Diabetic Nephropathy
Can Renoprotection Be Extrapolated to Cardiovascular Protection?
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Recent years have seen the seemingly unstoppable attack by cardiologists on all diseases that limit cardiovascular health. Nowhere is this more evident than in the case of diabetes mellitus, the subject of an important article in this issue of Circulation that relates to renoprotection in type 2 diabetes mellitus. As a background, type 2 diabetes is increasing in incidence and cardiological significance, particularly because of the finding that blood pressure control is crucially important in limiting the macrovascular disease that shortens life in patients with type 2 diabetes. As a negative prognostic factor, patients with type 2 diabetes without prior myocardial infarction have as high a risk of infarction as do nondiabetics with prior infarction. The adverse effects of type 2 diabetes are accelerated by diabetic nephropathy leading to a nearly 9-fold increase in relative cardiovascular mortality.

Microalbuminuria: A Marker of Endothelial Dysfunction?
Microalbuminuria could be viewed as a marker of generalized endothelial damage, which leads to nephropathy in patients with diabetes. This concept would link in with the 3 "H" pathogens in type 2 diabetes: (1) hyperglycemia, (2) hyperinsulinemia, and (3) hypertension. Hyperglycemia, common in type 2 diabetes, independently impairs endothelial function, probably acting in part through decreased generation of nitric oxide and in part through protein kinase C and formation of reactive oxygen species. Repetitive episodes of hyperglycemia may lead to sustained formation of advanced glycation end-products that induce long-term endothelial dysfunction. Hyperinsulinemia is an independent risk factor for ischemic heart disease among people without diabetes. Hyperinsulinemia causes endothelial dysfunction, possibly by increasing oxidant stress. Hypertension, also common in patients with diabetes, is associated with endothelial dysfunction, as shown by the effects of transiently increasing the intra-arterial pressure in human arteries. The severity of endothelial dysfunction is linked to the prognosis in hypertension, and there is no reason to suppose that it would be otherwise in patients with diabetes.

Thus, an attractive working hypothesis is that microalbuminuria reflects endothelial dysfunction, a warning of cardiovascular disease to come both in patients with diabetes and in others. The discovery of microalbuminuria, therefore, prompts a search for correctable cardiovascular risk factors in patients with diabetes and with particular focus on hypertension and lipid abnormalities. However, microalbuminuria also heralds future nephropathy that further worsens the cardiovascular outlook of the patient with type 2 diabetes. How, then, should it be treated? Two recent studies show the way forward. Parving and coworkers tested the effect of irbesartan, an angiotensin-receptor blocker (ARB), in delaying clinical albuminuria that signifies overt nephropathy in patients with diabetes and hypertension. The daily dose of 300 mg of irbesartan was more renoprotective, but the blood pressure (BP) was slightly lower at 141/83 mm Hg, versus 144/83 mm Hg in controls. Whether such small reductions in systolic but not diastolic BP are significant is doubtful. Furthermore, with 150 mg of irbesartan daily, the diastolic BPs were the same, the systolic BP was only 1 mm Hg lower, and microalbuminuria fell by 24%. Viberti and Wheelond studied hypertensive and normotensive type 2 diabetics, the latter group with a mean initial BP of only 129/79 mm Hg. Thus, prior hypertension was not required for valsartan, an ARB, to decrease microalbuminuria in patients with type 2 diabetes. A defect of their study is that they measured albumin excretion at night but BP during the day.

Cardiological Significance
Overall, the renoprotective effects of ARBs are at least partially BP independent. A decisive argument is that, in the
control arms of 2 outcome studies with conventional BP-lowering agents,19,20 the BP decreased by ≥10 mm Hg without decreasing proteinuria, which was in contrast to the ARB arm. What is the cardiological significance of this conclusion?

