CLINICAL RESEARCH

Effect of protein restriction in insulin dependent diabetics at risk of nephropathy

DAVID COHEN, ROSEMARY DODDS, GIANCARLO VIBERTI

Abstract

Persistent proteinuria is strongly associated with increased mortality in insulin dependent diabetes, and risk of this condition can be predicted many years in advance by subclinical increases in albumin excretion rate (microalbuminuria). Eight normotensive insulin dependent diabetics with microalbuminuria who had overnight albumin excretion rates of between 15 and 200 μg/min underwent a three week randomised crossover study of their normal protein diet (median 92 (range 55-117) g/day) and a low protein diet (47 (38-57) g/day). Both diets were isoenergetic, and the low protein diet was supplemented with calcium and phosphate. Median overnight albumin excretion rate fell from 23·0 (15·0-170·1) μg/min during the normal diet to 15·4 (4·1-97·8) μg/min during the low protein diet. No consistent change was found in urinary excretion of β_2 microglobulin during the two diets. The reduction in albumin excretion rate was accompanied by a significant fall in median glomerular filtration rate and fractional renal clearance of albumin. Kidney volume remained unchanged. There were no significant changes in glycaemic control or arterial blood pressure.

In these few patients restriction of dietary protein had a beneficial effect on microalbuminuria, independent of changes in glucose concentrations and arterial blood pressure.

Introduction

Persistent proteinuria in insulin dependent diabetics is associated with mortality up to 100 times that of the non-diabetic population. By contrast, in diabetics without persistent proteinuria relative mortality is only about two to four.[1] Subclinically raised albumin excretion rates ranging from 15 to 200 μg/min (microalbuminuria) predict clinical nephropathy in insulin dependent diabetics.[2-4] Treatment that normalises this early marker of disease may prevent or postpone persistent clinical proteinuria and therefore reduce premature death.

Intensified insulin treatment and strict glycaemic control have been shown to reduce albumin excretion in diabetics with microalbuminuria.[5,6] The effect of glycaemic control remains controversial, however, and recent work failed to show a reduction in the fractional clearance of albumin after long term improved metabolic control in insulin dependent diabetics selected for having persistent (that is, in at least two out of three determinations) subclinically raised 24 hour albumin excretion rates.[7,8] One of several possible reasons for these different findings is that "persistent" microalbuminuria represents a stage of renal disease in diabetes already partly unresponsive to metabolic correction. It is therefore important to test alternative therapeutic strategies.

Dietary protein has a profound effect on kidney function and has a role in the progression of renal failure in various renal diseases.[9-11] We therefore investigated the effect of restricting dietary protein intake on albuminuria, glomerular filtration rate, and kidney size in a group of insulin dependent diabetics with persistent microalbuminuria.

Patients and methods

We studied eight normotensive insulin dependent diabetics (six men, two women; mean age 38·7 (range 22-57) years) without clinical proteinuria (mean duration of diabetes 19·6 (11-29) years). They were selected because the urinary albumin excretion rate in a timed overnight sample was 15-200 μg/min on three successive occasions during a six week run in period. All patients were within 10% of their ideal body weight (Metropolitan Life Insurance Co tables, 1959) and taking no drugs other than insulin. They did not have neuropathy, known cardiac or renal disease, or urinary tract infection. Three had background retinopathy and one proliferative retinopathy.

After baseline assessment patients were randomly allocated to take in turn a low protein diet or their usual diet for three weeks. Five patients received the low protein diet first and three their usual diet first. To prevent carryover effects there was a one week interval of normal diet between the two experimental periods. The low protein diet provided 40 g mixed protein daily. It was designed to be isoenergetic with the usual diabetic diet, with 35% of the energy coming from fat and 55-60% from carbohydrate. This required the use of special low protein carbohydrate sources (GF Dietary Supplies, Stanmore, Middlesex, UK). To maintain similar fibre intakes during the low protein diet patients were encouraged to eat sources of

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vegetable fibre poor in protein. Calcium (mean 425 (range 200-800) mg/day) and phosphate (mean 500 (range 250-750) mg/day) tablets were prescribed to supplement the low protein diet to the same intake as the usual diet.

