Long term correction of hyperglycaemia and progression of renal failure in insulin dependent diabetes

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Abstract

The effect of long term correction of hyperglycaemia on the rate of deterioration of renal function was studied in six insulin dependent diabetics with proteinuria due to diabetic nephropathy. After a planned run in observation period of 10 to 24 months patients entered a programme of continuous subcutaneous insulin infusion for up to 24 months. Glycaemic control was promptly and significantly improved and optimal glycaemic values sustained throughout the study. Blood pressure was maintained stable. A control group of six nephropathic diabetics was studied receiving conventional insulin injection treatment but also with blood pressure control over the same period.

Despite greatly improved metabolic control in the infusion treated group no significant change in the rate of decline of glomerular filtration rate could be shown, the plasma creatinine concentrations continued to increase, and the fractional clearance of albumin and IgG rose progressively, indicating progression of glomerular damage. The conventionally treated control group behaved similarly. In a single patient receiving the continuous infusion the rate of decline of the glomerular filtration rate slowed considerably, suggesting that the response to strict diabetic control may differ in some patients.

These findings suggest that by the time glomerular function has started to fail in diabetic nephropathy the process culminating in end stage renal failure has become self perpetuating and is little influenced by the degree of metabolic control. A new definition of potential clinical diabetic nephropathy is proposed that will permit identification of patients at risk and earlier intervention by glycaemic correction in an attempt to arrest diabetic renal disease.

Introduction

The appearance of Albustix positive clinical proteinuria—that is, total urinary protein excretion exceeding about 0.5 g/24 h—in insulin dependent diabetes signals the onset of clinical diabetic nephropathy, defined by a progressive decline of glomerular function to end stage renal failure.¹⁻³ Without renal support treatment the mean survival after development of clinical proteinuria is about seven years.⁴ Decline of renal function during ordinary treatment with insulin is relentlessly progressive,³ though careful control of the blood pressure may slow the decline of the glomerular filtration rate in some cases.⁵

Strict control of glycaemic values with insulin improves morphological, histological, and hyperfunctional renal changes caused by experimentally induced diabetes in rats⁶ as well as

certain early abnormalities in the kidneys of patients with diabetes.⁷⁻¹⁰ Despite histological changes resembling those in man, animals do not develop clinical nephropathy and renal failure.¹¹ In preliminary uncontrolled studies in patients, maintaining near normal blood glucose concentrations did not reverse clinical proteinuria¹² or arrest the rise of serum creatinine values in two diabetics with renal failure¹³; no controlled study of the effect of long periods of greatly improved metabolic control on the progression of established diabetic nephropathy in man has been reported. The introduction of continuous subcutaneous insulin infusion made it possible to achieve and maintain near normal glycaemic values in ambulant diabetics for long periods.¹⁴ We have investigated the effect of long term (up to two years) strict glycaemic control with that treatment on the rate of deterioration of renal function in a group of insulin dependent diabetic patients with established clinical diabetic nephropathy.

Patients and methods

Six longstanding insulin dependent diabetics (table I) with clinical proteinuria and well established retinopathy were recruited for the study, which was approved by the hospital's ethical committee. In all cases the proteinuria had appeared more than 10 years after the diagnosis of diabetes and had been persistent for at least one year before the study. There was no clinical or biochemical evidence of non-diabetic renal disease; kidney biopsies in two patients showed diabetic changes only. During a non-intervention baseline period of 10 to 24 months (mean $16.8 \pm \text{SD } 5.9$) the rate of decline of the glomerular filtration rate was established for each patient. They were then switched from conventional injection treatment to continuous subcutaneous insulin infusion and followed up for a further 12 to 24 months (mean $20.5 \pm \text{SD } 4.8$).

A control group of six proteinuric insulin dependent diabetics (table I) closely comparable to the study group in durations of diabetes and persistent proteinuria, blood pressure, and male preponderance were studied over similar run in periods (7-25 months; mean $16.9 \pm \text{SD } 7.2$) to establish rates of decline of the glomerular filtration rate but were then continued with conventional treatment and followed up for 11.0 to 26.5 months (mean $18.2 \pm \text{SD } 6.2$).

