west of Scotland (Scottish Committee Action on Smoking and Health, personal communication). There are two likely reasons for this difference: firstly, the habit forming nature of cigarette smoking probably makes it easier for the average person to stop drinking rather than to stop smoking, and, secondly, the risks of the fetal alcohol syndrome have been widely publicised, particularly in the west of Scotland.

Little is known about clinical pharmacology during pregnancy. A survey of this type can identify those drugs that are most commonly used, highlighting where further research into safety and efficacy might appropriately be pursued. The limited available knowledge on the disposition of drugs during pregnancy indicates that in some instances, such as the use of anticonvulsants, substantial and clinically important changes require an approach to prescribing quite different from that in non-obstetric practice. A knowledge of those drugs most often used allows direction of research into clinical pharmacokinetics during pregnancy. There is virtually no available information on whether pregnancy influences the effect of drugs, and yet a typical obstetric unit can expect to see an average of two new patients each week who are receiving a drug such as a bronchodilator, β blocker, or anticonvulsant, the effect of which could, theoretically, be influenced by the physiological changes of pregnancy. An additional point to emerge from studies of this type is the question of whether the drugs used were really necessary. This, of course, is a matter not confined to pregnancy, but the lists given earlier suggest that the mother's health would not have been put at risk if some of the more commonly used groups of drugs were withheld.

In conclusion, we have described the pattern of use of drugs in a general obstetric unit in Glasgow during the mid-1980s. Most women did not take drugs or drink alcohol, but the extent of cigarette smoking, the use of self administered analgesics, and the

relatively common administration of drugs clearly not necessary for maternal health are matters worthy of further attention.

We thank Dr C J Bulpitt for advice in planning these studies, Dr M De Swiet for critical review of the manuscript, and the obstetricians at this hospital for allowing us to study their patients.

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(Accepted 11 October 1985)

Intermittent clinical proteinuria and renal function in diabetes: evolution and the effect of glycaemic control

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Abstract

The evolution of renal disease was studied in 12 insulin dependent diabetics selected for intermittent clinical proteinuria. After a run in period during which patients were studied three monthly for at least 12 months members of pairs of patients matched for age and duration of diabetes were allocated either to receive continuous subcutaneous insulin infusion or to continue with their usual conventional insulin injection therapy (controls) and studied three monthly for a further year. Mean (SEM) plasma glucose concentration and glycosylated haemoglobin (HbA_{1c}) value improved significantly in the insulin infusion group (glucose 10.1 (1.0) v 5.3 (0.3) mmol/l (182 (18) v 95 (5) mg/100 ml);

HbA_{1c} 9.6 (0.8) v 7.6 (0.5)%; $p < 0.001$ and $p < 0.005$, run in v experimental periods) but not in the control group. Blood pressure was kept normal throughout.

Glomerular filtration rate fell significantly in the insulin infusion and control groups throughout the study, from mean (SEM) baseline values of 114 (16) and 119 (15) ml/min/1.73 m² to final values of 92 (15) and 95 (13) ml/min/1.73 m² respectively ($p < 0.05$ and $p < 0.01$). The mean rate of decline in glomerular filtration rate did not change significantly in either group (run in v experimental periods: insulin infusion group 1.0 v 0.8 ml/min/month; controls 0.8 v 0.9 ml/min/month). Mean (SEM) plasma creatinine concentration rose slightly in the insulin infusion group only (93 (5) to 107 (11) μ mol/l (1.1 (0.06) to 1.2 (0.1) mg/100 ml), $0.1 > p > 0.05$; controls 94 (6) to 96 (6) μ mol/l (1.1 (0.07) and 1.1 (0.07) mg/100 ml)). The urinary excretion rate of albumin varied widely and unpredictably throughout, while β_2 microglobulin excretion remained normal and unchanged in both groups.

Thus (a) at the stage of intermittent clinical proteinuria when albumin excretion rate is unpredictably variable (breaking through the "clinically positive" threshold only episodically) renal function, though still in the "normal" range, is already declining progressively; and (b) the study failed to show that sustained improvement in mean glycaemia exerts a significant effect on this early deterioration of renal function.

