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Management of hypertension in patients with chronic kidney disease

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ARTICLE INFO

Article history:
Received 19 January 2015
Accepted 11 February 2015

1. Introduction

Chronic kidney disease (CKD) is an important area simply because reduced Glomerular filtration rate (GFR) and/or proteinuria is so very common in clinical practice. GFR below 60 is a very important part of care concern. In the United States (US), the relative percentage of people in each stage of CKD varies. Lower prevalence of patients with GFR below 30 ml/min/1.73 m^2 is probably because cardiovascular (CV) disease like strokes and heart attacks contribute to the deaths in such patients. Diagnosis of CKD is more likely to be predictive of CV events than even having a diagnosis of diabetes. CKD is more ominous from a prognostic standpoint.

2. Blood pressure and risk of renal injury

Glomeruli, the filtering units are vascular units within the kidney (Fig. 1). An afferent arteriole goes in and an efferent arteriole leaves out the glomerulus. It is an artery–artery connection. The afferent arteriole functions to limit the flow of blood going into the filter. The filter likes to operate at about one-half to two-thirds of systemic blood pressure. Efferent arteriole can vasoconstrict during situations of diminished effective arterial blood volume. That obviously, is very important for maintaining necessary pressure for filtration. So for this whole system to work, healthy blood vessels are needed so that one can modulate the amount of blood flow going in and modulate the amount of blood flow exiting.

The problem lies in the eccentric development of vascular disease which is quite important along the afferent arteriole. Increasing severity of the disease limits the ability of the kidney to auto-regulate its blood supply and thus, the kidneys' filters become more vulnerable to the effects of systemic blood pressure (BP). Experimental evidence of this had already been established using radio-telemetric techniques in various rodent models of hypertension (HTN). The amount of glomerulosclerosis directly correlates with BP. Studies have even shown glomerulosclerosis may differ depending on use of a calcium channel blocker (CCB) like amlodipine which is an afferent arteriolar dilator versus renin angiotensin system (RAS) blocker which preferentially dilates the efferent arteriole. Using CCB as a monotherapy dilates the afferent arteriole; if BP not lowered enough, then the risk for glomerular injury is markedly enhanced (Fig. 2). Thus practically one need to use RAS blockers first and then add CCB.

Determinants of hypertensive renal injury are related to BP load, BP transmission, and variety of other factors like local BP independent susceptibility mechanisms. There is probably very tight relationship between SBP and risk for renal injury suggesting that there is no right number but that lower indeed may be better.

3. Non-diabetic kidney disease

Increasing proteinuria increases more the likelihood of kidney disease progression and can happen more quickly. This allows opportunity to study effect of proteinuria on kidney outcomes with smaller number of patients and for a shorter period of time. On the other hand, in presence of microalbuminuria, it is unlikely to observe progression of kidney disease as such patients are more likely to die of CV events like strokes and heart attacks. Thus there is need of larger, longer duration studies which have not been done. In non-diabetic kidney

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http://dx.doi.org/10.1016/j.jicc.2015.03.019

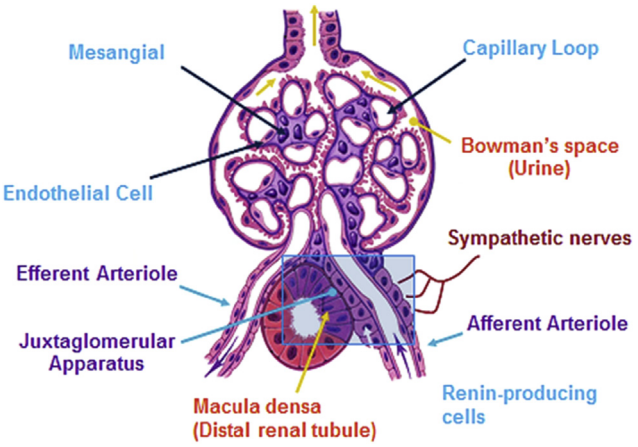

Fig. 1 – The glomerular apparatus of the kidney.

disease, probably the best data comes from the MDRD (The Modification of Diet in Renal Disease) study which was originally designed to look at the effect of diet on the progression of renal disease. Study also looked at two different BP - 140/90 versus 125/75 mmHg. Over a 36-month, for ≥3 g of proteinuria, benefit of 125/75 versus 140/90 was observed in just 8 month. On the other hand, for proteinuria between 1 and 3 g, again 125/75 looks better than 140/90 but it took nearly two years to start to see the benefit. For lower levels of proteinuria, it is unlikely to see any effect of BP within a three-year period of time (Fig. 3).