Urinary tract infection, monitored by frequent urine culture, recurred three times in a patient allocated to receive the infusion and twice in a control patient at the beginning of the run in period. All episodes were treated with antibiotics and the patient in the infusion group (case 4) left on low dose long term antibiotic treatment, which maintained the urine sterile. All other patients had consistently negative urine cultures throughout. Antihypertensive treatment was started if systolic or diastolic pressures were 160 or 100 mm Hg or more respectively on two consecutive visits. At least three standard assessments were made during the run in period at variable intervals (but never less than three months apart) and regularly at three and six monthly intervals (see figs 2 and 3) during the experimental period. During a 24 hour stay in a metabolic ward a blood glucose profile (glucose oxidase method, Analox GM 6) was constructed and the 24 hour urine output collected.

The following were measured at each visit: fasting glycosylated haemoglobin concentration,¹⁵ glomerular filtration rate (clearance of ⁵¹Cr EDTA),¹⁶ plasma and urine concentrations of creatinine (determined by a reaction rate method, LKB Ultralab System 2086 Reaction Rate Analyser), β_2 -microglobulin (Phadebas, β_2 -Microtest, Pharmacia Diagnostics AB, Uppsala, Sweden), IgG (Immunofluor, Bio-Rad Lab, Richmond, California 94804), and albumin.¹⁷ Blood pressure was measured sitting and lying with a mercury sphygmomanometer by a trained observer at least four times a day. Plasma creatinine concentration and glomerular filtration rate (⁵¹Cr EDTA) were measured in

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TABLE 1—Clinical features of patients at entry into study

Treatment group	Sex	Mean age in years (range)	Mean duration of diabetes in years (range)	Mean duration of persistent proteinuria in years (range)	Mean total urinary protein excretion (g/24 h) (range)	Other complications*	Mean blood pressure† (mm Hg) (range)
Continuous insulin infusion	4 M, 2 F	47.0 (32–58)	21.6 (14–28)	3.3 (1–9)	2.4 (0.61–5.4)	4 PR, 2 BR, 6 PN, 4 AN	106.2 (93–127)
Control	5 M, 1 F	39.8 (25–57)	19.2 (14–26)	2.8 (1–7)	4.1 (0.55–11.0)	5 PR, 1 BR, 4 PN, 3 AN	107.6 (97–127)

*PR = Proliferative retinopathy. BR = Background retinopathy. PN = Peripheral neuropathy. AN = Autonomic neuropathy.

†Mean blood pressure calculated as sum of diastolic pressure plus one third of pulse pressure.

all from recruitment to the study; other variables were measured on at least three successive occasions (roughly three to four months apart) before the start of the experimental period. Fractional urinary clearance of a protein was calculated by dividing its clearance by the glomerular filtration rate, corrected to 1.73 m² body surface area.

Statistical evaluation was by analysis of covariance for comparison of slopes of regression lines and Student's *t* test for paired and unpaired samples.

Results

There was a significant and sustained decline in glycosylated haemoglobin values after changing to continuous subcutaneous insulin infusion, the mean value falling to around 9.5% (normal range in our laboratory 5.5–8.5%). No significant change was seen in the six patients who continued with conventional treatment (fig 1). Plasma glucose profiles were also greatly improved during infusional treatment. Table II shows the mean ($\pm$ SD) of paired plasma glucose determinations during the run in and experimental periods in the six patients treated by continuous infusion.

