal function [21-26]. Such therapeutic failure is quite contradictory to the above concept of chronic renal ischemia as the crucial determinant of renal disease progression. This view needs an explanation. Recently, we have studied the vascular homeostasis in late stage DN which reveals multiple defects that are explainable to the treatment failure [3,27-30]. There are (1) defects in angiogenic factors such as endothelial progenitor cell, angiopoietin 1, VEGF receptor 1 leading to an impaired nitric oxide production, which explains the therapeutic resistance to vasodilator treatment. (2) abnormally elevated antiangiogenic factors such as VEGF receptor 2, angiopoietin 2 inducing the progression of renal microvascular disease. Such progression of renal microvascular disease

concur with the intrarenal hemodynamic alteration characterized by a progressive reduction in peritubular capillary flow as the clinical course of DN progresses [31]. The intrarenal hemodynamic study has recently confirmed the therapeutic resistance to vasodilator treatment in late stage DN associated with microalbuminuria and macroalbuminuria [4]. Treatment with ACEI and ARB in macroalbuminuric group revealed a progressive decline in both peritubular capillary flow and glomerular filtration rate. In DN patients associated with microalbuminuria, there was no definite improvement in peritubular capillary flow or glomerular filtration rate. These findings concur with the altered vascular homeostasis observed in late stage DN. In general, treatment in late stage DN patients simply slow the renal disease progression and is unable to restore renal function. Such practice leads to the general impression that this late stage CKD patient is a non-restorative disease, and therefore a follow-up measurement of renal function such as creatinine clearance determination is generally not included in the study protocol.

In conclusion, an unsuccessful restoration of renal function with vasodilator treatment in late stage DN under common practice is due to all of the following crucial issues namely (1) late recognition and treatment of DN due to insensitive diagnostic markers and (2) therapeutic unresponsiveness to vasodilators due to altered vascular homeostasis. Collectively, they lead to increase in number of patients entering end-stage renal disease.

## Innovative Strategy Towards Self-Sufficiency for DN

The preceding observations have addressed the issue of therapeutic failure under current practice which is unable to correct the renal ischemia with vasodilator treatment in DN. A crucial issue has been raised as to whether a restoration of renal perfusion and function is plausible in DN. In this regard, we have recently attended a group of DN patients associated with early stage CKD and normoalbuminuria by using a sustainably developmental strategy (Table 2).

### Application of sensitive diagnostic markers that recognize early stage DN

Conventional markers such as serum creatinine or microalbuminuria can not differentiate the early stage DN patients from healthy subjects. By applying new diagnostic markers such as creatinine clearance, fractional excretion of magnesium (FE Mg), and renal hemodynamic study such as peritubular capillary flow determination, the early stage DN patients can be recognized. This

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A	By applying sensitive diagnostic markers such as CCr, FE Mg, renal hemodynamics to recognize early stage DN
B.	By implementing an appropriate therapeutic target to correct the renal ischemia
C.	By initiating the therapy at early stage DN associated with an adequate nitric oxide production
D	By treating with combined ACEI and ARB to enhance peritubular capillary flow and renal function
E	Collectively, this innovative strategy can effectively prevent the end-stage renal disease in DN

**Table 2:** An innovation of therapeutic strategy of DN patients through a sustainable development toward self-sufficiency.

early stage DN patient is characterized by (1) an impaired creatinine clearance (normal 120 ml/min/1.73m<sup>2</sup>) (2) an abnormally elevated FE Mg (normal < 1.6+0.6%) which reflects the presence of tubulointerstitial fibrosis [5-7]. (3) a reduction in peritubular capillary flow (normal 480 ml/min/1.73m<sup>2</sup>) [4].

### Therapeutic target that is able to correct renal ischemia

Inasmuch as chronic renal ischemia is the crucial determinant inducing renal disease progression, treatment with vasodilators should be implemented to relax the efferent arteriolar resistance by which it would enhance the peritubular capillary flow supplying the tubulointerstitial structure. An improved peritubular capillary flow would inhibit the process of tubulointerstitial injury, and eventually induce renal regeneration. Clinically, FE Mg is usually declined following the treatment - an index indicating renal regeneration. In addition, an enhanced renal function by mean of creatinine clearance is also documented following the relaxation of the afferent arteriole — an index indicating the restoration of renal function. However, the creatinine clearance may initially drop temporary at the beginning of the vasodilator treatment. This is due to the correction of hyperfiltration phenomenon.

### Vascular homeostasis is adequately functional in early stage DN

The study on vascular homeostasis in early stage DN during normoalbuminuria reveals an adequate function relevant to both angiogenic as well as antiangiogenic factors. Such finding renders support that the mechanism of vascular repair is likely plausible to produce adequate nitric oxide [33].

### Combined ACEI and ARB treatment at early stage DN can enhance peritubular capillary flow and restore renal function

Combined ACEI and ARB treatment has been implemented at the early stage during normoalbuminuria. Encouragement of adequate fluid intake (3+ litres/day) is strongly recommended to avoid some minor side effect such as headache, a temporary drop of creatinine clearance. An enhancement in peritubular capillary flow documented following vasodilator treatment in these patients supports the adequacy of nitric oxide production in the renal microcirculation associated with early stage DN during normoalbuminuria [4,32]. In this regard, fifty-one DN patients who had normal values of serum creatinine and normoalbuminuria but recognized by new diagnostic markers, had been prescribed on ACE inhibitor (Enaril 5-20 mg/day), ARB (Telmisartan 40-80 mg/day or Losartan 50-100 mg/day + calcium channel blocker 5-10 mg/day), vitamin E (400-800 units/day), in addition to correction of metabolic disorders. Improvement in creatinine clearance is the therapeutic target by adjusting the doses of vasodilators [4]. They had shown a significant increase in peritubular capillary flow (354+66 to 414+72 ml/min/1.73m<sup>2</sup>;  $p < 0.01$ ) and in glomerular filtration rate (89+21 to 102+27 ml/min/1.73m<sup>2</sup>;  $p < 0.05$ ) following the treatment. A significant improvement in renal plasma flow following the vasodilator treatment is also documented by Ritt et al [32]. This appears to be the first evidence to substantiate that a correction of renal ischemia and a restoration of renal function with the combination of ACEI and ARB treatment is plausible in early stage DN. Moreover, an improvement in the mechanism of vascular repair is also documented to correlate with the improved renal function following the vasodilator treatment. This view supports that renal microvascular disease is repairable in early stage DN [34].

### Conclusion

An innovative strategy to successfully correct the renal ischemia with combined ACEI and ARB treatment can be accomplished in early stage DN during normoalbuminuria. This success is established through a sustainable development by implementing new diagnostic markers such as creatinine clearance, FE Mg or peritubular capillary flow determinations to differentiate the early DN patients from the healthy subjects, and initiating the treatment under appropriate environment favourable for angiogenesis and renal regeneration. This favourable outcome supports the patients to survive safely on their own kidneys - a novel strategy that follows “The Renown Theory of Self-Sufficiency” of His Majesty King Bhumiphol Adulyadej. It means that this innovative approach yields the most benefit to the patients to live naturally on their own kidneys, not artificially on renal replacement therapy. Thus, this strategy would minimize the end-stage renal disease under long-term outcome.

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