Angiotensin II harms endothelial function and promotes vascular disease.21 Conversely, losartan improves both endothelial function and arterial structure in arterioles from hypertensive humans.21 Furthermore, losartan decreases atherosclerosis independently of BP effects in primates.22 Thus, it might be expected that renoprotection by an ARB should go hand-in-hand with improved cardiovascular prognosis. It would help little if the kidneys were saved but the patients were to continue to die from cardiovascular causes. Yet cardiovascular outcomes in 2 major renoprotective trials are disappointing.19,20 Mortality was unchanged, but it should be recognized that end-stage renal disease, reduced in both trials, is a delayed death sentence without intervention by dialysis or renal transplantation. Although there can be no question about the overall benefit that patients with diabetes receive from strict BP control,2 there are no human data that prove BP-independent cardioprotection when ARBs are given for renoprotection. When given for hypertensive diabetes with left ventricular hypertrophy, the situation is different because losartan decreases mortality and cardiovascular end points versus atenolol.23

It is not easy to decipher why the cardiovascular end points in the ARB renoprotective outcome trials have not been as positive as they might have been, apart from the better prevention of heart failure. A speculative proposal is that, in renal failure, there are several other detrimental factors besides angiotensin II that impair endothelial function, thus overriding the cardiovascular benefit of ARBs.

Choice of Therapy

The 4 major principles of therapeutic intervention in diabetic nephropathy have been strict control of BP, blood sugar, and blood lipids, and the initial use of angiotensin-converting enzyme (ACE) inhibitors.24 Now the emphasis is shifting to early prevention rather than treatment of established nephropathy. Very tight control of BP and early detection of microalbuminuria are required in patients with type 2 diabetes. For cardio-vascular protection in high-risk diabetics, there are data favoring both ACE inhibitors25 and ARBs,26 although it has not yet been possible to be entirely sure that BP-independent renoprotection by ACE inhibitors could explain the benefits achieved.18

First, the closer the BP is to the physiologically ideal, the better. Thus, reducing an initial mean BP of ≈140/85 mm Hg to 128/81 mm Hg over 5 years delayed microalbuminuria and lessened stroke.26 This message is reinforced by the large prospective United Kingdom study in patients with type 2 diabetes over 8.4 years,2 in which the lowest risk of complications, including death and myocardial infarction, was with a systolic BP <120 mm Hg. In both studies, very tight BP control mattered more than whether or not an ACE inhibitor was initially used. In some studies, an ACE inhibitor or ARB emerged as the clear winner. For example, in patients with diabetes and left ventricular hypertrophy, BP reduction by the ARB losartan was clearly better than that achieved by atenolol, both of which were usually combined with a diuretic.23 In reality, several antihypertensives, including calcium antagonists, β-blockers, and diuretics will usually be needed to achieve the arbitrarily recommended goal of 130/80 mm Hg. A consideration of basic science and clinical data strongly suggests that an ACE inhibitor or ARB should be an essential component of the mix.27 In RENAAL (Reduction of End points in NIDDMM with the Angiotensin II Antagonist Losartan), in addition to 100 mg daily of losartan, ∼80% received a calcium antagonist, 84% a diuretic, 46% an A-blocker, and ∼33% a β-blocker, yet the final mean BP was 143/77 mm Hg,28 meaning that, ideally, even more vigorous therapy should have been given to reach the systolic goal.

Secondly, microproteinuria is now an essential component of cardiovascular risk assessment. When found in type 2 diabetes, it heralds serious danger ahead. It calls for renoprotection with an ARB or an ACE inhibitor while still aiming for very tight BP control. Only 3 small studies, without outcome data, have directly compared the renal effects of ACE inhibitors with ARBs in patients with hypertension and type 2 diabetes. Thus, microalbuminuria was similarly reduced by candesartan,28 valsartan,29 or losartan30 versus ACE inhibition. Yet data presently show that ARBs rather than ACE inhibitors have been used in a range of well-controlled and carefully monitored renoprotective studies, varying from overt hypertensive type 2 diabetic nephropathy19,20 to diabetic microalbuminuria with17 or without hypertension.1 The American Diabetes Association recommends ARBs as the first choice.31 It is probable, but not definitive, that ACE inhibitors would give similar renoprotection,18 and the only way to prove this hypothesis would be to launch comparative studies.

Acknowledgment

We thank Associate Professor Brian Rayner, Renal Unit and Director Hypertension Clinic, Department of Medicine, Groote Schuur Hospital, Capetown, for advice.

References


Key Words: Editorials diabetes mellitus angiotensin kidney nephropathy
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Circulation. 2002;106:643-645
doi: 10.1161/01.CIR.0000028099.24188.C4
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/106/6/643

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