Type 2 Diabetic Nephropathy: Never too Early to Treat?

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Type 2 diabetes mellitus is now the leading cause of end-stage renal disease in the United States and other developed countries (1). The pathogenesis of renal failure in type 2 diabetes is complex (1,2), but a role of the renin-angiotensin system (RAS) has been recognized for more than 15 years (3,4). In recent years, this notion has been confirmed by several large-scale clinical trials in patients with type 2 diabetes and renal disease (5). Blockers of the angiotensin II type 1 receptor (ARB) ameliorate the progression of overt nephropathy, independent from BP (6). Angiotensin-converting enzyme inhibitors (ACEI) as well as ARB decrease microalbuminuria and delay the progression from microalbuminuria to overt nephropathy (7,8). The recently published BENEDICT trial showed that ACEI retarded the development of new-onset microalbuminuria in hypertensive patients with type 2 diabetes, whereas a control antihypertensive drug did not (9). These trials supported a role of the RAS and marked a considerable step forward in the treatment of the disease. Nevertheless, several questions regarding the role of RAS blockade in type 2 diabetes remain to be answered. Are ARB superior to ACEI, or is a combination of both the most effective treatment? What are the optimal doses of ARB and ACEI? Can RAS blockade at best retard progression, or are these drugs able to reverse the loss of renal function as well? At what stage should RAS blockade be initiated? What is the role of nonhemodynamic mechanisms for the effects of RAS blockade?

This issue of the Journal of the American Society of Nephrology contains a report from an experimental study by Nagai and co-workers (10) which bears on several of these questions. The authors used Otsuka Long-Evans Tokushima Fatty (OLETF) rats, a model of type 2 diabetes (11). These rats carry a defective cholecystokinin type A receptor gene, but the development of type 2 diabetes is nevertheless polygenic, not monogenic (12). OLETF rats also suffer from obesity, high BP, and hyperlipidemia (11), which may contribute to the development of renal damage. This complex pathogenesis of kidney injury could be viewed as a limitation of the model, but clinicians will instantly recognize the similarity to the metabolic syndrome in human type 2 diabetes (1). Furthermore, unlike most rodent models of diabetes, OLETF rats do develop nodular glomerular lesions (11).

Blockade of the RAS is known to ameliorate the progression of nephropathy in OLETF rats (13), but Nagai et al. (10) take the matter an important step further. The authors treated prediabetic rats from week 4 to week 11 of life with an ARB, an ACEI, a combination of both drugs, or hydralazine for comparison. At this age, blood glucose, body weight, and BP did not yet differ between OLETF rats and the respective nondiabetic, lean control animals. Treatment was then stopped, and the rats were followed for another 39 wk. The most striking observation was that transient RAS blockade in young rats had a lasting beneficial effect on glomerular structure and proteinuria despite the fact that the treated rats developed obesity, hypertension, and hyperglycaemia to an extent similar to that of untreated OLETF rats (10). This effect of RAS blockade was evident regardless of whether ACEI, ARB, or a combination of both drugs was used but was absent in the hydralazine group. It was important that the RAS was inhibited at all; the choice of ACEI, ARB, or combination was secondary, at least in this model. The doses of the drugs were not precisely monitored but appeared to be in the moderate to high dose range for rodents.

How can such a striking, long-term, renoprotective effect of a transient RAS blockade be explained? The first reports on the benefits of RAS antagonists in diabetic nephropathy focused on the correction of glomerular hypertension and hyperfiltration (14). Such a mechanism, however, is rather unlikely to account for structural benefits observed 39 wk after cessation of RAS blockade (10). Moreover, the increase of glomerular size in OLETF rats was not affected by RAS blockade (10), indicating that hyperfiltration was present. In contrast, the results provide some evidence that nonhemodynamic, profibrotic effects of angiotensin II may account for the findings (15). The gene expression of connective tissue growth factor, and of collagens I and IV, was elevated in young OLETF rats and was almost normalized by RAS blockade. This effect was sustained until 50 wk of age (10). The lack of data on matrix metalloproteases and collagen deposition limits the impact of these results. However, the findings suggest that transient RAS blockade at a young age can ameliorate the programming of a profibrotic phenotype. The phenomenon should not be confused with the deleterious impairment of kidney development induced by RAS blockade at an much younger age, i.e., during the neonatal period (16). At least in rats, the optimal age to induce lasting renoprotection by transient RAS blockade appears to be adolescence and/or very early adulthood (4 to 10 wk of age), based on the data of Nagai
et al. (10) and the reports of others on the prevention of hypertensive nephrosclerosis (17). The molecular mechanisms of “re-programming” at this age are not fully understood and will require further study.

Blockade of the RAS could help alleviate the metabolic syndrome and delay the onset of type 2 diabetes. This phenomenon has been increasingly recognized in clinical studies during recent years (18). Nagai et al. (10) argue against such an explanation for their findings, but others have previously reported that RAS blockade leads to metabolic improvements also in OLETF rats (19). One has to be careful in extrapolating from data obtained in animal models. However, the results by Nagai et al. (10) support the notion that treatment with RAS blockers should be started early, before diabetes becomes obvious, in subjects at risk for developing type 2 diabetes. Whether such early treatment could possibly obviate the need for later, more intense treatment in humans remains to be investigated. Moreover, the findings underscore the pivotal role of a stimulation of the intrarenal RAS in the pathogenesis of diabetic nephropathy. The development of tests to evaluate the activity of the intrarenal RAS in humans could help identify the patients who will benefit most from early RAS blockade.

References