recommend a hydrolysate formula. The incidence and severity of eczema in the infants fed a casein hydrolysate formula were significantly reduced compared with those in infants fed conventional cows' milk or soy milk formulas. The incidence in the hydrolysate group was comparable with that in the breast fed infants whose mothers took dietary precautions during lactation, though the eczema was more severe. The incidence in the hydrolysate group was significantly lower than that in the breast fed group whose mothers were not on a restricted diet. In our prospective randomised study soy milk formula did not offer any preventive advantage in high risk infants, as also reported by others.[16,17]

In conclusion, mothers of infants with a family history of atopy should avoid common allergenic foods while breast feeding. Alternatively, the infants should be fed a milk hydrolysate formula.

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Prognosis in diabetic nephropathy

Hans-Henrik Parving, Eva Hommel

Abstract

***Objective*—To assess the effect of long term antihypertensive treatment on prognosis in diabetic nephropathy.**

***Design*—Prospective study of all insulin dependent diabetic patients aged under 50 with onset of diabetes before the age of 31 who developed diabetic nephropathy between 1974 and 1978 at Steno Memorial Hospital.**

***Setting*—Outpatient diabetic clinic in tertiary referral centre.**

***Patients*—Forty five patients (20 women) with a mean age of 30 (SD 7) years and a mean duration of diabetes of 18 (7) years at onset of persistent proteinuria were followed until death or for at least 10 years.**

***Interventions*—Antihypertensive treatment was started a median of three (0-13) years after onset of nephropathy. Four patients (9%) received no treatment, and 9 (20%), 13 (29%), and 19 (42%) were treated with one, two, or three drugs, respectively. The median follow up was 12 (4-15) years.**

***Main outcome measures*—Arterial blood pressure and death.**

***Results*—Mean blood pressure at start of antihypertensive treatment was 148/95 (15/50) mm Hg. Systolic blood pressure remained almost unchanged (slope −0·01 (95% confidence interval −0·39 to 0·37) mm Hg a year) while diastolic blood pressure decreased significantly (0·87 (0·65 to 1·10) mm Hg a year) during antihypertensive treatment. The cumulative death rate was 18% (8 to 32%) 10 years after onset of nephropathy, in contrast to previous reports of 50% to 77% 10 years after onset of nephropathy. As in previous studies, uraemia was the main cause of death (9 patients; 64%).**

***Conclusions*—The prognosis of diabetic nephropathy has improved during the past decade largely because of effective antihypertensive treatment.**

Hvidöre Hospital, DK-2930 Klampenborg, Denmark
Hans-Henrik Parving, MD, *chief physician*
Eva Hommel, MD, *registrar*

Correspondence to: Dr Parving.

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Introduction

About 35% of patients with insulin dependent diabetes develop persistent proteinuria, a decline in glomerular filtration rate, and increased arterial blood pressure, which collectively constitute the clinical syndrome of diabetic nephropathy.[1-3] Nephropathy is the main cause of the increased morbidity and mortality in insulin dependent diabetics.[1-5] The high mortality is due to an excess of cardiovascular mortality[6] and to end stage renal failure.[1-4] The cost of care for end stage renal disease in the United States currently exceeds $0·8 billion a year for diabetic nephropathy alone, and the amount is rapidly rising.[7] On average, death occurs five to 10 years after the start of persistent proteinuria.[1,2,4]

Several studies dealing with small numbers of patients have shown that effective antihypertensive treatment postpones renal insufficiency in insulin dependent diabetics with nephropathy.[8-12] The beneficial effect of such treatment on the prognosis of insulin dependent diabetic patients with nephropathy has not been elucidated. We therefore studied 45 insulin dependent diabetic patients with onset of diabetic nephropathy between 1974 and 1978, following them until death or for at least 10 years. Ninety one per cent of the patients received antihypertensive treatment.

