Microvascular Disease and Renal Disease Progression

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Chronic kidney disease has been a continuous threat due to the present therapeutic failure in preventing renal disease progression[1,2]. Two specific issues are needed to explain such therapeutic failure namely (1) the lack of sensitive diagnostic index for early screening of disease severity and (2) the lack of understanding in the appropriate mechanism of renal disease progression. With respect to the former, the present diagnostic armamentarium commonly practiced in routine screening for renal function is namely serum creatinine determination, creatinine clearance, urinalysis appears not to be sensitive enough in early screening of renal disease severity. Serum creatinine determination is very insensitive since the serum creatinine concentration may not change until the kidney function defect reaches fifty percent or greater. Determination of creatinine clearance is better than serum creatinine assessment but the clearance itself has several disadvantages such as the inaccuracy in completeness of urine collection, pitfalls from untrained personnel[2] and the effect of hyperfiltration[3]. Hyperfiltration is a common phenomenon observed in severe kidney disease where there is a reduction in renal plasma flow. Due to the preferential constriction of the efferent arteriole secondary to glomerular endothelial dysfunction, there is less blood perfusing through the efferent arteriole but at the same time allows more plasma perfusing through the glomerular filtration by which it induces hyperfiltration (Fig. 1,2).Therefore, in the early state of chronic kidney disease, the hyperfiltration would prevent the decrease in creatinine clearance which should normally be present. This state of hyperfiltration is usually delineated in nephrotic syndrome and early diabetic nephropathy but is less distinct in proliferative form of glomerular disease. With respect to the definition of renal disease severity, it has been a general concensus that the best and most sensitive index for renal disease severity or chronicity is the presence of tubulointerstitial fibrosis[4,5]. In this essence, it is quite obvious that creatinine clearance does not directly reflect tubulointerstitial disease. Therefore, an alternative approach is required to solve this problem. Recently, tubular function by means of fractional excretion of magnesium (FE Mg) has been substantiated to correlate directly with the magnitude of tubulointerstitial fibrosis[6] (Fig. 3). FE Mg is normal in a patient whose kidneys have

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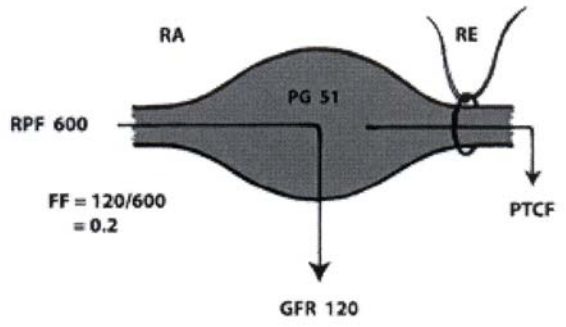

Fig. 1 illustrates normofiltration

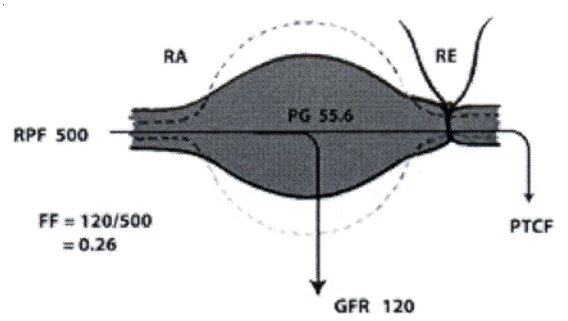

Fig. 2 illustrates hyperfiltration

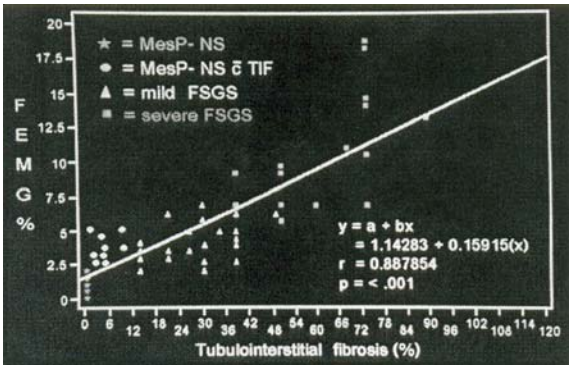

Fig. 3 FE Mg correlates directly with tubulointerstitial fibrosis

intact tubulointerstitial structure, whereas FE Mg is abnormally elevated in association with tubulointerstitial fibrosis. In other words, FE Mg can differentiate acute proliferative glomerulonephritis normally associated with intact tubulointerstitium from chronic glomerulonephritis with tubulointerstitial fibrosis. The mechanism for such tubular function can be explained as follows. FE Mg depends upon 2 crucial functions of renal tubular cell. First, it requires a normal function of tubular cell to reabsorb the portion of filtered magnesium from the glomerulus. Second, renal tubular cell contains magnesium as the second most abundant cations (next to potassium).