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Introduction

Intermittent clinical (Albustix positive) proteinuria in insulin dependent diabetes mellitus is a phase usually succeeded by persistent proteinuria in the evolution of diabetic nephropathy.^{1,2} The state of glomerular function and its change over time in this phase, however, are largely unknown. Watkins *et al* reviewed renal biopsy samples from 31 proteinuric diabetic patients taken 11 years previously³ in order to determine the course of diabetic renal disease. Two of these patients had experienced no significant decline in renal function (on the basis of serum creatinine estimations) after more than 12 years of intermittent proteinuria and a duration of diabetes of 22 and 23 years. Mogensen described a group of patients with intermittent proteinuria shown by Albustix testing as "nearly always having a highly elevated albumin excretion in the basal situation," with values of albumin excretion ranging from normal at about 6 µg/min to some 200 µg/min.⁴ Their glomerular filtration rates were significantly higher than normal and did not decline over three to four years.⁵ He also concluded that transition from normal albumin excretion to persistent clinical proteinuria occurs rapidly.⁵

In a small group of patients we have made a detailed prospective examination of the relation of intermittent clinical proteinuria to renal function in insulin dependent diabetes mellitus and the effect of glycaemic control.

Patients and methods

We defined intermittent clinical proteinuria as repeated Albustix tests (one plus or more) of sterile urine positive on no more than two consecutive occasions over a period of observation of at least one year during which a minimum of four tests were made. The study was restricted to patients aged

assigned to treatment with continuous subcutaneous insulin infusion and the other to continue unchanged with conventional injection therapy. This was followed by an experimental period of 12 months with assessments every three months. Table I shows the clinical features of the two groups.

TABLE I—Clinical characteristics of patients studied

	Treatment group	
	Conventional insulin injection therapy	Continuous subcutaneous insulin infusion
No of patients	5 M, 1 F	6 M
Mean age (years) (range)	35.8 (26-58)	36.7 (23-55)
Mean duration of diabetes (years) (range)	19.3 (11-28)	22.2 (18-28)
Complications*	3 NPR, 3 PR, 4 PN, 2 AN	3 NPR, 3 PR, 1 PN, 3 AN

*NPR=Non-proliferative retinopathy. PR=Proliferative retinopathy. PN=Peripheral neuropathy. AN=Autonomic neuropathy.

Assessments were made during a 24 hour admission to a metabolic ward, when the following measurements were made: two-hourly plasma glucose profile (Yellow Springs analyser, Yellow Springs, USA); fasting glycosylated haemoglobin (HbA_{1c}) concentration (isoelectric focusing method⁶); glomerular filtration rate (clearance of chromium-51 labelled edetic acid⁷) corrected to 1.73 m² of surface area; plasma creatinine and albumin concentrations; 24 hour urine collection for albumin and β₂ microglobulin excretion rates⁸; microscopy and culture of a clean midstream urine collection. Right brachial arterial pressure was measured by the same observer four times with the patient lying and standing using a standard mercury sphygmomanometer during each visit. Mean arterial pressure was calculated as the sum of the diastolic pressure plus one third of the pulse

FIG 1—Mean (and SEM) plasma glucose concentrations and glycosylated haemoglobin (HbA_{1c}) values in six insulin dependent diabetic patients with intermittent clinical proteinuria before (●—●) and after (○---○) random allocation to receive continuous subcutaneous insulin infusion (CSII) and in six insulin dependent diabetic patients with intermittent clinical proteinuria before (▲—▲) and after (△---△) random allocation to continue with conventional insulin injection therapy (CIT). Horizontal dashed line represents upper limit of normal for HbA_{1c} value (see text).

Compared with CIT: *p<0.02; **p<0.005; ***p<0.001.

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

under 55 with a duration of diabetes of at least 10 years and with ophthalmoscopically evident diabetic retinopathy. Insulin dependent patients who fulfilled these criteria and were without evidence of non-diabetic renal disease were recruited from the diabetic clinics of Guy's Hospital and King's College Hospital, London. All gave informed consent to the study, which was approved by the Guy's Hospital ethical committee.