Patients and methods

All insulin dependent diabetic patients with onset of diabetes before the age of 31 who were referred with proteinuria or who developed persistent proteinuria

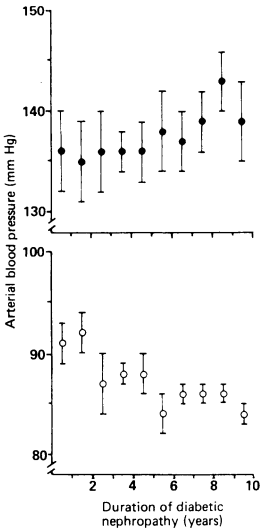

FIG 1—*Arterial blood pressure during antihypertensive treatment in insulin dependent diabetic patients suffering from nephropathy. Number of patients examined varied from 42 to 33 after 10 years' duration of diabetic nephropathy. Vertical bars represent SE*

between 1974 and 1978 at Steno Memorial Hospital were identified by one of us (H-HP). Owing to the time lag between onset of proteinuria and fully developed persistent proteinuria, as defined below, this identification took place between 1976 and 1980. Persistent proteinuria was shown in 74 patients. Nineteen patients who had been referred with proteinuria were excluded as the onset of persistent proteinuria could not be established. Eight patients were excluded because of kidney disease not due to diabetes: four had frequent urinary tract infections and four others had non-diabetic kidney disease proved by biopsy superimposed on a diabetic glomerulosclerosis—namely, two with sarcoidosis and two with glomerulonephritis. Two patients were excluded because persistent proteinuria developed after the age of 50. The remaining 45 patients fulfilled the inclusion criteria for the study: onset of diabetes before the age of 31, current age below 50 at onset of persistent proteinuria, and onset of persistent proteinuria between 1974 and 1978. All patients had depended on insulin from the time of diagnosis, and all received at least two daily injections of highly purified porcine insulin. They had a normal diabetic diet containing 45-55% carbohydrate, 30-35% fat, and 15-20% protein throughout the study. None of the patients had their intake of salt or protein restricted.

Of the 45 patients, 20 were women. At onset of persistent proteinuria the mean (SD) age and duration of diabetes were 18 (7) and 30 (7) years, respectively; three patients had no retinopathy and 14 had simple and 28 proliferative retinopathy.

Persistent proteinuria was defined as urinary excretion of protein >0·5 g/24 h on at least four consecutive visits to the outpatient clinic (interval between visits 8-16 weeks). The date of the first of the abnormal samples was taken as the onset of persistent proteinuria. Diabetic nephropathy was diagnosed clinically if there was persistent proteinuria, diabetic retinopathy, and no clinical or laboratory evidence of kidney or renal tract disease other than diabetic glomerulosclerosis.[9] Biopsy specimens were taken from the kidneys of the three patients who had had diabetes for less than 10 years, and diffuse diabetic glomerulosclerosis was found in all three.

Antihypertensive treatment was started if at least three consecutive measurements showed a diastolic blood pressure ≥95 mm Hg (28 patients) or if the patient had fluid retention and a sustained diastolic blood pressure of ≥90 (13 patients). Four patients remained normotensive during the observation period. Nine patients were treated with frusemide or bendrofluazide, 13 with a diuretic together with metoprolol (9 patients) or captopril (2) or methyldopa (2). The 19 patients receiving triple treatment took one of these drugs, a diuretic, and hydralazine. We aimed at achieving a stable reduction in diastolic blood pressure to below 90 mm Hg.

The patients visited the clinic every two to four months during the whole follow up period, which lasted a mean of 12 (4-15) years. The follow up was incomplete for only one patient, who later died from uraemia; this patient was included in the data on cumulative death. Blood pressure was measured with a standard clinical sphygmomanometer (cuff 25×12 cm) on the right arm, the patients having been supine or sitting for at least 10 minutes. The diastolic blood pressure was taken as the point at which the Korotkoff sounds disappeared (phase V). Serum creatinine concentration was measured at least annually. Haemoglobin A_{1c} concentration was measured by high performance liquid chromatography (Bio-Rad-Diamat, Richmond, California; normal range 4·3-6·2%) and by an isoelectric focusing method (normal range 4·1-6·1%).[13] Thirty five of the patients were followed regularly by one of us (H-HP).

Results are expressed as means (SE) unless otherwise stated. The 95% confidence interval for the 10 year mortality was calculated by the exact binomial method. The blood pressure data were analysed in a regression model with a separate intercept for each patient and a common regression coefficient describing the influence of duration. The analysis was performed separately for the data before and after start of antihypertensive treatment. The parallelism of the individual regression lines was analysed by an F test. Student's *t* test was used, and a p value <0·05 was considered significant.