Table III shows the mean blood pressures (calculated as the sum of diastolic plus one third of pulse pressure) before and after beginning the infusion. Pressures were maintained at or below run in values. In the control group the overall mean blood pressure was 106.7 $\pm$ SD 6.2 mm Hg in the run in and 105.1 $\pm$ 7.4 mm Hg in the experimental period (difference not significant). Raised arterial pressures were treated equally effectively in both groups. Four patients in each group were receiving hypotensive treatment with diuretics and selective beta-blockers together in some case with vasodilators. Individual glomerular filtration rates with the slopes of the calculated regression of rate with time in the six patients treated by infusion are shown in fig 2. No statistically significant difference was found between the slopes of the regression lines before or after beginning infusional treatment. In case 4, however, the rate of decline changed from 2.4 ml/min/month during conventional treatment to 0.2 ml/min/month after switching to the infusion. The rapid decline during conventional treatment

FIG 1—Mean ($\pm$ SEM) glycosylated haemoglobin (HbA_{1c}) values before (●) and after (○) beginning continuous subcutaneous insulin infusion (arrow) in six insulin dependent diabetics with clinical nephropathy, and in six control nephropathic diabetics (■) who continued with conventional insulin treatment. Numbers in parentheses indicate number of subjects when different from six.

**p* < 0.05 compared with run in (baseline) values.

TABLE IV—Mean ($\pm$ SEM) rate of decline of glomerular filtration rate in six patients treated by infusion and six controls during run in and experimental periods

Treatment group	Decline in glomerular filtration rate (ml/min/month)		Significance
	Run in period	Experimental period	
Continuous insulin infusion	1.35 $\pm$ 0.31	0.69 $\pm$ 0.13	NS
Control	1.24 $\pm$ 0.15	0.91 $\pm$ 0.33	NS
Significance	NS	NS	

NS = Not significant.

TABLE II—Mean ($\pm$ SD) plasma glucose concentrations in six insulin dependent diabetics with clinical nephropathy before and after beginning continuous insulin infusion

Case No	Plasma glucose (mmol/l)		p Value
	Run in period	Experimental period	
1	11.4 $\pm$ 7.4	7.8 $\pm$ 2.8	< 0.005
2	10.7 $\pm$ 4.5	6.5 $\pm$ 2.4	< 0.001
3	11.8 $\pm$ 4.5	7.3 $\pm$ 2.8	< 0.001
4	10.8 $\pm$ 6.8	6.2 $\pm$ 2.3	< 0.001
5	16.4 $\pm$ 8.0	6.6 $\pm$ 2.5	< 0.001
6	10.6 $\pm$ 4.8	5.6 $\pm$ 2.0	< 0.001

Conversion: SI to traditional units—Glucose: 1 mmol/l $\approx$ 18 mg/100 ml.

TABLE III—Mean ($\pm$ SD) of mean blood pressures (diastolic plus one third of pulse pressure) in six insulin dependent diabetics with clinical nephropathy before (only last 12 months of run in period shown) and after beginning continuous subcutaneous insulin infusion

	Run in period (months)			Start of infusion (time zero)	Experimental period (months)					
	-12	-6	-3		3	6	12	15*	18*	24†
Blood pressure (mm Hg):										
Mean	106.8	108.5	103.6	107.3	109.3	100.7	100.7	102.6	105.4	93.3
SD	13.4	14.8	15.3	15.0	12.5	7.3	8.1	2.5	9.1	5.0

*Value in five subjects only.

†Value in three subjects only.

treatment periods (-0.635 ml/min/month) were wide, ranging from 0.24 to -1.51 ml/min/month; hence there remains the possibility that a slowing of deterioration might have been missed because of small numbers.

In all but one of the patients in the infusional group the plasma creatinine concentration increased during treatment (fig 3); in case 4 it fluctuated in parallel with the changes in glomerular filtration rate. Mean plasma β_2 -microglobulin concentration increased similarly and was unaffected by the switch to infusion, again with fluctuating values in case 4.

Figure 4 shows the mean fractional clearance of albumin and IgG before and after beginning infusional insulin. All patients behaved similarly and there was a progressive and statistically significant increase in the fractional clearance of these proteins during treatment.

One of the two kidney biopsies was performed in case 4 because of anomalous behaviour 16 months after changing to the infusion. It showed only classical diabetic lesions with Kimmelsteil-Wilson nodules.