A normal tubular cell would reabsorb most of the filtered magnesium as well as preserve the intracellular portion of magnesium, thereby it allows a small amount of magnesium to pass into the urine (low FE Mg value); Fig. 4. In contrast, in patients associated with tubular cell injury or tubulointerstitial disease, the tubular cell can not maximally reabsorb the filtered magnesium as well as there is an increased leakage of intracellular magnesium by which it results in an abnormally high value of FE Mg. Another example of the usefulness of FE Mg, it has recently been demonstrated that FE Mg can assist in early screening for diabetic nephropathy even in the stage of normoalbuminuria[3]. It has been general acceptance that minoalbuminuria is the hallmark of diabetic nephropathy. However, in the presence of normoalbuminuria, most patients with type 2 diabetes have already shown an abnormally high value of FE Mg. Such abnormal FE Mg documented in patients with type 2 diabetes is observed in conjunction with low peritubular capillary flow which supplies the tubulointerstitial structure. Since peritubular capillary flow reduction correlates inversely with the magnitude of tubulointerstitial fibrosis[7] (Fig. 5), the reduction in peritubular capillary flow in patients with type 2 diabetes implies the presence of tubulointerstitial disease in such patients. The combination of reduction in peritubular capillary flow and the abnormally elevated FE Mg indicate that there is tubulointerstitial disease in normoalbuminuric patients with type 2 diabetes. Thus, FE Mg appears to be a sensitive index that can early detect the clinical severity in renal patients. The application of FE Mg in clinical practice would be advantageous to the early screening of renal disease severity and, therefore would allow an early initiation of therapeutic strategy for such patients.

With respect to the mechanism of renal disease progression, there are 2 conceptual views. The old concept ignores the significant and important

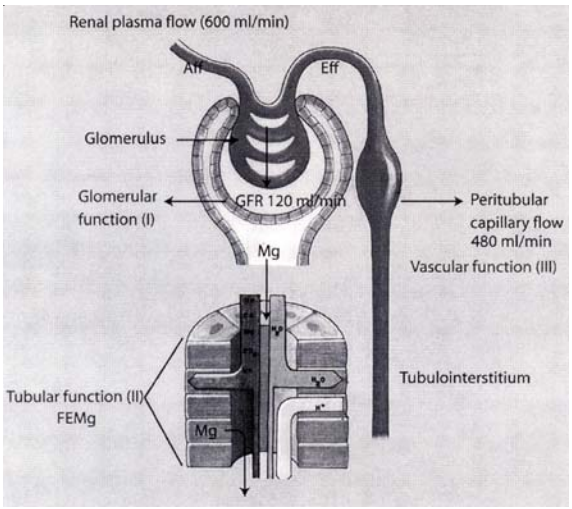

Fig. 4 Compartmental correlations between structure and function of nephron

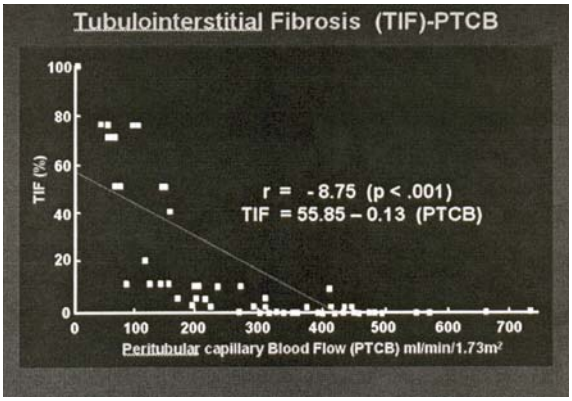

Fig. 5 Peritubular capillary flow reduction inversely correlates with tubulointerstitial fibrosis

role of microvascular disease in inducing tubulointerstitial fibrosis. The new concept appreciates the crucial participation of microvascular disease that induces tubulointerstitial fibrosis. In order to understand this conceptual view, a brief review of the integral relationship between structure and function of the nephron is required. A nephron consists of 2 crucial compartments. First, the vascular compartment consists of glomerular capillary and peritubular capillary flow. Second, the non-vascular compartment or tubulointerstitium. (Fig. 4) With respect to kidney disease, the glomerular capillary is generally the primary site of kidney inflammaton. It is a general belief that kidney inflammation occurs solely in the glomerular capillary is considered benign and usually self-limited. A spreading of inflammation into the tubulointerstitium is usually progressive and likely enters end-stage renal disease. How such kidney inflammation spreads into the tubulointerstitium is the crucial issue to be addressed. Inflammation of the glomerular capillary induces glomerular endothelial dysfunction[8].