Results

Thirty seven (82%) patients had onset of diabetes before the age of 21. The number of patients developing persistent proteinuria ranged from seven to 11 per calendar year during the enrolment period. Forty one patients (91%) received antihypertensive treatment and the median time interval from onset of nephropathy to start of this treatment was 3 (0-13) years. The average course of arterial blood pressure is shown in figure 1. Mean blood pressure at start of antihypertensive treatment was 148/95 (15/15) mm Hg, and systolic blood pressure remained almost unchanged, slope −0·01 (95% confidence interval −0·39 to 0·37) mm Hg a year while diastolic blood pressure decreased by 0·87 (95% confidence interval 0·65 to 1·10) mm Hg a year (p<0·001) during the treatment period. The individual regression lines were parallel for diastolic blood pressure (F=1·21, df 40, 253; p=0·16) but not for systolic blood pressure (F=1·78, df 40, 253; p<0·01). The average blood pressure was 138/87 (2/2) mm Hg during the first decade after onset of nephropathy.

All patients were followed until death or for at least 10 years. The median follow up was 12 (4-15) years. The cumulative death rate 10 years after onset of nephropathy was 18% (95% confidence interval 8 to

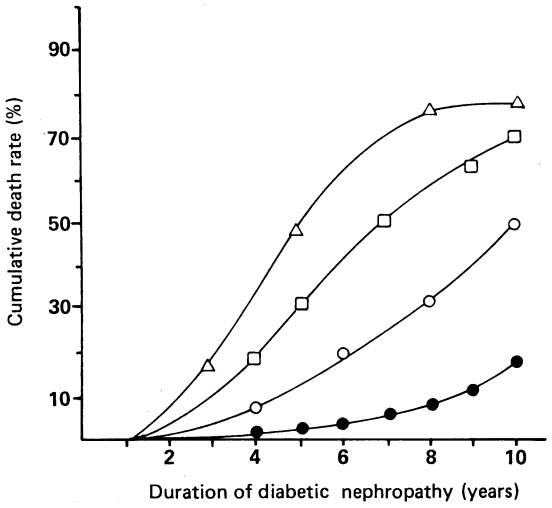

FIG 2—*Deaths from diabetic nephropathy in insulin dependent diabetic patients (△, n=45, Knowles[4]; □, n=360, Andersen et al[1]; ○, n=67, Krolewski et al[2]) compared with those who had effective antihypertensive treatment (●, n=45)*

TABLE I—*Causes of death in insulin dependent diabetic patients with nephropathy*

	Years of follow up		
	≤10	>10	0-15
Uraemia	4	5	9
Myocardial infarction	2	1	3
Pulmonary embolism	1		1
Ketoacidosis	1		1
Total	8	6	14

32%) (fig 2) and the overall mortality was 31% (14 patients). Uraemia (serum creatinine concentration >500 μmol/l) was the main cause of death (9 patients) followed by cardiovascular causes (table I). The patients dying from non-renal causes had normal or only slightly elevated serum creatinine concentrations (<150 μmol/l) (fig 3). Among the surviving 31 patients, only four had serum creatinine concentrations >150 μmol/l in 1988. The average haemoglobin A_{1c} concentration from 1984 to 1988 was 9·1 (0·1)%.

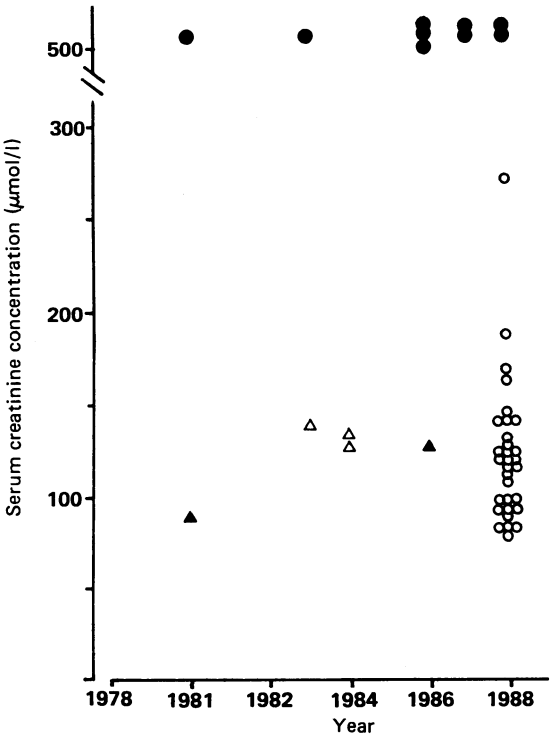

FIG 3—*Serum creatinine concentration related to deaths among insulin dependent diabetic patients receiving effective antihypertensive treatment. Four of the 45 patients were normotensive during study and received no antihypertensive treatment. Fourteen patients died: nine of end stage renal failure (●), three of acute myocardial infarction (△), and two of miscellaneous causes (▲); 31 patients survived (○) at end of study*