Discussion

In experimentally diabetic rats correcting hyperglycaemia prevents renal histological lesions^{18, 19} and reverses the albuminuria and some of the morphological abnormalities once they are established.⁶ In diabetic patients, as in the animal model, the early abnormalities of hyperfiltration, microproteinuria, and nephromegaly are reversible by strict glycaemic control,^{7, 10, 20} but no data are available in man concerning the reversibility of the early histological changes. Here, however, the resemblance ends. Features of advanced nephropathy and renal failure comparable to the clinical phase in man do not develop in diabetic rats.¹¹

FIG 2—Individual glomerular filtration rates before (●) and after (○) beginning continuous subcutaneous insulin infusion (arrow) in six insulin dependent diabetics with clinical nephropathy. Rate of decline calculated from slopes of regression lines; individual slopes, before and after infusion, compared by analysis of covariance.

FIG 3—Individual plasma creatinine concentrations ($\mu\text{mol/l}$) before (●; last 12 months of run in period shown) and after (○) beginning continuous subcutaneous insulin infusion (arrow) in six insulin dependent diabetics with clinical nephropathy.

Conversion: SI to traditional units—Creatinine: $1 \mu\text{mol/l} \approx 0.01 \text{ mg/100 ml}$.

FIG 4—Mean ($\pm$ SEM) fractional clearance (log scale) of albumin (●---●) and IgG (▲---▲) in six insulin dependent diabetics with clinical nephropathy before (last six months of run in period ● ▲) and after (○ △) beginning continuous subcutaneous insulin infusion (arrow). Numbers in parentheses as in fig 1.

* $p < 0.05$, ** $p < 0.02$ compared with run in (baseline) values.

This evidence has led to the suggestion that established clinical nephropathy in patients with diabetes may be slowed, arrested, or reversed by substantial and prolonged improvement of glycaemic control. Since raised arterial pressure also contributes to deterioration of renal function in diabetic nephropathy^{1, 5} efforts were made, successfully, to maintain normal blood pressure throughout the study in both the infusion treated and control patients to reduce the confounding effect in assessing response to glycaemic control. In this small trial we were unable

to find a statistically significant beneficial effect of metabolic correction on deterioration of renal function. From our data, however, we cannot conclude with certainty that improved control makes no difference. Glomerular filtration rate continued to fall, plasma concentrations of creatinine and β_2 -microglobulin to rise, and the fractional clearance of albumin and IgG to increase, indicating continuing deterioration and resembling the progression in nephropathic diabetics receiving conventional insulin injection treatment.^{3 21} In some patients switched to the infusion the rate of rise in plasma creatinine concentrations appeared to accelerate, but this probably reflected the curvilinear asymptotic relation between plasma creatinine concentration and glomerular filtration rate^{3 21} in renal failure in general; it is unlikely that improved metabolic control accelerated loss of renal function.

In only one of the infusion treated patients (case 4) did improved control appear to slow considerably the rate of fall of filtration rate and rise of plasma creatinine concentration. Investigation including renal biopsy brought no non-diabetic renal disease to light and we have no ready explanation for her anomalous behaviour. Her metabolic response to infusional insulin was neither notably better nor notably worse than the other infusion treated patients. We must allow that the response of advanced nephropathy to metabolic correction of diabetes may differ from patient to patient; though continuing deterioration of renal function is the rule, exceptions may exist. The factors determining the rate of decline of glomerular filtration rate are poorly understood, but untreated urinary tract infection probably accelerates deterioration. In case 4 urinary tract infection was eradicated at the beginning of the study and was therefore unlikely to be responsible for the patient's fluctuating course.

