Autosomal Dominant Polycystic Kidney Disease: Role of the Renin-Angiotensin System in Raised Blood Pressure in Progression of Renal and Cardiovascular Disease

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Abstract

Raised blood pressure (BP) is extremely common in individuals with autosomal dominant polycystic kidney disease (ADPKD) and is almost invariably raised once they develop renal failure. The underlying mechanisms for the rise in BP in individuals with ADPKD are unclear. The progressive number and enlargement of renal cysts, causing structural damage to the kidneys and, thereby, affecting tubular function as well as causing distortion of the glomeruli and renal ischaemia, is likely to be of primary importance. There is some evidence from animal models that there may be over-activity of the intra-renal renin-angiotensin system (RAS) that could account for the rise in BP. Studies in man have shown conflicting results, but a recent more carefully controlled study using both measurements of activity and pharmacological blockade of the RAS clearly demonstrated no evidence of over-activity of the circulating RAS in ADPKD compared to matched individuals with essential hypertension. A more likely explanation for the rise in BP that occurs in ADPKD is retention of sodium and water due to tubular damage. Disappointingly, in spite of good evidence that RAS blocking drugs slow the progression of other renal, particularly glomerular, diseases, there is little evidence to suggest this is true for patients with ADPKD. Nevertheless, there is no doubt that lowering BP in ADPKD is just as important, if not more important, as in essential hypertension to prevent cardiovascular disease and strokes, with a recommended BP target of < 120/80 mmHg.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic disorder affecting the kidneys in man, and accounts for nearly 6% of all patients accepted onto end-stage renal failure programmes in England and Wales. It is characterised by progressive development and enlargement of bilateral renal cysts, and presents in the third or fourth decade with haematuria, loin pain or raised blood pressure (BP). End-stage renal failure usually occurs by late middle age but this can vary depending on the type of genetic abnormality. Approximately 85–90% of families have an abnormality on chromosome 16, termed the PKD1 locus, which encodes a protein called polycystin-1 that is involved in adhesive protein-protein, cell-cell, and cell-matrix interactions. Most of the remaining affected individuals have a defect in the PKD2 locus encoding an abnormal gene on chromosome 4 that encodes for polycystin-2. Polycystin-1 is thought to be involved in cell calcium signalling. Those with PKD2 have later onset of macroscopic cyst development and a slower rate of progression; therefore, these individuals are older when they develop end-stage renal failure (74 years in PKD2 vs. 54 years in PKD1).

Raised BP develops ten years earlier in ADPKD patients than in the general population and is present in 60% of affected individuals before renal function becomes impaired. Once on dialysis nearly all affected individuals are hypertensive. Hypertension used to be thought to be a significant factor in the progression of renal failure in ADPKD, and it is the major risk factor for the premature cardiovascular disease that occurs, particularly in younger patients, and which in turn is the most frequent cause of mortality in ADPKD patients.

It is well recognised that deterioration of renal excretory function in ADPKD follows a unique time course in that glomerular filtration rate remains constant for many years and only declines relatively late in the course of the disease, when mechanical compression of normal renal tissue by cysts occurs. This initial stable phase makes it difficult to analyse the results of clinical studies in ADPKD, since prolonged follow-up may be needed to obtain conclusive results. Besides the presence of the PKD1 mutation, male gender and severity of interstitial fibrosis have also been shown to accelerate progression. In addition, there is a significant correlation between rate of growth of renal volume and rate of change in glomerular filtration rate in both men and women with ADPKD.
kidneys cause distortion of the architecture of the kidney, particularly to the tubules, glomeruli and renal vasculature. Those with raised BP seem to have significantly larger kidneys than those who do not. Histological examination of ADPKD kidneys has shown attenuation of the renal vascular tree with evidence of ischaemia, and compression of intra-renal arterioles by cysts is seen on angiographic studies. These structural changes, which clearly underlie the rise in BP, could contribute towards development of hypertension in a variety of different ways: firstly, by activating the renin-angiotensin system (RAS); secondly, by increasing activity of the sympathetic nervous system (SNS); and thirdly, by affecting renal tubular sodium handling.

Renin-Angiotensin System (RAS)

Studies of the measurement of various markers of RAS activity in ADPKD patients have, on the whole, shown inconclusive results. One small study compared hypertensive ADPKD patients with normal historical controls, and found highly variable plasma renin activity (PRA) responses to sodium depletion. Valvo et al. studied normotensive and hypertensive ADPKD patients. PRA was non-significantly higher in the hypertensive group but since plasma volume and BP were also higher in these individuals, it was argued that, in fact, PRA was inappropriately elevated in this group. However, another study found identical suppression of PRA following sodium loading in hypertensive ADPKD patients and healthy controls. In a better controlled study, Bell and co-workers studied NT and HT ADPKD patients on a low (20 mmol/day) and high (200 mmol/day) sodium intake, and generally found no differences in responses of PRA or BP to the change in sodium intake or the administration of captopril. Very similar findings have recently been reported by Ramunni et al.