This discussion is important is because one needs to be cautious and know about the clinical trial design before making assumptions about clinical trial data.

4. Clinical studies in non-diabetic kidney disease: Effect of BP on renal outcomes

There are actually only three studies. These are MDRD (The Modification of Diet in Renal Disease) study, REIN-2 (Ramipril Efficacy In Nephropathy) trial, the AASK (The African American Study of Kidney Disease and Hypertension) study and a meta-analysis of a number of the clinical trials.

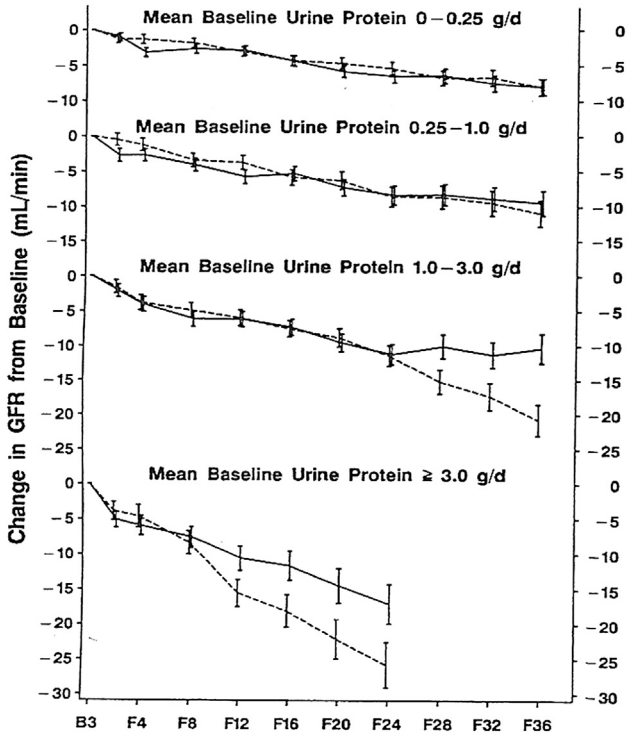

Fig. 3 – Estimated mean decline in glomerular filtration rate (GFR) from baseline to selected follow-up times in MDRD (Continuous line: BP125/75, dashed line: BP 140/90). Source: Peterson JC, et al. Annals of Internal Medicine 1995;123: 754–762

4.1. *MDRD study*

In this trial 840 patients with quite low GFR (13–55 ml/min/1.73 m^2) were randomized in to two target BP groups (140/90

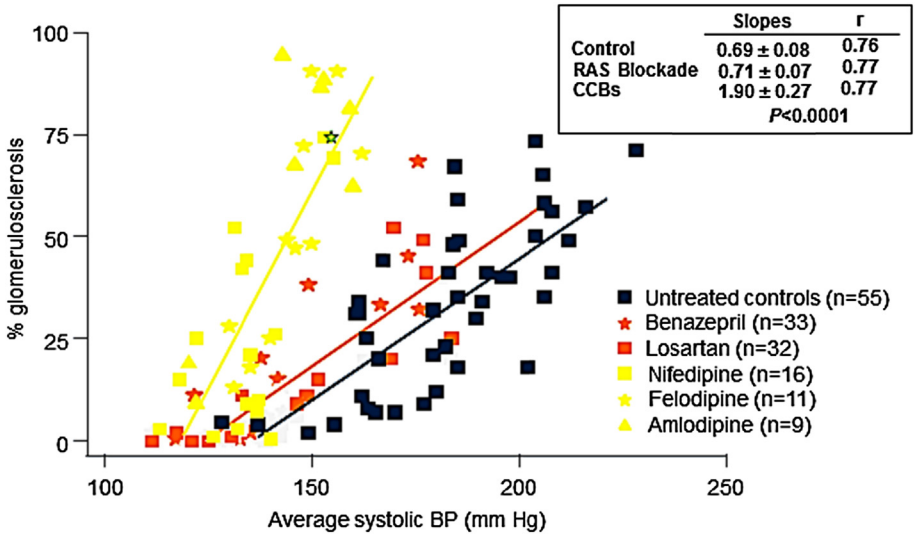

Fig. 2 – Relationship of renal damage to blood pressure.