Our failure to detect a renal response to the near normal glycaemic values induced by infusional insulin in these patients with diabetic nephropathy may be interpreted in different ways. The degree of glycaemic control we achieved with the infusion, though greatly improved, might still not have been good enough. The quality of glycaemic control was at least as good as that known to reverse the early renal changes in diabetic man and animals^{6 8 9 10 22 23} and approached what we could consider to be the optimal response of these patients to the treatment. Glycosylated haemoglobin concentrations settled slightly above the upper limit of our normal range, but in uraemic patients the increased proportion of carbamylated haemoglobin is indistinguishable from glycohaemoglobin using the microcolumn method.²⁴ The treatment period may have been inadequate; longer periods of improved control may be necessary to affect processes that take many years to develop, even though one would expect an effect after one to two years of infusional treatment. The failure of metabolic correction to influence progressive renal deterioration is probably explained by the fact that by the time renal function is deteriorating measurably the nephropathic process has become self generating and independent of the diabetic metabolic abnormality which initiated it. When the kidney is seriously damaged further progressive deterioration of renal function loss to end stage renal failure is common to many nephropathic processes; strong experimental evidence has been presented that the compensatory hyperfiltration process in surviving nephrons after major nephron loss is ultimately self destructive.²⁵

The important question arises whether there is a degree of diabetic renal damage beyond which this self generating process begins to operate—that is, a point of diabetic no return for the kidney, as appears to be the case in proliferative diabetic retinopathy.^{12 26} A major problem in answering this question is the difficulty in quantifying renal damage in the diabetic in the phase before evident loss of renal function. At present repeated renal biopsy with its ethical and interpretative problems seems to offer the only approach; the development of less invasive, reliable methods for quantifying “total residual renal functional capacity” and monitoring the effect of treatment on it would be of great value.

Our findings strongly suggest that by the time proteinuria exceeds 0.5 g/24 h (Albustix positive) the chance of affecting the deterioration of renal function by correcting the glycaemic value has passed. Clinical diabetic nephropathy is currently defined by the appearance of Albustix positive proteinuria. Recent reports^{27 28} indicate that by using more sensitive measures of albuminuria^{17 29} diabetic patients at risk of nephropathy may be identified earlier, when renal abnormalities may still be influenced by improved diabetic control.^{8 9 20} These lesser degrees of urinary albumin hyperexcretion may be reduced or normalised, at least over the short term, by metabolic correction.^{8 9} Albuminuria is a far better indicator of diabetic glomerular damage than urinary excretion of total proteins.^{20 30} The introduction of a new definition of potential clinical diabetic nephropathy to include diabetics with a urinary albumin excretion between 50 and 200 mg/24 h²⁷ might therefore prove useful. This degree of microalbuminuria appears to be a marker for that proportion of insulin dependent diabetics susceptible to renal failure. It is to these patients that the most vigorous therapeutic efforts should be directed and in them that the effectiveness of glycaemic near normalisation on the development of clinical diabetic nephropathy should be tested.

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SHORT REPORTS

Successful completed pregnancy in a patient maintained on home parenteral nutrition

Total parenteral nutrition is an accepted treatment for intestinal failure resulting from conditions such as short bowel or extensive Crohn's disease.¹ The effect of total parenteral nutrition on human pregnancy is not well documented. Heller² cites hyperemesis gravidarum as an indication for short-term total parenteral nutrition but considers that lipid emulsions are contraindicated because of effects on the placenta. There have been several isolated reports of total parenteral nutrition in the third trimester, either in hospital^{3,4} or at home,⁵ but we do not know of any previous instance of a pregnancy maintained from conception to delivery in a patient nourished entirely by parenteral nutrition.

Case report

A 31 year old woman was referred to the nutrition unit at Hope Hospital, Salford, in June 1981 with a six year history of severe abdominal pain whenever she ate. In addition she was amenorrhoeic. Barium studies showed extensive small-bowel Crohn's disease unsuitable for surgery. Intensive medical treatment had failed to prevent frequent admissions to hospital. Severe weight loss (down to a minimum of 28 kg) and weakness resulted in her being confined to a wheelchair. Total parenteral nutrition was started with considerable symptomatic relief and pronounced weight gain. She was referred to our unit for training in home parenteral nutrition.