Figure 1

Changes in mean arterial pressure (MAP), plasma renin activity (PRA) and 24-hour urinary sodium (UNa) excretions on changing from a high (350 mmol/day, HS) to low (50 mmol/day, LS) sodium diet in ADPKD patients (n=11) and control subjects (n=8). Light bars indicate HS diet; dark bars indicate LS diet. *p=0.073, **p<0.01, ***p<0.001 compared with HS diet. (Adapted from Doulton et al.)

Figure 2

Changes in mean arterial pressure (MAP), plasma renin activity (PRA), and 24-hour urinary sodium (UNa) excretions following administration of enalapril (5 mg twice a day, for three days) during low-sodium (LS) diet in ADPKD patients (n=11) and control subjects. *p<0.01, ***p<0.001 vs LS diet alone. (Adapted from Doulton et al.)
normotensive volunteers or normotensive ADPKD patients as control subjects in studies with hypertensive ADPKD patients. Instead it might be better to compare the latter group against individuals with essential hypertension, matched for BP, renal function and age.

Chapman et al. studied two groups of ADPKD patients on their normal salt intake. 29 In the first study, ADPKD patients with high BP were compared to matched controls with essential hypertension. Basal and post-captopril PRA were higher in ADPKD patients than controls. However, paradoxically, the fall in BP with captopril was the same in both groups. In the second study there was no difference in PRA between normotensive ADPKD patients and normotensive controls, although the former group had higher BP and so it was argued that PRA was not appropriately suppressed in these individuals. Dietary salt intake was not controlled in this study, and no information was provided on the ethnic origin of study participants. In our view, these represent significant shortcomings of this study, since these variables are major determinants of RAS activity. 30

To try and overcome some of the shortcomings in the above studies we studied hypertensive ADPKD patients with normal renal function who were matched to individuals with essential hypertension on both a low- (50 mmol/day) and a high- (350 mmol/day) sodium diet and measured changes in BP and PRA before and after administration of an angiotensin-converting enzyme (ACE) inhibitor. 30 All subjects were Caucasian. There was no difference whatsoever between the two groups in the level of PRA on different salt intakes, and in their response to an ACE inhibitor (ACE-I) (Figures 1 and 2). This makes it unlikely that the rise in BP in ADPKD is related to abnormal activity of the circulating RAS. 31 Moreover, these findings are in accordance with another recently published study which found no differences in PRA, angiotensin II (Ang II) and aldosterone between hypertensive ADPKD patients and essential hypertensives that were matched for BP, but, unfortunately, not renal function. 40 Other studies in normotensive ADPKD patients with unaffected family members acting as controls showed little to suggest abnormal RAS activation, 31,35 with the exception of a single study in which PRA was higher in ADPKD patients than controls. 35 However, interpretation of these studies is again confounded by significantly higher BP in ADPKD patients than in controls.

Studies of biopsy, nephrectomy and autopsy specimens have demonstrated increased numbers of renin granules within the juxta-glomerular apparatus (JGA), 36 and increased levels of tubular immunoreactive renin and high intracystic renin concentrations in patients with ADPKD. 37,38 More recently it has been shown that angiotensinogen is produced by cysts and dilated tubules, that other components of the RAS (ACE and the Ang II type 1 receptor) are present within cysts and tubules, and that these continue to be produced by cyst-lining epithelial cells in culture. 39 Furthermore, the tubulo-cystic fluid contains relatively high Ang II concentrations. Additionally, ACE-independent generation of Ang II occurs via chymase-like pathways in ADPKD kidneys. 40 It is possible, therefore, that excessive and ectopic Ang II production could increase intratubular Ang II concentrations thereby resulting in excessive renal tubular sodium reabsorption which would not be subject to the normal regulatory feedback mechanisms and, thereby, could cause a rise in BP due to the retention of sodium and water. Supporting this are experimental studies in transgenic mice which have shown that up-regulation of the intra-renal RAS is associated with increases in systemic BP without changes in activity of the classical circulating RAS. 41 These findings have been confirmed by cross-transplantation experiments which have demonstrated equal contributions of the intra-renal RAS and the circulating RAS in systemic BP regulation. 40 It is therefore possible that activation of the intra-renal RAS sufficient to result in raised BP but without affecting the circulating RAS, could occur in ADPKD.