STUDY DESIGN

After a run in period with assessments every three months for at least a year in order to obtain stable baseline data the patients were paired by closest matching for age, sex, and duration of diabetes. One member was randomly

pressure. The mean of the four measurements was used for calculation. Arterial pressure was maintained below 160/90 mm Hg throughout; two patients in each group received antihypertensive medication. Initiation and long term outpatient follow up of continuous subcutaneous insulin infusion was as described.^{9,10} No dietary change was recommended. Protein intake was similar in the two groups and remained unchanged during the study, being on average 79.8 (SD 20.7) g/day.

Statistical evaluation was by analysis of covariance for comparison of slopes of regression lines and Student's *t* test for paired and unpaired samples. The relation between absolute values of glomerular filtration rate at the beginning and end of the study and changes in rate during the study to absolute values and changes in blood pressure, plasma glucose concentration, HbA_{1c} value, and fractional clearance of albumin were evaluated by univariate regression analysis. Values for albumin and β₂ microglobulin

excretion rates were log transformed because of their skewed distributions. The 95% confidence limits for changes in glomerular filtration rate and albumin excretion were calculated.

Results

Figure 1 shows the mean plasma glucose concentrations and HbA₁ values for both groups during the run in and experimental phases of the study. Some improvement in glycaemic control in patients who continued with their conventional injection therapy was noted during the run in phase. A non-significant fall in mean blood glucose concentration six months after entering the experimental phase was not sustained. In the insulin infusion treated patients the mean plasma glucose concentration at most time points during the experimental phase of the study was significantly lower than that of the control group and approached normoglycaemia. During the experimental phase HbA₁ values were unchanged in the controls but fell significantly in the insulin infusion group, by 12 months entering our normal

range (5.5-7.5%, two standard deviations from the mean of 100 non-diabetic subjects). Figure 2 shows the change with time of the mean glomerular filtration rate values for each group. Although rates were all still in the normal range, there was a significant decline in rates in both the control and insulin infusion groups throughout the entire study (controls 119 (SEM 15) ml/min/1.73 m² to 95 (13) ml/min/1.73 m² (p<0.05); insulin infusion group 114 (SEM 16) ml/min/1.73 m² to 92 (15) ml/min/1.73 m² (p<0.01)). The decline in glomerular filtration rate continued in the infusion group during the experimental period despite the substantial, significant, and sustained fall in mean glycaemia. In the control group the decline in glomerular filtration rate during the experimental phase was 0.9 ml/min/month, hardly differing from the decrement of 0.8 ml/min/month noted during the run in phase. Similarly, a fall in the glomerular filtration rate during the experimental phase of 0.8 ml/min/month did not differ significantly from that of 1.0 ml/min/month in the run in phase in the insulin infusion group. The 95% confidence limits of the mean of the differences between the two treatment periods (insulin infusion group -0.1 ml/min/month; control group +0.5 ml/min/month) ranged from -0.99 to +0.78 ml/min/month (insulin

TABLE II—Glomerular filtration rates (ml/min/1.73 m²) for each patient with intermittent clinical proteinuria at beginning and end of run in and experimental periods of study

Time in months	Cases treated by conventional insulin injection therapy							Cases treated by continuous subcutaneous insulin infusion						
	1	2	3	4	5	6	Mean (SEM)	7	8	9	10	11	12	Mean (SEM)
-12	78	130	99	182	132	95	119 (15)	65	133	99	82	145	162	114 (16)
0	68	117	116	171	111	78	110 (15)	59	126	93	78	145	125	104 (13)
+12	53	98	103	148	101	68	95 (13)	45	111	67	75	149	105	92 (15)

FIG 2—Calculated slopes of mean (and SEM) glomerular filtration rates in patients with intermittent clinical proteinuria before and after random allocation either to receive continuous subcutaneous insulin infusion (CSII) or to continue with conventional insulin injection therapy (CIT). Symbols as in fig 1.

FIG 3—Mean (and SEM) fractional clearances of albumin (log scale) in patients with intermittent clinical proteinuria before and after random allocation to either continuous subcutaneous insulin infusion (CSII) or unchanged conventional insulin injection therapy (CIT). Symbols as in fig 1.