On admission she weighed 41.8 kg (76% of ideal weight for height). Resting energy expenditure was measured by indirect calorimetry using a Beckman metabolic cart. A Broviac catheter was positioned in the superior vena cava. The patient was trained to administer her own parenteral nutrition as a nighttime infusion. Her initial daily regimen provided 14 g nitrogen (Synthamin, Travenol Laboratories) and 7.5 MJ (1800 kcal), half as dextrose and half as lipid emulsion (Intralipid, KabiVitrum). Trace elements and vitamins were added to the infusate.

The patient was discharged in August 1981, to continue home parenteral nutrition: her weight at discharge was 53.4 kg (97% of ideal). Iron and folate were given by mouth, and vitamin B₁₂ by monthly intramuscular injections. She remained free of pain provided she did not eat at all and restricted her fluid intake. She was able to lead an essentially normal life at home and care for her family unaided. The amenorrhoea persisted.

By October 1981, her weight had risen to 57 kg (104% of ideal for her height). This was thought to be due to excessive energy provision, therefore her energy intake was reduced to 4.2 MJ (1000 kcal) per day. In March 1982, the patient and her medical advisors realised she was pregnant. Ultrasound scan confirmed a normal fetus: she had conceived about mid October 1981. The patient now weighed 58 kg and had a resting energy expenditure of 6 MJ (1450 kcal) per day. Energy intake was increased to 10 MJ (2400 kcal) per day, with lipid emulsion providing about 18% of the energy. The pregnancy progressed normally, monitored by weekly assessment of maternal weight gain, ultrasound, and serial estimations of plasma oestriol, human placental lactogen, and urate concentrations (table). In the 37th week she had a normal vaginal delivery of a healthy girl, weighing 2.62 kg. The head circumference and length were on the 50th centile for 37 weeks and the 90th

Measurements recorded during monitoring of pregnancy

Gestation (wks)*	Patient's weight (kg)	Plasma oestriol (nmol/l)	Plasma human placental lactogen (mg/l)	Plasma urate (mmol/l)
28	58	97		
30	59	113		
32	61	100	5.9	
34	62	104	7.5	0.25
36	62.5	217	6.0	0.33
36½		226	5.1	
37		326	5.8	

*Gestational age assessed by fetal biparietal diameter on ultrasound scan.

Conversion: SI to traditional units—Oestriol: 1 nmol/l ≈ 28.8 ng/100 ml. Urate: 1 mmol/l ≈ 17 mg/100 ml.

centile for 40 weeks. Weight was only about the 20th centile for 37 weeks and below the 10th centile for 40 weeks.

Histological examination of the placenta showed it to be normal with no evidence of lipid thrombi or deposition.

Comment

Patients with Crohn's disease and severe malnutrition are often amenorrhoeic and subfertile. Though home parenteral nutrition was effective in correcting malnutrition and restoring a high quality of life in this case it did not affect the amenorrhoea. Our main problem was a total lack of information on intravenous nutritional requirements in pregnancy. We were able to measure direct the requirements for amino acids and energy, but the need for minerals, trace elements, and vitamins was more difficult to determine. Our ultimate dosage regimen was only marginally different from that given to normal patients during pregnancy.

Despite Heller's assertions² that fat emulsions are contraindicated in pregnancy, neither patient nor baby showed ill effects from administration of lipids. Similarly, Heller's suggestion that intravenous fat emulsion may induce premature labour is not borne out by this case.

The low birth weight of the baby may be a result of inadvertent temporary reduction in energy intake during early pregnancy when an increase would have been more appropriate. Our experience has shown that home parenteral nutrition is capable of maintaining a normal pregnancy from conception to delivery. The patient described spent only four days in hospital (for assessment) throughout her pregnancy.

We thank Dr D Shreeve for referring this patient; Sister G McCannon, Dr I Holbrook, Mrs K Shipley, Dr J Shaffer, Miss C Clark, and the MRC Trauma Unit for their help in managing this case.

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