A New Therapeutic Paradigm for Chronic Kidney Disease

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Abstract

Chronic kidney disease is underrecognized worldwide. This is mainly due to the lack of sensitivity of present diagnostic markers in common medical practice, such as serum creatinine, and microalbuminuria which usually detect late stage chronic kidney disease (actual creatinine clearance less than 60 ml/min/1.73m^2) but are unable to screen for early stage chronic kidney disease (actual creatinine clearance over 60 ml/min/ 1.73m^2). The insensitiveness of the present diagnostic markers unrecognizes the presence of underlying early stage of chronic kidney disease, and usually allow the diseased stage to slowly progress towards late stage, without any appropriate therapeutic intervention. It is very unfortunate for the patient to generally receive treatment at the late stage of chronic kidney disease, since it has recently been demonstrated that the mechanism of vascular repair is markedly impaired at the late stage. Therefore, it is not surprising to realize the progressive increment in number of chronic kidney disease patients entering end-stage renal disease, which is a growing public health threat.

In contrast to the present therapeutic failure observed in late stage chronic kidney disease, we have recently demonstrated that the mechanism of vascular repair for renal regeneration appears to function (adequately) at the early stage of chronic kidney disease. Treatment initiated at the early stage of chronic kidney disease can improve renal perfusion, with clinical impact on the restoration of renal function, since integrity of renal structure and function is modulated by renal perfusion.

In accordance with the preceding information, a new therapeutic paradigm to effectively prevent end-stage renal disease can be implemented by (1) all physicians to discard the old conceptual view attached to low sensitivity diagnostic markers, and to treatment at late stage of chronic kidney disease, and change to a new therapeutic paradigm at the early stage of chronic kidney disease by using a new sensitive

diagnostic marker such as fractional excretion of magnesium (FE Mg) (2) appropriate treatment to improve renal perfusion by correcting the hemodynamic maladjustment which is the crucial determinant inducing renal disease progression.

Key words: chronic kidney disease, vascular repair, renal regeneration, hemodynamic maladjustment

Common diagnostic markers detect only late stage of chronic kidney disease

As a practising physician, it is not unusual to be asked a common question "Do I have kidney disease?". The common response is to perform a blood test to assess serum creatinine for screening of chronic kidney disease. The usual answer to the patient is "Your kidneys are perfect, don't worry". The physician's answer is only in part correct, for it is based upon the general acceptance of serum creatinine which can only screen late stage chronic kidney disease, when more than 50 percent of the kidney have already been damaged[1]. The change in serum creatinine becomes apparent at a late stage when the actual creatinine clearance has dropped to a level of less than 60 ml/min/1.73m^2. At the same time, the physician's answer is also incorrect, because it has ignored the early stage chronic kidney disease which the patient might already have. Who should be blamed for this unfortunate event? The physician claims that he is following the recommendation defined by The National Kidney Foundation K/DOQI Clinical Practice Guidelines, which inappropriately defines a chronic kidney disease patient as one with creatinine clearance of less than 60 ml/min/1.73m^2 (normal 120 ml/min/1.73m^2)[2]. In this regard, chronic kidney disease is underrecognized by such a definition[3]. This implies that a general physician under common practice around the world leaves most chronic kidney disease patients at the early stage unattended, without any specific recommendation of treatment. This early stage chronic kidney disease is allowed to slowly progress towards late stage chronic kidney disease. The patient would generally receive treatment at the late stage of chronic disease.

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[1] Futrakul N, Sila-asna M, Futrakul P. Therapeutic strategy towards renal restoration in chronic kidney disease. *Asian Biomedicine 2007*; 1:33-44.

[2] Nation Kidney Foundation. K/DOQ1 clinical practice guidelines for chronic kidney disease : evaluation, classification, and stratification. *An J Kidney Dis 2002*; 39S(suppl 1):S1-S266.

[3] Obrador GT, Pereira BJ, Kausz AT. Chronic kidney disease in the United States : an under recognized problem. *Semin Nephrol 2002*; 22:441-448.

Similarly, microalbuminuria, a diagnostic marker to reflect diabetic nephropathy, is also unable to detect early stage chronic kidney disease. Today, a common question from a diabetic patient as to whether he has a kidney disease or not, remains to be further modified. We have also recently demonstrated that microalbuminuria reflects only late stage chronic kidney disease[4]. In this regard, even at this stage of normoalbuminuria, renal function has already been impaired. The actual creatinine clearance is definitely defective, despite the fact that the creatinine clearance is overestimated due to hyperfiltration, which implies that the real creatinine clearance should be less than the actual reading. In this stage of normoalbuminuria, renal ischemia which is reflected by the reduction in peritubular capillary flow has already been apparent. In this stage of normoalbuminuria, fractional excretion of magnesium (FE Mg), a diagnostic marker that reflects tubular cell function, or tubulointerstitial disease or fibrosis, has already been abnormally elevated, since FE Mg has earlier been demonstrated to correlate directly with the magnitude of tubulointerstitial fibrosis[5]. Therefore, the abnormally elevated FE Mg implies that tubulointerstial fibrosis is already present at this stage of normoalbuminuria. Under present practice, if we wait until microalbuminuria becomes apparent, the actual creatinine clearance has usually dropped to a level of 50 percent or below. It is unfortunate that the treatment of diabetic nephropathy in general practice is initiated at the late stage of chronic kidney disease. This implies that diabetic patients with normal serum creatinine concentration, or normoalbuminuria, have been misinformed as having no renal disease, whereas they may in fact already have underlying early stage diabetic nephropathy. Diabetic patients with early stage diabetic nephropathy are often allowed to progress towards late stage chronic kidney disease without appropriate therapeutic intervention. This evidence concurs substantially with the incidence of progressive increase in diabetic nephropathic patients entering end-stage renal disease, which has become the primary cause of end-stage renal disease worldwide today.

