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Review Article

Renal Microvascular Disease and Therapeutic Implicaiton

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ABSTRACT **An effective strategy to prevent renal disease progression in chronic kidney diseases is to early initiate therapy in the early course of disease when there is still an adequate renal functional reserve. Given the assistances of FE Mg for early screening of disease severity and of appropriate correction of hemodynamic maladjustment with multidrug vasodilators, an effective restoration of renal function is generally achieved in normoalbuminuric type 2 diabetic nephropathy and in a variety of chronic kidney diseases with minimal renal impairment.**

Key words : **Renal failure, renal microvascular disease, FE Mg, hemodynamic maladjustment, renal regeneration**

Much evidence convincingly supports the continuously progressive increment in number of chronic kidney disease patients entering end stage renal failure worldwide[1]. Such fact indicates the present failure in preventive and therapeutic strategies commonly practiced which is yet unable to completely cease the progression of renal disease but simply slows its path towards the umbrella of renal replacement therapy. The failure addresses to 2 crucial issues namely (1) Failure to early screening of the disease severity by the present diagnostic approaches and (2) gnorance of the crucial role of renal microvascular disease as a determinant of renal disease progression. With respect to the former, the common diagnostic approaches such as the determinations of serum creatinine, creatinine clearance are rather insensitive. The change in serum creatinine usually observed in later course or after renal damage is greater than 50 percent. The creatinine clearance observed in a variety of clinical kidney diseases also has certain handicap due to the phenomenon of hyperfiltration[2]. The common practice of wait-and-see the response to therapy usually looses time for the preventive strategy that might still be able to halt progression and allows the continuation of underlying renal disease progression. A direct examination of the renal histopathology by identifying the extent of tubulointerstitial disease or fibrosis which is the universally acceptable marker for disease severity or chronicity, is an appropriate diagnostic approach[3]. However, the kidney biopsy has certain draw back since it is impractical to do it immediately in most cases and quite often is delayed until the renal impairment has been established. In order to solve this clinical problem, an alternatively non-invasive diagnostic approach by determining the fractional excretion of magnesium (FE Mg) which reflects the ability of renal tubular cell to reabsorb the glomerular filtrate of magnesium as well as to retain the intratubular magnesium which is the second most abundant cation next to the potassium, has recently been proposed with wider acceptance[4,5]. FE Mg is usually in the low normal range (< 2.2 percent) in the presence of intact tubulointerstitial structure, and is abnormally elevated

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in association with tubulointerstitial disease. By multiple regression analysis, FE Mg correlates directly with the magnitude of tubulointerstitial fibrosis. Recently, FE Mg appears to be a useful marker for early screening of renal disease severity by which it leads to early appropriate preventive and therapeutic strategies.

With respect to the mechanism of progressive renal disease, accumulative evidence renders support for the crucial role of renal microvascular disease as the determinant of renal disease progression[6-8].

A Renal Microvascular Disease

Given the nephronal structure consisting of (1) vascular component namely glomerular microcirculation and its extending portion so called peritubular capillary microcirculation and (2) non-vascular component or tubulointerstitium, the primary site of nephronal injury in a variety of clinical kidney diseases is likely to be the glomerular capillary triggered by abnormally elevated circulating toxins (Figure 1).

Such toxins are derived from the oxidative stress[9] (elevated level of reactive oxygen radicals plus defective antioxidants), immunocirculatory imbalance due to the elevated level of proinflammatory cytokines tumor necrosis factor alpha, transforming growth factor beta and the decreased level of anti-inflammatory cytokine interleukin-10[10]. These circulating toxins are capable of