Renovascular Resistance

Several studies have shown higher renovascular resistance in hypertensive 24-26 and normotensive 27 ADPKD patients compared to controls, and it has been suggested this may be indicative of increased intra-renal RAS activity. However, renovascular resistance is also increased in individuals with essential hypertension, 42 and may be no higher in ADPKD subjects than in matched essential hypertensive subjects. Indeed, renovascular resistance was the same in ADPKD patients and controls in one study where BP was well matched and was reduced by chronic ACE-I therapy in both groups. 27

Sympathetic Nervous System (SNS) Activity

SNS activity plays a very important role, not only in regulating systemic BP, but also RAS activity, intra-renal vascular tone and renal tubular sodium reabsorption. There is also a complex feedback loop from the kidney to the central nervous system which, in itself, regulates sympathetic activity. 43,44 Circulating measurements of the activity of the SNS are generally considered to be unreliable. Muscle sympathetic nerve activity (MSNA), usually determined by the placement of tungsten microelectrodes into the peroneal nerve, is thought to be a more reliable index of the activity of the SNS, but may not necessarily reflect sympathetic activity in the
kidney. Using this technique Klein et al. showed that hypertensive ADPKD patients with normal renal function had greater SNS activation than both normotensive ADPKD and healthy controls. There was also a significant correlation between MSNA and PRA, but no difference in PRA between the hypertensive and normotensive ADPKD patients. These results are difficult to interpret, but suggest a direct effect of structural renal damage on central SNS outflow, rather than the latter being up-regulated by increased intra-renal RAS activity.

**Tubular Sodium Handling, Pressure-Natriuresis and Extra-Cellular Fluid Volume**

The activation, if it exists, of the intra-renal RAS and the structural distortion of the tubules that occur, and the progressive destruction of the glomeruli are very likely to affect renal tubular sodium handling, causing increased retention of sodium and water. There is good evidence that the pressure-natriuresis curve is shifted towards the right in hypertensive ADPKD patients. However, it is still not clear whether this is primary – i.e. directly due to abnormalities of tubular sodium handling – or secondary to activation of the intra-renal RAS. Supporting retention of sodium and water is the fact that plasma volume, extracellular fluid volume and exchangeable sodium are expanded in ADPKD patients prior to the development of renal failure. Not surprisingly, as occurs in essential hypertension, acute sodium loading does not increase plasma volume or BP and, indeed, as in essential hypertension there may be an exaggerated natriuresis following sodium loading due to sensitised mechanisms trying to correct the expansion of extra-cellular volume. This concept is supported by our finding in ADPKD patients that the change in BP with reduction of salt intake was no different from that in matched patients with essential hypertension, and there was no difference in the responses of atrial natriuretic peptides.

**Raised Blood Pressure and Progression of Renal Impairment**

In most renal diseases, particularly those primarily affecting the glomeruli, raised BP contributes in a major way to the progressive and irreversible decline in function that often occurs. Several studies have shown in both diabetic and non-diabetic kidney disease that lowering of BP slows down the rate of progression of renal impairment and, in particular, inhibition of the RAS may carry specific additional benefits. In an early retrospective study in ADPKD patients ACE inhibition appeared to result in slower deterioration in renal function compared with thiazide diuretics, but this finding was confounded by inadequate matching for gender and age, and a non-significant difference in achieved systolic BP. Furthermore, and in contrast to other studies in chronic kidney disease, non-randomised and randomised studies have found no particular advantage of ACE-Is in terms of ameliorating decline in renal function in ADPKD. Van Dijk and colleagues, in a well conducted and adequately powered study, compared an atenolol-based regime against an enalapril-based regime. There was no difference in decline in renal function in both normotensive and hypertensive ADPKD patients over a three year follow-up. However, the dose of enalapril used was relatively low, which may have diminished any beneficial effect of ACE inhibition. Moreover, considering the natural history of ADPKD, the duration of follow-up may have been insufficient in this study. A recent meta-analysis found that the data supporting the use of ACE-I for renoprotection in advanced ADPKD was inconclusive, although ACE inhibitors did reduce proteinuria more than comparator drugs after adjustment of baseline characteristics and differences in BP during follow-up. Perhaps more important and disappointing was the finding that rigorous control of BP with a combination of therapies did not result in a reduction in the rate of decline of renal function when BP was reduced to 120/80 mmHg compared to 135–140/85–90 mmHg.

**Risks of Raised Blood Pressure in ADPKD**

The high prevalence of raised BP puts individuals with ADPKD, who are often younger than those with essential hypertension, at increased risk of stroke and cardiovascular disease. Not surprisingly, because ADPKD is relatively uncommon, there are no studies showing that lowering of BP reduces the risk of ischaemic stroke and cardiovascular disease in this population. In addition, it would seem likely that treating hypertension would also help to reduce the morbidity and mortality resulting from ruptured intracranial aneurysms associated with ADPKD, although there have been no studies to confirm this.