A nutritionist assessed dietary intake initially and during each experimental period by interview and a three day, weighed food record. A 24 hour urine collection for measurement of urea excretion was made during each of the last two weeks of each dietary period to obtain an objective measure of protein intake and compliance. The mean of the two collections was used to calculate protein intake from the urinary urea nitrogen (UUN) and an estimated non-urea nitrogen (NUN) of 31 mg/kg/day[12]: UUN+NUN=nitrogen intake (I_n); $I_n \times 6{\cdot}25$=protein intake in g/day (assuming constant nitrogen balance).[13] Twenty four hour urinary excretion of creatinine, calcium, and phosphate and plasma urea and albumin concentrations were measured at the same time. Patients were weighed unshod in indoor clothes at the end of each dietary period.

During both dietary periods the patients collected weekly seven point blood glucose profiles (BM-Test Glycemie 20-800), the samples being taken before and two hours after main meals and at bedtime; the profiles were immediately posted to our laboratory and read by a Reflolux meter. Not all patients managed to perform three full seven point profiles, but the same number of samples at the same time points during the day were compared for each patient. Sample numbers varied from 10 to 21 with each diet. Mean blood glucose concentration for each patient was calculated as the mean of all relevant samples during each dietary period.

At the end of each dietary period fructosamine concentration, an integrated index of short term glycaemic control,[14] was measured by CobasBio autoanalyser (normal range in our laboratory 1·8-2·7 mmol/l), glomerular filtration rate by clearance of edetic acid labelled with chromium-51,[15] and kidney volume by ultrasonography.[16] Normal ranges for glomerular filtration rate and kidney volume in our laboratory are 84-135 ml/min/1·73 m^2 and 210-298 ml/1·73 m^2 respectively.[15 17] Precisely timed (to the nearest minute) overnight urine collections were made on the last two days of the two dietary periods for measurement of urinary albumin concentration by radioimmunoassay[18] and β_2 microglobulin by β_2-Micro RIA (Pharmacia Diagnostics, Uppsala, Sweden). The average of the two results was used for calculations. A Vickers multichannel analyser was used to measure concentrations of albumin in plasma and creatinine, calcium, phosphate, and urea in urine and plasma. Fractional clearance of albumin was calculated by dividing the albumin clearance (UV/P), where U and P were the urinary and plasma albumin concentrations respectively and V the urine flow, by the glomerular filtration rate.

At the end of each dietary period blood pressure (phase I/V) was measured to the nearest 2 mm Hg on two occasions three minutes apart, firstly with the patient supine after five minutes' rest and then immediately after standing, by the same observer (DC) using a random zero mercury sphygmomanometer (Hawksley UK); the readings were then averaged.

All subjects gave informed consent to the study, which was approved by the hospital ethical committee.

Analyses were performed with the Wilcoxon test for paired data. Albumin and β_2 microglobulin excretion rates were logarithmically transformed before analysis because of their positively skewed distribution. Results are given as medians with ranges. Significance was taken as $p<0{\cdot}05$.

TABLE I—*Dietary data for eight insulin dependent diabetics with microalbuminuria taking their normal diet and a low protein diet. Values are medians (and ranges)*

	Normal diet	Low protein diet	Significance
Energy intake (MJ/day)	9·3 (6·6-12·6)	8·9 (5·2-10·4)	NS
Protein intake (g/day):			
From food records	92 (55-117)	47 (38-57)	p<0·01
From urea excretion	94 (42-137)	51 (29-87)	p<0·01
Carbohydrate intake (g/day)	210 (148-288)	290 (176-340)	p<0·01
Fat intake (g/day)	119 (72-154)	94 (56-111)	p<0·05
Fibre intake (g/day)	22 (12-38)	26 (18-41)	NS
Urinary urea (mmol/24 h)	482 (161-789)	204 (88-402)	p<0·01
Urinary creatinine (mmol/24 h)	13·4 (9·0-19·2)	11·5 (9·8-23·9)	NS
Urinary calcium (mmol/24 h)	4·8 (1·9-8·6)	2·9 (1·1-5·6)	p<0·05
Urinary phosphate (mmol/24 h)	38·2 (17·6-46·6)	26·7 (11·9-38·3)	p<0·02
Plasma urea (mmol/l)	6·9 (4·4-7·9)	3·7 (2·5-6·9)	p<0·02
Plasma albumin (g/l)	39·6 (35·4-44·8)	40·0 (35·5-43·5)	NS
Body weight (kg)	73·7 (56·2-90·0)	74·2 (56·7-89·1)	NS