Discussion

In the three previous studies that described the course of diabetic nephropathy in insulin dependent diabetic patients,[1 2 4] the cumulative death rate 10 years after onset of nephropathy ranged from 50% to 77%. The 50% figure is a minimum value as Krolewski *et al* included only death due to end stage renal failure.[2] In our study the cumulative death rate 10 years after onset of nephropathy was only 18%. The antihypertensive treatment was effective: a significant reduction in diastolic blood pressure occurred during the treatment period. Uraemia was the main cause of death, as in the three earlier studies.

All four studies are comparable with respect to sex ratio, age at onset of diabetes, and criteria applied for the clinical diagnosis of nephropathy. The median calendar year of the diagnosis of diabetes was almost the same in our study and two of the previous three studies (table II). The possible impact of calendar year of diagnosis of diabetes on the prognosis in diabetic nephropathy has been elucidated by Krolewski *et al*, who found no effect on the cumulative death rate in three cohorts of proteinuric insulin dependent diabetic patients with onset of diabetes in 1939, 1949, and 1959.[2] The finding is supported by studies investigating the natural course of glomerular filtration rate in 1970-82.[8 14 15] We have previously shown an average rate of decline in glomerular filtration rate before antihypertensive treatment of 10 ml/min/year[15] compared with a mean value of 14 ml/min/year observed by Mogensen and by Viberti *et al*.[8 14] If, as suggested in these studies, the rate of decline in glomerular filtration rate (about 12 ml/min/year) is linear with time then the median survival time from onset of persistent proteinuria can be estimated to be 8-11 years, depending on the initial glomerular filtration rate. This estimate agrees closely with the observed median survival of 5-10 years from onset of persistent proteinuria in insulin dependent diabetics. These findings suggest that patients given antihypertensive treatment can be compared with untreated patients, but the possibility of a change in the natural course of the disease cannot be entirely ruled out. Unfortunately blood pressure of untreated patients was not reported.

All our patients had a normal diabetic diet without salt or protein restriction. We previously found a protein intake of 1·1 g/kg/day in our insulin dependent diabetic patients with nephropathy,[2] which is comparable with the intake reported in other proteinuric insulin dependent diabetic patients taking a normal diabetic diet (1·3 g/kg/day and 1·1 g/kg/day.[16 17]) Furthermore, Nyberg *et al* found no evidence that dietary protein is important in the progression of diabetic nephropathy in insulin dependent diabetics.[17]

Hyperglycaemia is well documented as a factor of pathogenetic importance in the development of diabetic nephropathy, but it loses its importance once clinical diabetic nephropathy has developed.[2 18-20] Improved metabolic control achieved by continuous subcutaneous infusion of insulin does not reduce the rate of decline in glomerular filtration rate in diabetic nephropathy.[21] Nyberg *et al* suggested that hyperglycaemia is a risk factor for the progression of clinical diabetic nephropathy in insulin dependent diabetic patients with impaired renal function (glomerular filtration rate <50 ml/min),[22] but Viberti *et al* were unable to confirm their findings.[23] All our patients received conventional insulin treatment with at least two daily injections of insulin, and their average haemoglobin A_{1c} concentration was 9·1%.

Raised arterial blood pressure is often found early in diabetic nephropathy.[24 25] A progressive rise in blood pressure occurs with declining kidney function.[12 15 24] Several studies have shown a significant correlation between arterial blood pressure and rate of decline in glomerular filtration rate.[9 19 20] The interval between onset of persistent proteinuria and raising of serum creatinine concentrations above the normal limit is considerably shorter in hypertensive compared with normotensive insulin dependent diabetics with nephropathy.[19] Systemic and glomerular hypertension enhances the development of diabetic glomerulopathy.[26] Conversely, effective antihypertensive treatment reduces albuminuria and diminishes the rate of decline in glomerular filtration rate.[8 12] Thus effective antihypertensive treatment, which postpones end stage renal failure, is the most likely explanation of the improved prognosis in insulin dependent diabetics with diabetic nephropathy. It may also improve