On the other hand, left ventricular hypertrophy (LVH) may be used as a surrogate endpoint for cardiovascular events in clinical studies, since it is a well-established marker of end-organ response to raised BP, as well as being a causal risk factor for cardiovascular disease by itself. Furthermore, LVH is one of the strongest independent risk factors for cardiovascular mortality in the general population after aging. LVH is more prevalent in individuals with ADPKD than without (41% vs 16%) and undoubtedly raised BP plays a significant role in the development of LVH in both hypertensive adults and children with ADPKD. Although earlier studies suggested that normotensive ADPKD patients had higher left
ventricular mass than matched control subjects,\textsuperscript{67,69} these individuals have, in fact, different day-night BP profiles compared to controls with a tendency towards greater prevalence of non-dipping amongst the ADPKD patients.\textsuperscript{5} Furthermore both ambulatory systolic and diastolic BP, but not office BP, correlate with left ventricular mass in apparently normotensive ADPKD patients.\textsuperscript{30,66} thus underlining the importance of raised BP in the development of LVH in these individuals. Importantly, studies in ADPKD patients with LVH have not found greater RAS activation in affected individuals compared with normotensive ADPKD patients with LVH or essential hypertensive controls.\textsuperscript{68,69} In a small uncontrolled study, treatment with enalapril for seven years reduced LVH but BP was also reduced, and so the role of RAS inhibition in LVH regression was not clarified.\textsuperscript{70} In a subsequent non-randomised prospective study, enalapril appeared to reduce LVH to a greater degree than the comparator drug amlodipine for a similar reduction in BP.\textsuperscript{66} Regression of LVMi to within normal limits was achieved in 67% of participants receiving enalapril \textit{vs.} 36% taking amlodipine, and this was particularly pronounced in those subjects allocated to rigorous (<120/80 mmHg) versus standard control. There are, as yet, no studies with angiotensin receptor blockers, either on the progression of renal failure or of LVH, but there is little to suggest from other clinical studies that their effects would be different from that of ACE-Is.

\textbf{Novel Therapies in ADPKD}

Tao \textit{et al.} found that the mTOR inhibitor and potent antiproliferative agent rapamycin reduced kidney volume and cyst volume density, decreased proliferation in cystic and non-cystic tubules, and prevented the loss of kidney function when given to Han:SPRD rats (an animal model of ADPKD).\textsuperscript{71} Furthermore, kidney size decreases in ADPKD patients treated with rapamycin after renal transplantation, compared with those treated with other immunosuppressive agents.\textsuperscript{72} Phase I and II trials of mTOR inhibitors using computerised tomography (CT) and magnetic resonance imaging (MRI) to measure renal volume are currently in progress.

Vasopressin-2 receptor (V2R) antagonists have considerable potential as novel therapeutic agents in ADPKD. The V2R spans the membrane of epithelial cells in the distal tubules and collecting ducts and, via the second messenger cAMP, mediates insertion of aquaporins into the plasma membrane of these cells. These allow diffusion of water from the tubular lumen back into the interstitium, thereby potentially contributing towards cyst growth.\textsuperscript{73} V2R antagonists have been shown to reduce cyst and kidney volumes in a PKD2-deficient mouse model.\textsuperscript{74} Interestingly, the effect of these agents was not confined to the distal nephron despite the absence of a confirmed V2R promoter in cells of proximal tubular origin, thereby suggesting other possible modes of action of V2R antagonists.\textsuperscript{73} A phase III clinical trial of the V2R antagonist tolvaptan is planned in ADPKD patients.

\textbf{Conclusions}

Most patients with ADPKD have high BP particularly when they develop renal failure. There is conflicting evidence as to the mechanism of this rise in BP, but the evidence suggests that the circulating RAS is not of primary importance. However, this does not exclude a role for the intra-renal RAS, which may be activated and disregulated in ADPKD, and could thereby contribute to the development of hypertension, particularly in combination with structural damage to the tubules and glomeruli. All of these factors would cause an increase in tubular sodium reabsorption.

Rigorous control of BP to less than 120/80 mmHg reduces LVH and is also likely to prevent strokes and cardiovascular disease in a population at high risk of these complications. However, there is little evidence that lowering BP in any way affects the development of renal failure. It is not to say that if individuals with ADPKD were treated very early in the course of the disease it might be different, but it seems unlikely. Instead, since raised BP and renal failure are probably a direct consequence of destruction of normal renal tissue by increasing numbers and size of cysts, it is likely that specific novel therapies directed at this underlying pathogenesis will be required to prevent the development of hypertension and progression to end-stage renal failure in ADPKD.

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