THE EFFECT OF CONTINUOUS SUBCUTANEOUS INSULIN INFUSION ON RENAL FUNCTION IN TYPE I DIABETIC PATIENTS WITH AND WITHOUT PROTEINURIA

E van Ballegooie, P E de Jong, A J M Donker, W J Sluiter

University Hospital, Groningen, The Netherlands

Summary

The effect of continuous subcutaneous insulin infusion on renal function was studied in 12 patients with insulin-dependent diabetes mellitus. Serum creatinine was <110µmol/L in all patients. Total urinary protein excretion was less than 250mg/24hr in seven patients (group I) and exceeded 0.5g/24hr in five (group II). Initial glomerular filtration rate was higher in group I compared with group II: 136.0 ± 8.5ml/min versus 103.2 ± 4.6ml/min (mean ± SEM; p <0.02). After one to three months pump therapy glomerular filtration rate decreased in both groups. It remained stable during 32–36 months in group I (126.3 ± 6.1, and 127.9 ± 7.7ml/min, respectively) but deteriorated in group II (98.6 ± 4.4, and 60.0 ± 6.8ml/min, respectively; p <0.01 compared with group I).

These results indicate that strict blood glucose control with continuous subcutaneous insulin infusion does not prevent deterioration of renal function in type I diabetic patients with clinical proteinuria. This suggests that other factors than metabolic control are involved in the course of diabetic nephropathy;

Introduction

The occurrence of clinical nephropathy is a poor prognostic sign in patients with insulin-dependent (type I) diabetes mellitus. Without renal support treatment approximately 50 per cent of these patients die within seven years of the onset of persistent proteinuria (>0.5g/24hr) [1]. Although the factors responsible for the initiation and progression of diabetic nephropathy in man are largely unknown poor glycaemic control is associated with an increased risk [2], suggesting a potential beneficial effect of strict metabolic control in preventing deterioration of renal function. We studied the influence of long-term treatment with continuous subcutaneous insulin infusion (CSII) on renal function in 12 type I diabetic patients with and without proteinuria.
Patients and methods

Twelve non-obese, C-peptide negative diabetic patients were treated with CSII for 32–36 months. Their mean age was 31.4 years (range, 23–58 years); the mean duration of diabetes was 17.2 years (range, 4–46 years). All had developed diabetes before age 30. None of the patients had urinary tract infections, a history of non-diabetic renal disease, or signs of heart failure. One patient was adequately treated with a thiazide diuretic because of mild hypertension. Serum creatinine was <110μmol/L in all patients. Total urinary protein excretion was less than 250mg/24hr in seven patients (group I) and exceeded 0.5g/24hr in five (group II).

CSII was performed with either a Mill Hill Infuser, model 1001 AM or HM, or an Auto-Syringe infusion pump, model AS6C.

All patients made 24 hour blood glucose profiles (8 capillary samples) every three to six weeks to assess the degree of glycaemic control.

Glycosylated haemoglobin (HbA₁) was measured every three to six weeks by a colorimetric method [3] (normal range 6–8.5%).

Home blood glucose monitoring was performed three to eight times daily. Individual algorithms were made to ease adjustment of the insulin dose. Renal function studies were performed just before the start of CSII, and after one to three months and 32 to 36 months, respectively.

Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were measured simultaneously using a constant infusion of ¹³¹I-hippuran and ¹²⁵I-iothalamate, respectively [4]. Results were expressed as values per 1.73m² body surface area.

Wilcoxon’s rank sum test and signed rank test for paired differences were used for statistical analysis. Results are reported as mean ± SEM.

Results

During conventional treatment mean GFR and ERPF of both groups were 122.3 ± 6.8 and 560.2 ± 24.8ml/min, respectively. Initial GFR was higher in group I compared with group II (136.5 ± 8.5 and 103.2 ± 4.6ml/min, respectively; p<0.02). ERPF similarly was higher in group I (582.0 ± 37.0 versus 529.6 ± 32.8ml/min, respectively). After the start of CSII mean blood glucose fell from 13.0 ± 0.4 to 6.1 ± 0.4mmol/L (p<0.01). Glycosylated haemoglobin fell from 12.0 ± 0.05 per cent to 8.2 ± 0.2 per cent (p<0.01). The improvement in glycaemic control was similar in group I and group II.

After one to three months CSII mean group GFR and ERPF had decreased to 114.7 ± 6.1ml/min (p<0.05) and 531.3 ± 22.6ml/min (n.s.), respectively. These changes were similar in both groups. Thirty-two to 36 months after the start of CSII GFR and ERPF had remained stable in group I (127.9 ± 7.7ml/min and 536.5 ± 39.4ml/min, respectively; not significant compared with pre-CSII values), but had deteriorated in group II (60.8 ± 6.8ml/min and 331.6 ± 25.8ml/min, respectively i.e. a reduction by 42 per cent and 37 per cent compared with pre-CSII values; p<0.01 compared with group I). There were no significant changes in blood pressure in both groups during the study period.
Discussion

The introduction of insulin infusion pumps brought about the hope that long-term maintenance of (near) normoglycaemia could slow, arrest, or perhaps reverse renal abnormalities in patients with established clinical diabetic nephropathy. This and a similar study, however, show that deterioration of renal function still occurs in type I diabetic patients with clinical proteinuria despite strict blood glucose control [5]. The variable clinical course of diabetic nephropathy and the absence of a control group make it difficult to say whether the progression was less severe than could be expected with unchanged conventional treatment. The rates of decline of GFR, however, show close resemblance with those reported for conventionally treated diabetic patients with proteinuria [6].

These and similar findings by other investigators raise the question whether there is a stage of glomerular damage beyond which the decline of renal function becomes an autonomous process, little or not influenced by the quality of glycaemic control. Compensatory intrarenal haemodynamic changes i.e. single nephron hyperfiltration seem to be a reasonable explanation for this self-perpetuating deterioration [7]. However, it could be that at the clinically overt nephropathic stage additional measures like protein restriction and/or antiplatelet aggregating agents are necessary to lower intra-glomerular pressure in order to influence the progression to renal insufficiency. Whether the process of glomerular damage is initiated by the commonly found hyperfiltration, as has been suggested by some investigators, is still unclear. The finding that most of our patients in group I still had no signs of clinical nephropathy despite long-standing supranormal GFR indicates that other factors play a role in this process. Whether correction of the elevated GFR is useful in preventing the development of proteinuria remains to be established.

References

2. Pirart J. Diabetes Care 1978; 1: 166