TABLE II—*Prognosis in insulin dependent diabetic patients with persistent proteinuria*

	No of patients	% Of women	% With onset of diabetes before age 21	Age at onset of diabetes (range)	Median year of onset of diabetes (range)	Cumulative mortality (%) after 10 years with proteinuria (95% confidence interval)
Knowles (1971)[4]	45	48	100	9 (0-16)	1952 (1930-1962)	77
Andersen *et al* (1983)[1]	360	37	70	14 (0-30)	(1923-1952)	70
Krolewski *et al* (1985)[2]	67	46	100	12 (0-20)	1959	50*
Present study	45	44	82	12 (1-32)	1959 (1937-1971)	18 (8-32)

*Death due to non-renal disease in patients who did not have serum creatinine concentrations >2·5 mg/dl not taken into account; death from end stage renal failure only.

the prognosis by reducing the excess cardiovascular mortality in diabetic nephropathy.

We thank Dr Philip Hougaard for help and advice with the statistical analyses.

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Local bone mineral response to brief exercise that stresses the skeleton

Michael C Beverly, Trudy A Rider, Michael J Evans, Roger Smith

Abstract

***Objective*—To compare grip strength and bone mineral content in the forearm in women and to test the effects on bone mineral content of short periods of exercise that stresses the skeleton.**

***Design*—Assessment of both wrists in 69 volunteers and of the non-fractured wrist in 30 patients followed by an exercise regimen entailing squeezing a tennis ball as hard as possible for 30 seconds each day for six weeks.**

***Setting*—Old people's homes and outpatient departments of Hammersmith and Northampton general hospitals.**

***Patients*—99 Women, of whom 69 were volunteers and 30 had a fractured forearm.**

***Main outcome measure*—Grip strength and bone mineral content after six weeks and at six months after the exercises had stopped.**

***Results*—The bone mineral content of the women's forearms was measured with a densitometer and the grip strength with a semi-inflated bag connected to an anaeroid barometer. Measurements before exercise showed that the two variables correlated closely, irrespective of age, and that there were significant differences in both between the dominant and non-dominant arms of the volunteers. After six weeks of exercise there was a mean increase in grip strength of 14·5% (95% confidence interval 9·9 to 19·2%) and in bone mineral content of 3·4% (1·4 to 5·3%) in the stressed forearms of the 77 women who attended for examination. After six months without exercise the improvements in the 33 women who attended for follow up had reversed. Women who had had a fractured forearm (n=13), however, had continued to gain grip strength and bone mineral content in the arm that had not been injured.**

***Conclusions*—Grip strength in the forearm is a good indicator of bone mineral content. Both variables may be increased by brief periods of stressful exercise. If this principle can be applied to the whole skeleton it may provide a means of reversing osteoporosis.**

Nuffield Orthopaedic Centre, Oxford OX3 7LD
Michael C Beverly, FRCS, *orthopaedic senior registrar*
Roger Smith, FRCP, *consultant physician*

Northampton General Hospital, Northampton NN1 5BD
Trudy A Rider, FRCS, *orthopaedic senior house officer*

Hammersmith Hospital, London W12 0HS
Michael J Evans, FRCS, *consultant orthopaedic surgeon*

Correspondence to:
Mr Beverly,
30 Sheen Road, Richmond,
Surrey TW9 1AW.

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Introduction

Physical activity is commonly accepted to have some role in preventing and treating osteoporosis,[1-3] but the role is unclear.[4] Female marathon runners, for example, may become osteoporotic,[5] and infantry recruits subjected to severe exercise developed either hypertrophy of the tibia or stress fractures.[6] Pathological bone remodelling was shown by Wolff nearly a century ago,[7] and Nilsson and Westlin showed that localised changes in bone density in athletes were related to the stresses put on their arms and legs during their particular sport.[8] Rubin and Lanyon produced an osteogenic response to short periods of abnormal loading in the functionally isolated wing bone of a rooster.[9]

Patients with fractures of the arm or leg commonly develop a localised osteoporosis, which reverses as use returns. We examined the relation between bone mineral content in the forearm and the peak stress, equivalent to maximum grip strength, commonly experienced by the forearm and tried to modify grip strength in female volunteers and women with a fractured forearm.

Subjects and methods

We tested the grip strength of 99 women (69 volunteers and 30 patients with a fractured forearm)