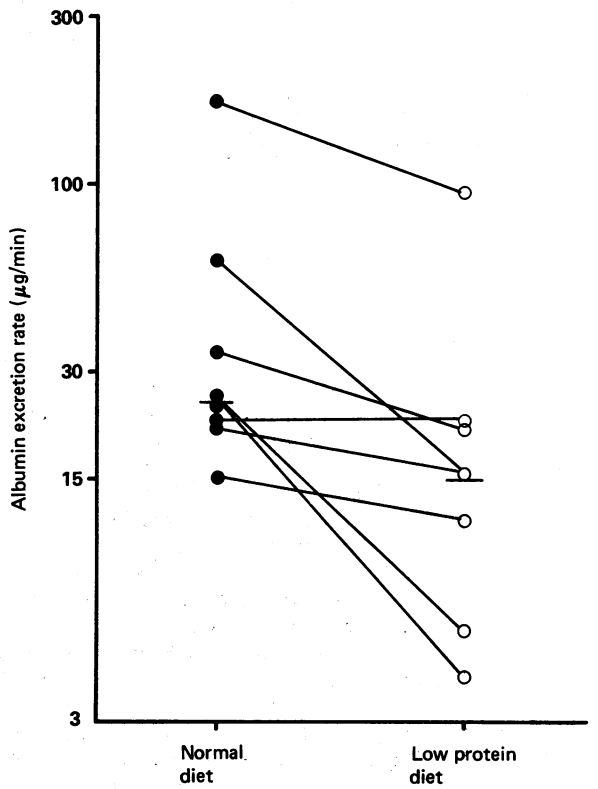

FIG 1—Albumin excretion rates during a normal diet and low protein diet in eight insulin dependent diabetics with microalbuminuria. Horizontal bars indicate the median values (p=0·01).

Results

Table I shows dietary data. The median protein intake assessed by the three daily weighed food records was similar to that calculated from urinary urea excretion. Both measures confirmed a significantly lower protein intake in all patients during the low protein diet, which approached that prescribed. The significantly lower urea excretion and plasma urea concentration during the low protein diet supported the patients' compliance. Energy intake was unchanged during the low protein diet because of a considerable increase in carbohydrate. Fat intake fell during the low protein diet but fibre intake was not different. Despite supplementation urinary excretion of phosphate and calcium was lower during the low protein diet; creatinine excretion remained unchanged. There was no change in body weight or plasma albumin concentration.

Albumin excretion rate was lower in all patients during the low protein diet (15·4 (4·1-97·8) μg/min) compared with the normal diet (23·0 (15·0-170·1) μg/min) (p=0·01) (fig 1). In contrast, there were no consistent changes in β_2 microglobulin excretion during the two diets (59·0 (35·9-166·2) ng/min during the normal diet *v* 82·1 (9·8-140·0) ng/min during the low protein diet). Glomerular filtration rate, measured in seven patients, fell from 109 (76-135) ml/min/1·73 m^2 during the normal diet to 100 (72-114) ml/min/1·73 m^2 during the low protein diet (p=0·02) (fig 2). Fractional clearance of albumin fell significantly from $5{\cdot}5\ (2{\cdot}7\text{-}19{\cdot}7)\times10^{-6}$ during the normal diet to $3{\cdot}4\ (0{\cdot}9\text{-}6{\cdot}9)\times10^{-6}$ during the low protein diet (p=0·02) (table II). Kidney volume, measured for technical reasons in only six patients, showed no significant change (338 (279-431) ml/1·73 m^2 during the normal diet and 334 (262-450) ml/1·73 m^2 during the low protein diet). Four patients had nephromegaly (that is, kidney volume >300 ml/1·73 m^2). Blood glucose concentration (fig 3), fructosamine concentration, and arterial pressure (table III) were not significantly different during the two diets. Three patients were advised to reduce their insulin dosage by up to 10 U/day during the low protein diet to maintain comparable glycaemic control.

