A diabetic patient with renal impairment

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A 60-year-old housewife who had been diagnosed as suffering from type 2 diabetes mellitus and hypertension for many years was being followed-up at a general outpatient clinic. In April 2003, the patient's blood urea level was found to have increased to 10.6 mmol/L and the serum creatinine was 131 µmol/L (Table), indicating that renal function was significantly impaired. The patient's estimated glomerular filtration rate (eGFR), calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study formula, was 37 mL/minute. By August 2004, the serum creatinine level had increased further to 187 µmol/L, while her eGFR had declined to 25 mL/minute. The patient was diagnosed with relatively advanced diabetic nephropathy, but her medications remained unchanged, namely metoprolol (Betaloc), indapamide (Natrilix), metformin, and glibenclamide (glyburide, Daonil).

Table. Biochemical results

	03/04/03	08/04
Na+	141	142
K+	5.1	6.0
Urea	10.6	18.2
Creatinine	131	187
FBG	6.5	5.8
HbA1c	6.9	7.0
TC	5.1	5.3
TG	1.4	1.4

(FBG = fasting blood glucose, HbA1c = glycosylated haemoglobin, TC = total cholesterol, TG = triglycerides).

Unless treated appropriately, renal impairment progresses to end-stage renal disease (ESRD), the incidence of which is increasing worldwide, together with corresponding increases in the risk of morbidity and mortality [1]. The second leading cause of ESRD in developed countries such as the USA, hypertension is also an important contributor to diabetic renal disease – the leading cause of ESRD – with complex interactions existing between hypertension and renal disease [2]. In addition, compared to those with hypertension alone, the risk of ESRD is five to six times higher in patients with co-existing diabetes and hypertension, who also have an additional risk of cardiovascular disease [3,4].

For the present case, the most important aspect of treatment was therefore to prevent or delay the progression of renal deterioration to ESRD. This can be achieved with good early control of blood sugar concentrations. In the United Kingdom Prospective Diabetes Study (UKPDS), for example, reducing the glycosylated haemoglobin (HbA1c) concentration from 7.9% to 7.0% reduced the risk of microalbuminuria by 11% and that of proteinuria by 3.5% over 12 years, due to partial reversal of glomerular hyperfiltration [5].

Effective early control of elevated blood pressure levels is also important, in particular through the use of anti-hypertensive agents that block the renin-angiotensin-aldosterone system (RAS), such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs). Accumulating evidence suggests that, in addition to their proven anti-hypertensive efficacy, ACE inhibitors and ARBs are effective in preventing or delaying the progression of microalbuminuria and hence progression to overt nephropathy and delaying the onset of ESRD in patients with renal impairment, with these beneficial renoprotective effects having been seen in patients with and without diabetes and in hypertensive and normotensive patients. Agents that block the RAS should therefore be considered as the first choice in hypertension and diabetes, as they provide enhanced renoprotection compared with other anti-hypertensive classes, such as the beta-blockers and calcium antagonists [6].

In view of the present patient's severe renal impairment, cessation of metformin was necessary, as there is a small but significant risk of potentially fatal lactic acidosis associated with the use metformin in renal failure patients. The use of glibenclamide (glyburide) was also considered inappropriate, as it is a long-acting drug and there would be accumulation in patients with renal failure, such as the present case, with resulting hypoglycaemia. The patient's diabetic condition was treated with glyclazide (Diamicron), a short-acting sulphonylurea, in combination with rosiglitazone (Avandia). A member of the thiazolinedione (TZD) class of drugs, rosiglitazone acts as an insulin sensitizer with no danger of lactic acidosis.

Insulin-sensitizing agents such as rosiglitazone are most suited for use early in the course of diabetes, when there is remaining pancreatic beta-cell function. For example, in the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) study, the rate of patients with impaired glucose tolerance (IGT)

converting to new onset diabetes was reduced by 60% with rosiglitazone versus placebo [7]. Insulin sensitizers also delay disease progression after diagnosis. In A Diabetes Outcomes Progression Trial (ADOPT), rosiglitazone significantly delayed the loss of glycaemic control compared with metformin and glibenclamide in 4,360 recently diagnosed type 2 diabetes patients, again demonstrating the benefits of early intervention with rosiglitazone [8].

Combination treatment with rosiglitazone and a sulphonylurea can significantly improve glycaemic control in type 2 diabetic patients who are inadequately controlled with sulphonylurea alone. In a Chinese double-blind, randomized controlled clinical trial to evaluate the efficacy and safety of low-dose rosiglitazone combined with sulphonylurea therapy in type 2 diabetic patients inadequately controlled with sulphonylurea alone, patients were treated with 4 mg rosiglitazone once daily plus sulphonylurea (test group) or 0.5 g metformin twice daily plus sulphonylurea as controls for 12 weeks [9].

Mean levels of HbA1c decreased by 1.09% and 0.95% in the test group (n=102) and controls (n=96), respectively. Fasting and postprandial plasma glucose levels in the test group decreased by 25.0% and 35.6%, respectively, and in controls decreased by 17.7% and 23.8% versus baseline (both P<0.01).

In view of the present patient's diabetic nephropathy, the use of an ACE inhibitor or an ARB was also indicated, so she was started on treatment with the ACE inhibitor enalapril 10 mg/day in place of the metoprolol, with good control of blood pressure being achieved. The patient is presently being followed up every 2 months. She remains well and her diabetes has been stabilized. While the patient's renal function is not improving, there is no indication of progression to ESRD. However, without the change in her treatment regimen, the patient would by now have been on dialysis.

References

1. Weening JJ. Advancing nephrology around the globe: an invitation to contribute. *J Am Soc Nephrol* 2004;15:2761–62.
2. Chobanian AV, et al and the National High Blood Pressure Education Program Coordinating Committee: the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report. *J Am Med Assoc* 2003;289:2560–72.
3. Nelson RG, et al. Kidney diseases in diabetes. In: National Diabetes Data Group (eds). Diabetes in America, 2nd Ed. NIH Publication No 95-1468. US Department of Health and Social Services, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; Bethesda, MD, 1995;349–400.
4. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2005;28(Suppl 1):S4–S36.
5. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 1998;352:837–53.
6. Karalliedde J, Viberti G. Evidence for renal protection by blockade of the rennin-angiotensin-aldosterone system in hypertension and diabetes. *J Hum Hypertens* 2006;20:239–53.
7. The DREAM Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. *Lancet* 2006;368:1096–105.
8. Kahn SE, et al. Glycemic durability of rosiglitazone, metformin and glyburide monotherapy. N Engl J Med 2006;355:2427–43.
9. Wang J, et al. Effect of addition of low-dose rosiglitazone to sulphonylurea. *Chinese Med J* 2003;116:785–77.

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QUESTIONS

Please indicate whether the following statements are true or false

1. Diabetic renal disease is the leading cause of ESRD.
2. In one study, reducing the HbA1c concentration from 7.9% to 7.0% reduced the risk of microalbuminuria by 21%.
3. In the DREAM study, the rate of patients with IGT converting to new onset diabetes was reduced by 60% with rosiglitazone versus placebo.
4. Rosiglitazone acts as an insulin sensitizer but there is danger of lactic acidosis.

ANSWER FORM

1 ☐ 3 ☐
2 ☐ 4 ☐

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