TABLE III—Albumin excretion rates (µg/min) for 12 insulin dependent diabetic patients with intermittent clinical proteinuria studied at three month intervals during run in and experimental phases of study

Case No	Run in period (months)					Experimental period (months)			
	-12	-9	-6	-3	0	3	6	9	12
Conventional insulin injection therapy									
1	57	32	21	19	20	53	25	20	20
2	96	54	83	26	5	64	113	53	52
3	65	94	25	37	7	28	53	37	50
4	6	5	6	10	11	9	13	8	42
5	13	21	12	15	15	8	17	18	20
6	234	232	229	474	459	565	671	760	651
Geometric mean	43	40	30	34	19	40	53	40	55
SD	58	52	40	46	32	62	78	64	71
Continuous subcutaneous insulin infusion									
7	83	109	78	85	24	1123	31	31	17
8	10	19	9	3	6	5	7	9	6
9	73	60	48	44	42	9	18	58	43
10	199	96	32	37	37	21	34	29	15
11	29	16	8	17	9	10	14	35	32
12	5	8	52	5	5	5	4	7	5
Geometric mean	35	34	28	18	15	19	14	22	15
SD	48	36	26	24	14	40	12	18	13

infusion group) and -0.51 to +1.58 ml/min/month (controls). The possibility that a change in the slope of the glomerular filtration rate over time in the infusion group might have been missed because of small numbers cannot entirely be excluded but appears unlikely. Table II shows the individual changes in glomerular filtration rate. No change was recorded in two patients (one in each group) during the 24 months studied. Plasma creatinine concentrations remained within the normal range and did not rise significantly in either group throughout the two years of observation (control group: start 94 (SEM 6) µmol/l (1.1 (0.07) mg/100 ml), end 96 (6) µmol/l (1.1 (0.07) mg/100 ml); insulin infusion group: start 93 (5) µmol/l (1.1 (0.06) mg/100 ml), end 107 (11) µmol/l (1.2 (0.12) mg/100 ml)). The mean fractional clearance of albumin—that is, UV/P divided by glomerular filtration rate, where U=urinary albumin concentration, P=plasma albumin concentration, and V=urine flow—was similar in the two groups and not affected by blood glucose control (fig 3). The albumin excretion rate proved to be widely different at baseline among different subjects, ranging from a normal 7 µg/min to 286 µg/min. Great variability

occurred in each patient throughout the study (table III) without a clear pattern of response to treatment changes. In the control group one patient (case 6) with a record of intermittent Albustix positive testing was Albustix positive at recruitment and continued to show persistent and increasing proteinuria. Four were microalbuminuric (albumin excretion rate $>12 \mu\text{g}/\text{min}$, the mean plus 2 SD of normal people in our laboratory being $12 \mu\text{g}/\text{min}$) on most occasions. One patient had a normal albumin excretion rate in all but two collections. In the insulin infusion group no patient became persistently proteinuric but four were consistently microalbuminuric, even though on one occasion one patient (case 11) had a normal albumin excretion rate and another (case 7) had a rate well into the clinically proteinuric range. Two patients had a normal albumin excretion rate for most of the time. The mean β_2 microglobulin excretion rate (not shown) was normal and unchanged in both groups throughout the study.

The mean blood pressure for both groups was similar at the start of the run in period and was maintained unchanged in both groups throughout the entire study (insulin infusion group: start 99 (SEM 3), end 93 (2) mm Hg; control group: start 98 (3), end 92 (2) mm Hg. At entry to the study there was a significant inverse correlation in all 12 patients between the absolute glomerular filtration rate on the one hand and blood pressure ($r = -0.77$; $p < 0.05$) and fractional clearance of albumin ($r = -0.66$; $p < 0.05$) on the other. Blood pressure and fractional clearance of albumin were significantly positively related to each other ($r = 0.64$; $p < 0.05$). Glomerular filtration rate did not correlate significantly with plasma glucose or HbA_{1c} value, nor did change in glomerular filtration rate over the 24 month study period correlate significantly with change in any of the other variables. Final glomerular filtration rate still correlated inversely with fractional clearance of albumin.