A dysfunctioning glomerular endothelium is defective in releasing vasodilators and at the same time it increases release of more vasoconstrictors namely angiotensin II, endothelin, thromboxane A2. This defective function of glomerular endothelium can be assessed in vivo by intrarenal hemodynamic study. It has been noted that all chronic kidney diseases share common hemodynamic alteration, the so called hemodynamic maladjustment which is characterized by preferential constriction at the efferent arteriole[9-14]. Such a constriction exerts 3 significant hemodynamic impacts. *Proximal to the constriction*, it induces intraglomerular hypertension and hyperfiltration. Intraglomerular hypertension induces glomerular capillary dilation as elegantly demonstrated by Kriz[15] and Rennke[16] which causes podocyte detachment from the basement membrane due to its non-distensible and non-proliferative characteristics. Podocyte injury causes defective production of vascular endothelial growth factor[17] which is essential to the survival and growth of glomerular endothelial cells. Further injury to the glomerular endothelial cell would aggravate in a viscious cycle manner, a greater magnitude of hemodynamic maladjustment and further injury to the podocyte (Fig. 6).

Distal to the constriction, it exaggeratedly reduces peritubular capillary flow which supplies the tubulointerstitial structure. Chronic ischemia to the tubulointerstitium has been proposed to induce tubulointerstitial fibrosis. Such a cause - and - effect relationship has recently been verified by our colleagues that reduction in peritubular capillary flow precedes the development of tubulointerstitial fibrosis[7]. In addition, elevated level of angiotensin II has been demonstrated to activate the profibrotic pathway through nuclear factor kappa B, by which it enhances release of proinflammatory cytokines, adhesion molecules and reactive oxygen species[18,19]. These known toxic factors are capable of suppressing the production of vascular endothelial growth factor by tubular epithelial cells[20-22]. A suppression of vascular endothelial growth factor would injure the endothelium of peritubular microvasculature by which it induces endothelial dysfunction, expression of adhesion molecules and induction of local intravascular coagulation in the peritubular microvasculature. Thus, the profibrotic effect of angiotensin II in conjunction with the chronically sustained reduction in peritubular capillary flow, would culminate in the development of tubulointerstitial fibrosis. In fact, microvascular disease has been substantiated to be correlated with tubulointerstitial disease by many investigators such as Bohle[23], Kang[24], Yenrudi[25] and Futrakul[26]. Recently, chronic hypoxia or chronic hypoxia and ischemia has also been proposed to induce tubulointerstitial disease[27-29].

This new conceptual view of peritubular capillary reduction secondary to microvascular disease inducing tubulointerstitial fibrosis appears

