stenoisis. For the individual patient rather than the individual kidney the outcome will depend on the patency of the contralateral renal artery.

An intervention to decrease the rate progression of both the renal artery lesion and the decline in renal function in an individual kidney would appear attractive. At the present time there are no prospective studies to support either surgical or angioplasty intervention demonstrating increased longevity or reduction in rate of loss of renal function. Studies are, however, under way which may answer this question. The decision to perform angioplasty in a kidney with 60% or greater renal artery stenosis would appear reasonable as the likelihood of progression is high. This decision cannot be supported as yet by any outcome data in terms of patient survival or stabilization of renal function.

In dialysis-dependent patients and those with 'flash pulmonary oedema' there are clear indications for intervention and not the 'wait-and-see' approach. The difficult group is those patients picked up on routine angiography of another vascular bed. It is tempting to suggest that measures such as low-dose aspirin and/or lipid-lowering therapy should be used in these patients. No studies have addressed this problem, and the 'wait-and-see' approach may be entirely appropriate in the asymptomatic patients until data can demonstrate an improved outcome on therapy.

The effect of ACE inhibitors and other antihypertensive agents on insulin resistance

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Definition of insulin resistance

Insulin resistance is defined as the relative impairment of insulin to promote glucose uptake in peripheral tissues. This relative dysfunction of insulin probably may have many different causes on the molecular, intracellular and tissue level. It is seldom caused by a defective variant of the insulin molecule itself. In most cases insulin resistance results in compensatory hyperinsulinemia. The clinical importance of insulin resistance is well recognized in the case of non-insulin dependent diabetes. Diabetes develops when the compensatory mechanisms become insufficient and there is a relative lack of insulin molecules in the circulation. It is only during the last 10 years when the potential importance of insulin resistance as a risk factor for coronary heart disease has been brought in focus that its relevance for clinical medicine has become wider acknowledged. High insulin concentrations may themselves be important as causal risk factor for arteriosclerosis but the greatest impact of insulin resistance is probably related to its influence on other risk factors for coronary heart disease. Several mechanisms have been described whereby the status of insulin resistance with hyperinsulinemia can result in dyslipoproteinemia, defective fibrinolysis, and hypertension [1].

Many hypertensive patients are insulin resistant

Several studies of hypertensive patients have now indicated that a large proportion of the patients are insulin resistant, maybe as much as 50% [2]. It seems likely that it is among this subgroup that the patients are recruited who later develop non-insulin dependent diabetes mellitus. There are now four prospective studies of populations among which the hypertensives who have been treated with beta-blockers or diuretics had

References

an increased risk for development of diabetes. Thus, it seems likely that these classes of drugs may affect either insulin resistance (by worsening it) or the glucose stimulated release of insulin (by impairing it).

**Effect of beta-blockers and diuretics**

The experience over the last 6–7 years is that beta-blockers and diuretics in general impair insulin resistance by about 20%. However, it has also been shown that this is not a pure class effect because among the beta-blockers there is a clear separation in effect between those that have intrinsic sympathetic activity (ISA) and those that do not have ISA. Thus, propranolol treatment is associated with a worsening of insulin resistance by 32% [3]. In contrast to the effect of this non-selective beta-blocker without ISA is the effect of pindolol, similarly a non-selective beta-blocker but with ISA, that had a significantly smaller effect on insulin resistance (by 17%) [3]. The non-selective beta-blocker dilevalol has a very pronounced ISA with regard to beta_2_ receptors. Treatment with this drug in fact decreased the insulin resistance slightly (~10%) [4]. These beta-blockers also differ with respect to their effect on haemodynamics. Propranolol is a vasoconstrictor and the other two, in particular dilevalol, vasodilators. Blood flow has been demonstrated to be related to the insulin-stimulated glucose uptake [5] and it is reasonable to assume that the difference between these drugs has to do with their different haemodynamic profiles. One other aspect, but maybe less important, is that both the beta-blockers without ISA and diuretics cause a slight inhibition of the early insulin response to glucose stimulation. These two drug-induced effects on important factors for removal of glucose from the blood stream are therefore not surprisingly associated with an impairment of glucose tolerance.

**Insulin resistance in patients with renal failure**

Patients with renal failure often have pronounced insulin resistance and hypertension together with impaired glucose tolerance or diabetes mellitus. This patient group also has a high incidence of cardiovascular diseases. For these patients it therefore seems pertinent to find treatment modalities that are not associated with impairment of insulin resistance and its associated cardiovascular risk factors.