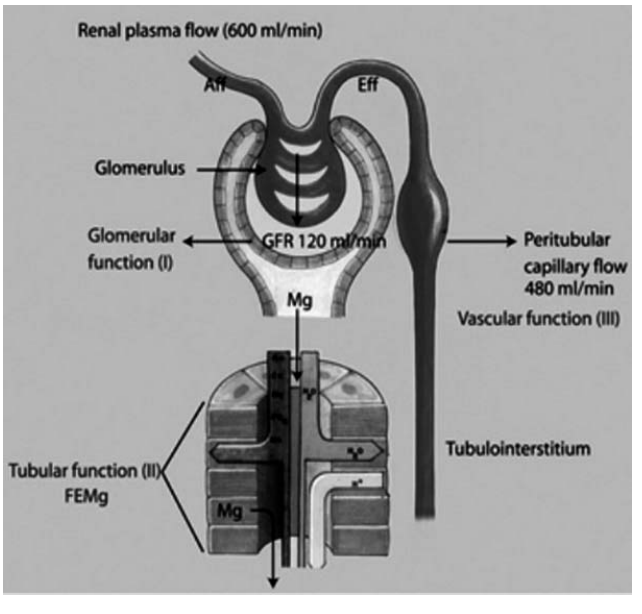

Figure 1 Illustrates nephronal structure

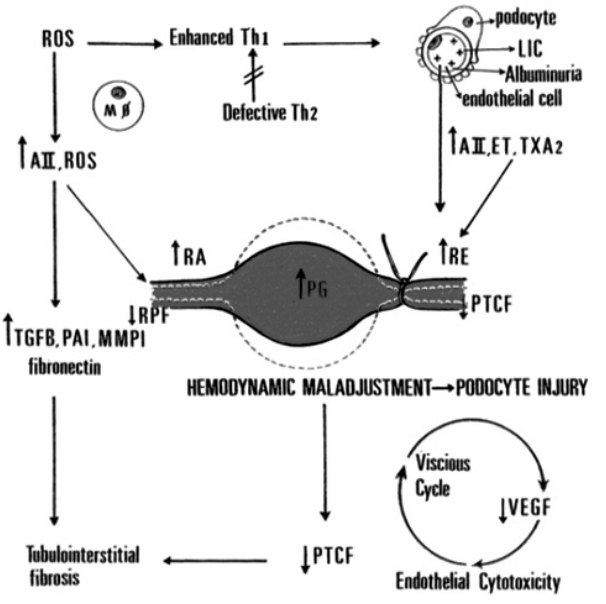

Figure 2 Illustrates pathogenesis of hemodynamic maladjustment

inducing glomerular endothelial injury observed in chronic kidney diseases such as focal segmental glomerulosclerosis or diabetic nephropathy[11-13] which can be reflected by endothelial cell cytotoxicity test[14] or circulating endothelial cell count[15]. Glomerular endothelial injury is observed earlier in the clinical course even in minimal change disease or normoalbuminuric diabetic nephropathy[16]. The dysfunctioining glomerular endothelium has been established in chronic kidney diseases by mean of intrarenal hemodynamic study which reveals hemodynamic maladjustment characterized by a preferential constriction of the efferent arteriole. Such constriction induces proximally, an elevated intraglomerular hydrostatic pressure, glomerular capillary distention with subsequent detachment of podocyte and distally decreases the peritubular capillary flow which supplies the tubulointerstitium. Podocyte detachment decreases the vascular endothelial growth factor which further enhances the magnitude of glomerular endothelial injury, by which it magnifies the magnitude of hemodynamic maladjustment and progressive reduction in peritubular capillary flow in a viscious cycle manner (Figure 2).

Therapeutic implication towards minimizing end-stage renal disease

Present failure in preventing chronic kidney disease patients entering end-stage renal disease is partly relevant

to the insensitiveness of diagnostic tool which delays the treatment and often looses time that the preventive strategy might still be able to halt progression. FE Mg, in this regard would assist in screening the early chronic kidney disease and then initiate an early therapy at the suitable time when there is an adequate renal functional reserve for renal regeneration. In addition, the present therapeutic failure is also due to the therapy aiming at the inappropriate target such as the suppression of proteinuria, or the high blood pressure control, by which it discards the correction of hemodynamic maladjustment which is the crucial determinant of tubulointerstitial fibrosis and disease progression. It is noted that proteinuria does not correlate with the disease progression, since many patients with heavy proteinuria can have spontaneous remission such as a majority of patients with idiopathic nephrotic syndrome, and many chronic kidney patients have disease progression regardless of the change in degree of proteinuria. With respect to the blood pressure, not all chronic kidney disease patients have high blood pressure, which indicates that systemic blood pressure does not correlate with the intrarenal microvascular resistance.

The preceding information indicates that a correction of the hemodynamic maladjustment should be a surrogate end point for therapeutic strategy in chronic kidney disease patients. Since monodrug therapy is generally unsuccessful in correcting the hemodynamic maladjustment, multidrug vasodilators consisting of ACE inhibitor, AT1 receptor antagonist, calcium channel blocker, and antiplatelet can effectively correct such hemodynamic maladjustment, and eventually restores the renal function as having been substantiated in normoalbuminuric type 2 diabetic nephropathy, nephrosis associated with focal segmental glomerulosclerosis[16,18].

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