Discussion

In this small group of patients a diet restricted in protein significantly reduced microalbuminuria, which is an important risk factor for persistent proteinuria and clinical nephropathy in insulin dependent diabetes. This effect is consistent with the results reported in non-diabetic patients with heavier proteinuria and overt renal disease[10 19] and was obtained independently of changes in blood glucose concentration and blood pressure, which are two factors that influence albumin excretion rate in diabetes.[5 8 20-23] The low protein diet not only achieved a significant reduction in protein intake but also lowered fat and phosphate intakes, despite supplementation, and increased carbohydrate intake. Although any

or all of these changes may have contributed to the observed effect on albuminuria,[24] there is convincing evidence that protein and possibly phosphate intake may be the main determinants.[25 26] Several studies in animal models of renal disease support the idea that low protein intake has a beneficial effect on albuminuria and renal lesions seen on histological examination.[9 27]

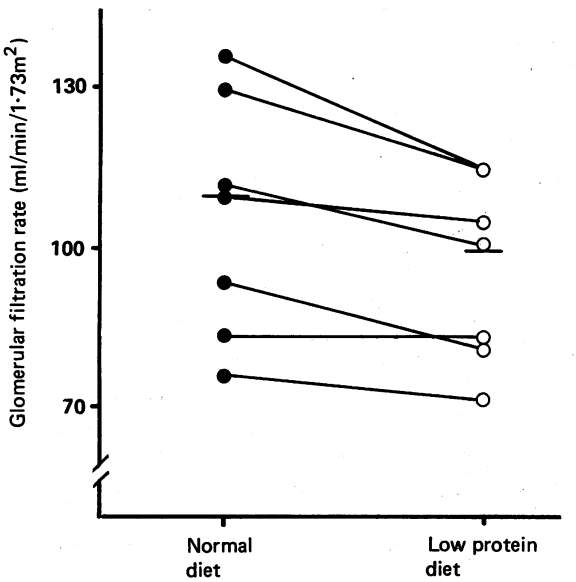

FIG 2—Glomerular filtration rate, measured by clearance of edetic acid labelled with chromium-51, during normal diet and low protein diet in seven insulin dependent diabetics with microalbuminuria. Horizontal bars indicate median values (p=0·02).

TABLE II—*Fractional clearance of albumin (×10⁻⁶) in seven insulin dependent diabetics with microalbuminuria during normal and low protein diets*

Case No	Normal diet	Low protein diet
1	3·8	3·4
2	4·6	0·9
3	2·7	2·3
4	9·7	6·9
5	5·5	1·4
6	19·7	5·9
7	6·9	6·8
Median (range)	5·5 (2·7-19·7)	3·4 (0·9-6·9)*

*p=0·02.

There are several possible explanations for the reduction in albumin excretion rate. It may have fallen as a result of a reduced load of filtered albumin: although plasma albumin concentration was not changed, the concomitant fall in glomerular filtration rate might have produced this effect. The lower fractional clearance of albumin during the low protein diet suggests, however, that the change in albumin excretion reflected changes in the ultrafiltration properties of the glomerulus (changes in the selective permeability of the membrane or haemodynamic changes, or both). This is consistent with work in diabetic animals, in which the reduced albuminuria after dietary protein restriction has been associated with reduced intraglomerular pressures.[27] These modifications of renal function prevented the renal lesions of diabetes in rats.[27]

Other workers have suggested that naturally occurring cationic polyamino acids generated by the digestion of animal proteins, especially meat, may neutralise the anionic glomerular charge and facilitate transglomerular flux of anionic albumin.[28] Reduced generation of these polycations by a low protein intake may therefore help reduce albuminuria. The quantitative aspects of this putative phenomenon have not, however, been elucidated. Alternatively, the fall in albumin excretion may have been the result of changes in tubular reabsorption of protein. This, however, is unlikely because the stability of β_2 microglobulin excretion, a marker of tubular function,[29] suggests that the tubular handling of proteins remained unchanged.