**Effects of calcium channel blockers and alpha_1_-blockers**

In studies on patients with essential hypertension it has now been demonstrated by different groups and with different techniques that treatment with calcium channel blockers, ACE inhibitors and alpha_1_-blockers are not associated with similar effects as with beta-blockers and diuretics. The alpha_1_-blockers seem to be the drugs that most consistently have been demonstrated to have positive effects, i.e. they decrease insulin resistance and improve glucose and insulin patterns at glucose tolerance tests [6]. Several calcium channel blockers are neutral in their effects. However, the experience with nifedipine is somewhat controversial in that an impairment of insulin resistance was demonstrated in one study [7], whereas an improvement was found in another [8]. This probably has to do with the different formulations that were used in the two studies; a short-acting type in the former and a drug with prolonged release of nifedipine in the latter. These two different administration forms may elicit different responses in the sympathetic nervous system which may explain the different metabolic effects of the same drug.

**Effects of ACE-inhibitors**

The first ACE-inhibitor to be tested was captopril. Treatment with captopril was associated with an improvement of insulin resistance by 18% [9]. It was assumed that this was a class effect. In later studies in the same clinical setting and with the same techniques for measurement of insulin resistance it has not been possible to demonstrate any improvement of insulin resistance with either fosinopril [10], lisinopril [11], or enalapril. However, in a separate study in elderly patients it was shown that six different ACE-inhibitors all improved insulin resistance [12]. It is not clear what the reasons for the different results are. In the latter study the patients were older than in the other studies and the treatment period was rather short. The degree of insulin resistance and the severity of hypertension are other factors that may be of importance to explain the different results.

**The stereochemistry of the ACE inhibitors**

The different ACE-inhibitors have very similar effects with regard to blood pressure lowering. This is achieved by inhibition of one particular site of molecule of the angiotensin converting enzyme. Another site exists that is of less importance for the blood pressure lowering effect. This enzyme has, however, also other effects than the conversion of angiotensin I to angiotensin II. Some of these functions may be of relevance for blood glucose regulation. The break-down of bradykinin is one such example. Bradykinin may have insulin-like effects on blood glucose. An accumulation of bradykinin might explain the effect of captopril. Captopril is a rather small molecule in comparison with several more recently developed ACE inhibitors. It is possible that the stereochemistry of the molecule permits it to inhibit both sites [13]. This may be difficult to achieve with the more recently developed ACE inhibitors.
Conclusions

Great achievements have been obtained in clinical medicine with the development of ACE-inhibitors. This is particularly true for the patient group consisting of patients with renal failure in combination with hypertension. The renal protective effect and the impact on mortality are of extraordinary importance and may be class effects. In the context of cardiovascular disease ACE-inhibitors decrease mortality in patients with cardiac insufficiency after myocardial infarction. It remains to be established if this effect can be obtained in other patient groups at high risk. One important feature in obtaining such an effect may be related to their neutral metabolic effects, not worsening insulin resistance and glucose tolerance.

References


Editor's note

Please see also the article by D. Fliser et al. (on pp. 643-647 in this issue).

Acute renal failure in glomerular bleeding: a puzzling phenomenon

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In glomerulonephritis, renal failure usually derives from obliteration of the glomerular tuft with diminution of the effective filtration surface, and abnormal balance of vasomotor resistance of the glomerular afferent and efferent arterioles. In addition, intrarenal vasculitis and immune-mediated tubulo-interstitial disease may contribute to the deterioration of kidney function. Yet another mechanism for the sudden decline in kidney function during glomerulonephritis could be intraluminal obstruction by red blood cells or products of glomerular inflammation.

Acute tubular injury is now recognized as a cause of rapid deterioration in kidney function during acute glomerulonephritis. Most cases have been encountered in association with IgA nephropathy, where bouts of gross hematuria often herald a transient decline in kidney function [1]. In the present issue of Nephrology Dialysis Transplantation, Fogazzi et al. [2] describes seven patients with acute glomerulonephritis (including IgA nephropathy, post-infectious and pauci-immune glomerulonephritis), who developed reversible acute renal failure, out of proportion to the degree of glomerular disease. Features common to these patients and previous case reports are: gross hematuria, persisting for several days or weeks prior to the deterioration in renal function and morphological evidence for tubulo-interstitial disease on the kidney biopsy. The latter revealed acute tubular necrosis, interstitial edema, hemorrhage, erythropagocytosis by tubular cells with intracellular accumulation of hemosiderin and inflammatory reaction. Failure to identify Tamm-Horsfall protein (produced by distal nephrons) in glomeruli is offered by the authors as evidence against tubular obstruction playing an important role in the deterioration of renal function.

What could be the mechanisms for tubular damage...