Discussion

This study of 12 selected insulin dependent patients disclosed that renal function, as assessed by the glomerular filtration rate, and though still within the normal range, is already declining progressively at the stage of intermittent clinical proteinuria. The rate of fall in glomerular filtration rate ($\approx 0.9 \text{ ml}/\text{min}/\text{month}$) is comparable in magnitude with that observed during the later stages of diabetic renal failure, when Albustix positive proteinuria has become persistent.⁸ These observations are at variance with reports that renal function does not deteriorate during several years of intermittent proteinuria.^{3,5} Assessment of renal function in earlier work, however, was often based on serum creatinine concentrations and considerable loss of glomerular function may go undetected by this method. A significant rise in serum creatinine concentrations occurs late and only when the glomerular filtration rate has been reduced to about half of normal.¹¹ Only three of our patients had raised glomerular filtration rates at entry to the study; in two of these the rates fell consistently with time and one remained unchanged. This differs from earlier reports that patients with intermittent proteinuria may sustain a high glomerular filtration rate for several years.⁵ It agrees, however, with a more recent report of the loss of glomerular function and progression to clinical proteinuria over 10 years in insulin dependent diabetic patients with microalbuminuria and a high glomerular filtration rate.¹² Although on average renal function declined significantly in both groups, in two patients there was no change in glomerular filtration rate during the 24 month study period. Whether they were behaving differently, or perhaps represented an earlier stage of diabetic nephropathy, remains to be seen.

Many of the albumin excretion rates for individual patients in this study lay in the microalbuminuric range, though, on occasions, falling into the normal range or breaking through the threshold to clinical proteinuria. The reasons for this variability in albumin excretion are unknown and we can only speculate about the mechanisms. A major determinant of transcapillary albumin flux is the transglomerular pressure gradient, itself regulated by both local and systemic factors. Fluctuations in this pressure could well determine fluctuations in the albumin excretion rate, especially as the glomerular barriers become decrepit.

Whatever the mechanism, care should be taken not inadvertently to class as microalbuminuric patients who show intermittent clinical proteinuria. This term is best restricted to diabetic patients with supranormal albumin excretion rates who are persistently Albustix test negative and have no record of clinical proteinuria

(corresponding roughly to an albumin excretion rate of $200 \mu\text{g}/\text{min}$ or more). A series of previous negative test results over prolonged periods is necessary for confident classification as microalbuminuric to escape the error of including patients with intermittent proteinuria on the basis of short term screening. The inclusion of such intermittently proteinuric patients may partly explain the apparent failure of some groups to reduce microalbuminuria by strict blood glucose control.¹³ Statistically significant and substantial improvement in glycaemic control failed to influence the albumin excretion rate and fractional clearance and had no detectable effect on the rate at which glomerular function was already declining in these patients. This failure was not attributable to a rise in arterial pressure. Even though arterial pressure was inversely related at entry to both glomerular filtration rate and fractional albumin excretion—a finding also reported by others in diabetics with renal abnormalities^{12,14-16}—it was maintained unchanged throughout the study and changes in glomerular filtration rate did not relate to changes in arterial pressure. This agrees with previous reports.^{8,17,18} Dietary composition remained unaltered and is therefore unlikely to have affected glomerular filtration rate.

Over the relatively short duration of this study clinical proteinuria became persistently positive in one patient. Whether this will be the fate of them all and the rate at which this will occur remain to be established. The time interval between the initial appearance of proteinuria and persistent clinical proteinuria varies considerably in different people.¹⁹ The reasons for this variability are unknown but eventually almost all intermittently positive patients appear to progress to persistent clinical proteinuria and renal failure.¹⁹

Intermittent clinical proteinuria therefore represents a late phase of diabetic nephropathy when glomerular function is already declining; its progression appears not to be influenced by intensified metabolic control. The point of "metabolic no return" for the diabetic kidney must therefore lie at an earlier phase in the development of renal disease.

We thank the staff of Peter Bishop metabolic ward and our diabetic patients for their help. Andrea Collins performed the glycosylated haemoglobin estimations and Angela Goodwin provided valuable statistical help. This study was supported in part by Nordisk-UK and the British Diabetic Association.

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(Accepted 27 September 1985)