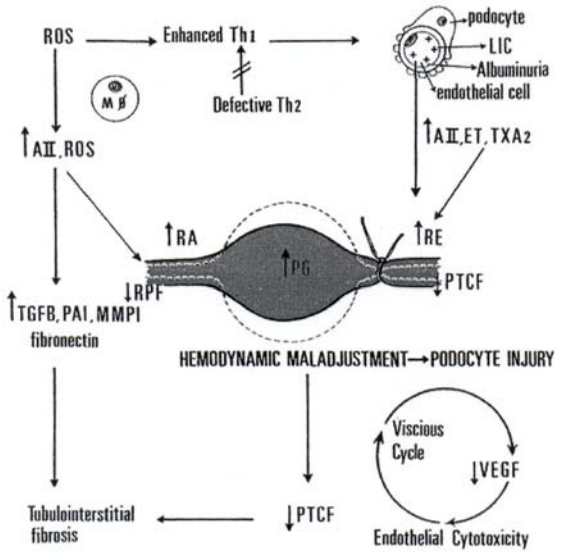

Fig. 6 Pathogenetic mechanism of renal disease progression

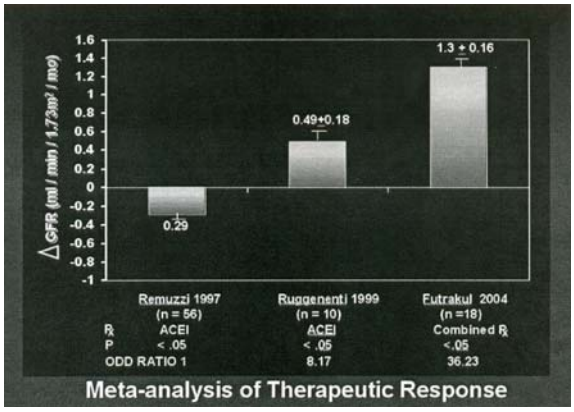

Fig. 7 Meta-analysis of treatments in chronic kidney disease (Focal segmental glomerulosclerosis)

to be essential to the therapeutic strategy. Correction of hemodynamic maladjustment by vasodilators (ACEI AII receptor antagonist, calcium channel blocker and antiplatelet has been proven to be beneficial to the therapeutic strategy and such treatment is capable of improving the renal perfusion and restoring the renal function in a variety of chronic kidney diseases[30-33]. It is for the first time that restoration of renal function to the level above the pretreatment value is plausible under this new therapeutic strategy with combined vasodilators. This is in contrast to the conventional therapy in which hemodynamic maladjustment is inappropriately corrected, such treatment simply retards the renal disease progression but eventally the patients usually enter end-stage renal failure[34,35] (Fig. 7).

In conclusion, prevention of renal disease progression can be accomplished by (1) application of FE Mg to early screening of renal disease severity and thus initiate an early preventive and effective therapeutic strategy and (2) correction of hemodynamic maladjustment with combined formulas consist of ACEI, AII receptor antagonist, calcium channel blocker and antiplatelet.

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โรคหลอดเลือดจุลภาคกับการทำลายไต

นริสา ฟูตระกูล, ประสิทธิ์ ฟูตระกูล

โรคไตเรื้อรังเป็นปัญหาสำคัญต่อเนื่องซึ่งเกิดจากสาเหตุสำคัญ 2 ประการ คือ (1) การขาดตัวดัชนีคัดกรองความรุนแรงของโรคไตแต่เนิ่น ๆ กับ (2) ความไม่เข้าใจในกลไกการทำลายไตที่แท้จริง เพื่อแก้ไขปัญหาดังกล่าว ผู้เขียนได้นำ (1) การตรวจการทำงานของไต โดยวิธี fractional excretion of magnesium (FE Mg) มาช่วยคัดกรองความรุนแรงของโรคไตแต่เนิ่น ๆ ได้ เนื่องจาก FE Mg สัมพันธ์โดยตรงกับอัตราตายของเนื้อไตชนิดเพิ่มพังพืด FE Mg จะมีค่าผิดปกติในผู้ป่วยโรคไตที่มีการตายของเนื้อไตชนิดเพิ่มพังพืด (tubulointerstitial fibrosis) และมีค่าปกติในผู้ป่วยโรคไตที่เซลล์บุท่อไตปกติ การสามารถคัดกรองความรุนแรงของโรคไต้แต่เนิ่น ๆ ทำให้สามารถเริ่มการรักษาได้ไวในขณะที่เนื้อไตส่วนใหญ่ยังดีอยู่ (2) องค์ความรู้เรื่อง "ภาวะหลอดเลือดออกจากโกลเมอรูลัสหดรัดตัวผิดปกติ (hemodynamic maladjustment) ทำให้เกิดการขาดเลือด peritubular capillary flow ที่ไปหล่อเลี้ยงเนื้อไตส่วนเซลล์บุท่อไต เป็นสาเหตุสำคัญที่ทำให้เกิดการตายของเนื้อไตชนิดเพิ่มพังพืด" มาประยุกต์ใช้รักษาป้องกันการทำลายไตโดยแก้ไขภาวะหลอดเลือดออกจากโกลเมอรูลัสหดรัดตัวผิดปกติด้วยยาออกฤทธิ์ขยายหลอดเลือดต่าง ๆ อาทิ ACEI, AII receptor antagonist, calcium channel blocker และยาต้านเกร็ดเลือด การรักษาดังกล่าวทำให้เพิ่ม peritubular capillary flow, และฟื้นฟูการทำงานของไตดีขึ้นกว่าก่อนการรักษา ซึ่งต่างจากผลการรักษาทั่วไปที่ได้ผลเพียงชลออัตราลดการทำงานของไตให้ช้าลงเท่านั้น