TABLE III—*Serum fructosamine concentration and systolic and diastolic blood pressures during normal and low protein diets in eight insulin dependent diabetics with microalbuminuria. Values are medians (and ranges)*

	Normal diet	Low protein diet	Significance
Fructosamine (mmol/l)	3·25 (3·1-3·8)	3·13 (2·8-3·5)	NS
Systolic blood pressure (mm Hg)	126 (105-136)	128 (94-142)	NS
Diastolic blood pressure (mm Hg)	75 (71-88)	74 (64-80)	NS

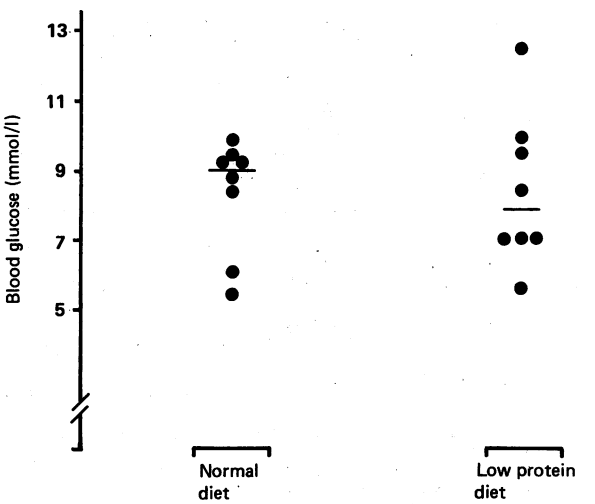

FIG 3—Individual mean blood glucose concentrations in samples collected at home during normal diet and low protein diet in eight insulin dependent diabetics with microalbuminuria. Horizontal bars indicate the group median.

Kidney volume was not reduced by three weeks of the low protein diet. Enlargement of the kidney can be prevented in diabetes by strict metabolic control,[30] but reversal of nephromegaly has proved difficult in both diabetic animals and man.[15 31 32] In man three weeks of a low protein diet may not be long enough to affect kidney size. Alternatively, the reduction in dietary protein may not have been large enough to produce an effect or may have affected selected renal structures such as glomeruli, which are a fairly small part of total kidney volume.[33] The dissociation between the effect of a low protein diet on renal function and renal size is similar to that seen with strict glycaemic control[15 31] and suggests that important functional changes take place in the kidney in the short term without changes in total renal volume.

Our findings provide an alternative approach to managing microalbuminuria in diabetes. Strict blood glucose control is not without risk[5 34 35] and may not be totally successful[7 8]; similarly, the value of treating the subclinical increase in arterial pressure that may accompany microalbuminuria[3 4 22] is still uncertain.[36 37] Diets containing roughly 45 g protein have no untoward long term nutritional effects in patients with established renal disease.[10 25 38] The short term efficacy of the protein restricted diet in our eight diabetics at risk of nephropathy should encourage more extensive investigations into the long term effect on renal function and structure. Protein restriction may complement other preventive treatment in these patients.

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Bone mineral density in Addison's disease: evidence for an effect of adrenal androgens on bone mass

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Abstract

It is unknown whether replacement doses of cortisone acetate and the absence of the small amounts of androgens secreted by the adrenal cortex may cause osteoporosis. This was studied in 35 patients (12 men and 23 women) suffering from primary adrenocortical failure and taking cortisone acetate 25-37·5 mg and fludrocortisone 50-100 μg daily. Bone mineral density was measured by single photon absorptiometry at the midshaft of the radius, representing cortical bone, and at the distal part of the radius, a site with a significant trabecular component. The bone mineral density was normal in premenopausal female patients as well as in male patients, showing that replacement doses of cortisone acetate do not affect bone mass. By contrast, in postmenopausal patients there was a dramatic bone loss in addition to the physiological postmenopausal decrease in bone mass.

This loss, combined with the low plasma concentrations of androstenedione, dehydroepiandrosterone, and testosterone (and low concentrations of oestrone of adrenal origin), indicates that adrenal androgens may be essential for the maintenance of bone mass in postmenopausal women with Addison's disease. In addition, these data indicate that the small amounts of androgens secreted by the adrenal cortex have a role in the maintenance of bone mass in normal postmenopausal women.

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Introduction

It is well known that supraphysiological amounts of glucocorticoids may induce osteoporosis. The question whether physiological doses of glucocorticoids are devoid of this side effect has not been settled, however, as we have discussed elsewhere with regard to rheumatoid arthritis.[1] As rheumatoid arthritis may influence peripheral bone mass we sought to resolve this problem by studying patients suffering from primary adrenocortical failure (Addison's disease) and receiving treatment with glucocorticoid substitutes. At the same time we investigated whether the adrenal androgens played a part in the maintenance of bone mass.