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[4] Futrakul N, Vongthavarawat V, Sirisalipotch S, et al. Tubular dysfunction and hemodynamic alteration in normoalbuminuric type 2 diabetes. *Clin Hemorheol Microcirc 2005*; 32:59-65.

[5] Futrakul P, Yenrudi S, Futrakul N, et al. Tubular function and tubulointerstitial disease. *Am J Kidney Dis 1999*; 33:886-891.

To solve the issue of lack of sensitivity of present diagnostic markers, we would like to propose FE Mg as a screen for early stage chronic kidney disease which is crucial for the new therapeutic paradigm towards renal regeneration, since the damage is reversible at the early stage of chronic kidney disease[6].

Renal microvascular disease is the crucial determinant inducing renal disease progression in chronic kidney disease

Accumulating evidence renders support for the theory that renal microvascular disease determines renal disease progression in chronic kidney disease. A spatial relationship between renal microvascular disease and tubulointerstitial fibrosis can be addressed by referring to the diagram representing a nephronal structure[7] Figure 1.

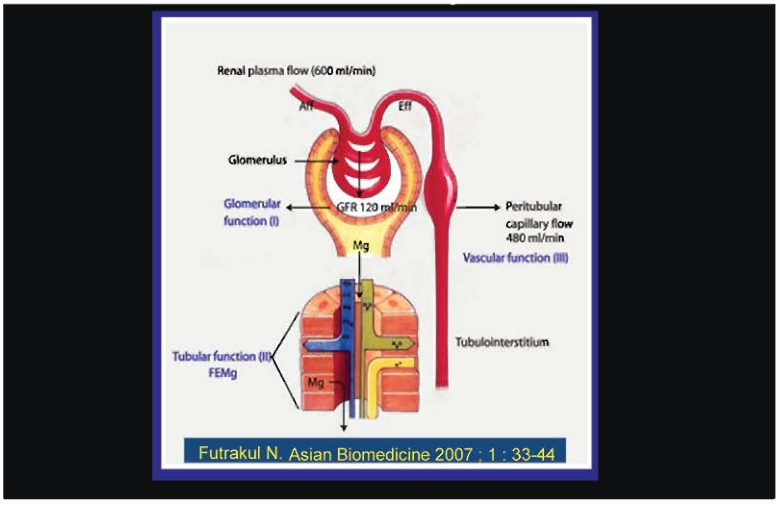

Figure 1.

A nephron consists of 2 components (1) the vascular component of glomerular capillary and peritubular capillary flow and (2) the tubulointerstitium. These two components are closely interrelated. Tubulointerstitium is dependent upon peritubular capillary flow. Under normal circumstances glomerular capillary modulates flow through the peritubular capillary by releasing vasodilators such as prostacyclin and nitric oxide,

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[6] Futrakul N, Futrakul P. Vascular homeostasis determines renal microvascular disease progression in chronic kidney disease. *Clin Hemorheol Microcirc* (in press 2009)

[7] Futrakul N, Futrakul P. *Prevention of end-stage renal disease. An innovative strategy.* Editors Futrakul N, Futrakul P. Chulalongkorn University Printing House, Bangkok 2008 pp 12.

which relax the efferent arteriole, allowing maximum blood flow through the peritubular capillary, and adequate supply to the tubulointerstitium. In the diseased state, the glomerular capillary is the primary site where inflammation in the kidney takes place. Any injury to the glomerular capillary endothelium would have a clinical impact upon the peritubular capillary flow, by releasing vasoconstrictors such as angiotensin II, endothelin and thromboxane A2, which would constrict the efferent arteriole, reducing the peritubular capillary flow, inducing an ischemic injury to the tubulointerstitium, and eventually leading to tubulointerstitial fibrosis. To induce injury to the glomerular capillary endothelium, it has been demonstrated that there is a progressive accumulation of circulating toxins in humans. Among these are oxidative stress, and glycation end products, lipids, sugars, proinflammatory cytokins, vasoconstrictors, etc. Such circulating toxins induce endothelial cell injury, or vascular disease which is unfortunately subclinical, and asymptomatic. Vascular disease usually becomes symptomatic only in the advanced stage, or when there is a significant reduction in vascular perfusion to the organ, and established organ damage. Nevertheless, such early stage vascular disease can be reflected by demonstrating the increased number of endothelial cells that detach from the vascular wall into the circulation[8].

In addition to endothelial cell injury, the endothelial cell also becomes dysfunctional, in particular the glomerular endothelial cell which is reflected by intrarenal hemodynamic study as follows. In brief, circulating toxins induce glomerular endothelial dysfunction which subsequently releases vasoconstrictors such as angiotensin II, endothelium and thromboxane A2. Such increased vasoconstrictors induce the hemodynamic maladjustment characterized by preferential constriction of the efferent arteriole, and a subsequent reduction in peritubular capillary flow which supplies the tubulointerstitium. In has been noted that the reduction in peritubular capillary flow becomes progressively worse as the disease severity progresses. To explain this response, the constriction at the efferent arteriole induces intraglomerular capillary pressure elevation, and subsequent capillary dilation. The capillary dilation detachs the podocytes from the basement membrane. Such podocyte injury depletes vascular endothelial growth factor production, which is essential for the endothelial cell's survival. The depleted vascular endothelial growth factor provokes further injury to the

[8] Futrakul N, Butthep P, Siriviriyakul P, Futrakul P. Glomerular endothelial dysfunction and microvascular disorder in chronic kidney disease. *Microcirculation Annual 2005*; 21:19-20.

endothelium, a greater release of vasoconstrictors, and eventually a higher magnitude of hemodynamic maladjustment in a vicious circle. Taken together, they induce a progressive reduction in peritubular capillary flow, and chronic ischemic injury to the tubulointerstitium. Together with the fact that the circulating toxins can directly provoke the profibrotic pathway, this process eventually progresses to the development of tubulointerstitial fibrosis (Figure 2). The preceding information forms the body of knowledge relevant to the mechanism of renal disease progression.

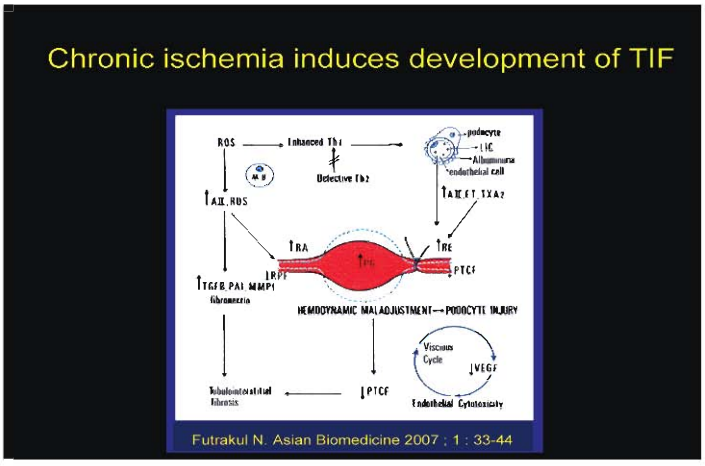

Figure 2.

A new therapeutic paradigm towards renal restoration to effectively prevent end-stage renal disease

Current therapeutic failure is due to the lack of sensitivity of diagnostic marker that can detect only late stage chronic kidney disease. This explains the failure due to the common practice of usually initiating treatment at the late stage of chronic kidney disease, when it is resistant to vascular repair and renal regeneration[9]. To establish a new therapeutic strategy, it is essential to apply the preceding information by implementing (1) a sensitive diagnostic marker such as FE Mg that can detect early stage chronic kidney disease. (2) Initiation of treatment at the early stage of chronic kidney disease, when mechanism of vascular repair is still adequate. (3) Correction of hemodynamic maladjustment and of reduction in peritubular capillary flow as a specific therapeutic target for intervention. Treatment at such an early stage can induce

[9] Futrakul N, Butthep P, Futrakul P. Altered vascular homeostasis in chronic kidney disease. *Clin Hemorheol Microcirc 2008*; 38:201-207.

angiogenesis, and improve renal perfusion as well as renal function. Therapeutic target achievement is demonstrated by increased creatinine clearance following treatment. This would result in a reduction in the number of patients entering end-stage renal disease, as well as an avoidance of renal replacement therapy. Moreover, this new therapeutic paradigm would allow the patient to remain independent.

It has been demonstrated that treatment to at an early stage of chronic kidney disease, in conjunction with an appropriate correction of the mechanism of renal disease progression, can effectively improve renal perfusion and restore renal function[10,11]. The preceding information implies that this new therapeutic paradigm can be successfully implemented, world wide. Such a conceptual view cannot be achieved without physician cooperation and a change in his conceptual view to this new strategic paradigm. Moreover, such success would also require cooperation from the National Kidney Foundation to redefine chronic kidney disease by shifting more attention to the patient at the early stage of chronic kidney disease.

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[10] Futrakul N, Futrakul P, Siriviriyakul P. Correction of peritubular capillary flow reduction with vasodilators restores function in focal segmental glomerulosclerotic nephrosis. *Clin Hemorheol Microcirc 2004*; 31:197-205.

[11] Campbell R, Sangalli F, Perticucci E, et al. Effects of combined ACE inhibitor and angiotensin II antagonist treatment in human chronic nephropathies. *Kidney Int 2003*; 63:1094-10103.