Dietary treatment of diabetic nephropathy with chronic renal failure

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Abstract. Thirty-two patients with diabetes mellitus (22 IDDM and 10 NIDDM, 21 males and 11 females, age 44±11.8 years) were followed for 5.2±3.8 years after the onset of chronic renal failure, with the aim of evaluating the effect of low protein diets on the rate of decline of the residual renal function. During the 1.8±1.6 year follow-up period on free or uncontrolled low protein diet the mean rate of decline of creatinine clearance was 0.9±0.6 ml/min/month, significantly greater than that observed during 3.7±3.1 years on low or very low protein diets. The reduction of protein intake was followed by a significant decrease in daily urinary protein loss. A better glycaemic control was obtained on the low protein diet, and the daily insulin requirement decreased. The anthropometry, as well as the serum concentrations of rapid turnover proteins, did not change, in spite of the low or very low protein dietary supply for a long duration. The values of mean arterial pressure were quite similar during the follow-up period on free or uncontrolled low protein diet and during the study period on the low protein diet. A good compliance with reduced dietary intake (as demonstrated by the measurement of the daily urea excretion) was obtained in a large number of patients. In conclusion, our study confirms the protective effect on the residual renal function of low protein diets in IDDM and NIDDM patients with chronic renal failure due to diabetic nephropathy, in the absence of any sign of protein malnutrition.

Key words: chronic renal failure; diabetic nephropathy; low protein diet

Introduction

Diabetic nephropathy is one of the most common causes of end-stage renal disease (ESRD) in developed countries. In the US, diabetic nephropathy accounts for about one-third of all new patients accepted on the maintenance haemodialysis programme every year [1]. In Italy, this prevalence is lower but steadily increasing, especially in the last few years. Both insulin-dependent (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) patients can develop nephropathy, but ESRD is less frequent in the latter than in the former [2]. Mortality of diabetic patients on haemodialysis replacement therapy is undoubtedly higher than in other ESRD patients [3], while the survival on continuous ambulatory peritoneal dialysis (CAPD) programme seems to be more prolonged [4,5].

Survival after kidney transplant has improved over the last few years, but life expectancy is lower in diabetic than in non-diabetic ESRD patients. Better results can be observed in diabetic patients receiving a double kidney–pancreas transplant [5].

Once overt proteinuria has appeared, there is no therapeutic intervention which can completely halt the progressive loss of renal function with time. The decline to ESRD is often rapid, but its rate varies substantially from patient to patient, with a mean rate of decline of glomerular filtration rate (GFR) of ~1 ml/min/month [5]. Within 3–4 years after the GFR has declined to 50 ml/min, ~50% of diabetic patients will progress to ESRD [5]. A very tight metabolic control may prevent diabetic nephropathy [6], but its institution after the onset of overt proteinuria does not significantly influence the rate of decline of the GFR [7]. Parving et al. demonstrated some years ago [8] that efficient antihypertensive treatment delayed the progression of renal failure in IDDM once blood pressure was lowered to <140/90 mmHg. Angiotensin-converting enzyme (ACE) inhibitors seem to exert a renal protective effect in overt diabetic nephropathy independently of the effect on blood pressure, as would appear to be the case according to a recent meta-analysis study [9]. At present, a strict control of hypertension and the use of ACE inhibitors (when not contraindicated by other causes) appear to be of great importance for the protection of renal function in diabetic patients with incipient or overt nephropathy. The role of low protein diet alone is discussed in this report.

The role of low protein diets in diabetic nephropathy with chronic renal failure

Ten years ago [10], we demonstrated that a very low protein (0.3 g/kg/day), low phosphorus (5 mg/kg/day)
diet, supplemented with a mixture of essential amino acids (EAAs) and keto analogues (KAs) (supplemented diet) significantly decreased the rate of decline of creatinine clearance in eight IDDM patients with overt diabetic nephropathy and renal failure [10]. One year later, Walker et al. demonstrated that a low protein (0.6 g of protein/kg/day), low phosphorus diet, as opposed to an ordinary diet of at least 1 g of protein/kg/day, improved the rate of decline of GFR in IDDM patients with overt diabetic nephropathy [11]. A more recent randomized study from Zeller et al. [12] showed most impressive results: the rate of decline in GFR over a 5 year study period was reduced 3- to 4-fold in a group of IDDM patients receiving an EAA and KA mixture in tablets: one tablet per 6 kg of body weight.

The protective effect on residual renal function of low protein, low phoshorus diets supplemented with EAAs and KAs in IDDM and NIDDM patients with overt diabetic nephropathy and renal failure—our recent experience

Patients and methods

Thirty-two (22 IDDM and 10 NIDDM) patients with overt diabetic nephropathy (21 males and 11 females, mean age 44.4±13.8 years) were followed-up for a cumulative period of 5.2±3.8 years (3–10 years) after the onset of chronic renal failure (CRF). After a 1–4 year (mean 1.8±1.6) follow-up period on a free diet or on an uncontrolled low protein diet, 19 patients with a creatinine clearance ranging from 19 to 6.5 ml/min (mean 8.9±5.6 ml/min) were assigned to a very low protein (0.3 g/kg/day), very low phosphorus (6 mg/kg/day) dietary regime (A diet), and 13 patients showing better residual renal function (creatinine clearance 60–22 ml/min; mean 44.6±12.8 ml/min) were assigned to a low protein (0.7 g/kg/day), low phosphorus (10 mg/kg/day) vegetarian diet (B diet).

Proteinuria ranged from 1.5 to 9 g/day at the beginning of the diet. Antihypertensive treatment was quite similar during the uncontrolled low protein diet or free diet follow-up period and during the 2–8 year (mean 3.7±3.1 years) study period on both the A and B diet.

Diets

The composition of the A and B diets is reported in Table 1. Both A and B diets were supplemented with a mixture of EAAs and KAs in tablet form (Alfa Kappa®, Forma Biagini, Castelvecchio Pascoli, Italy) at daily doses of one tablet per 6 kg of body weight.

<table>
<thead>
<tr>
<th>A diet</th>
<th>B diet</th>
</tr>
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<tbody>
<tr>
<td>Protein supply (g/kg/day)</td>
<td>0.3</td>
</tr>
<tr>
<td>Energy supply (kcal/kg/day)</td>
<td>30–35</td>
</tr>
<tr>
<td>% carbohydrates</td>
<td>63.0</td>
</tr>
<tr>
<td>% lipids (vegetable source)</td>
<td>33.6</td>
</tr>
<tr>
<td>% proteins (vegetable source)</td>
<td>3.4</td>
</tr>
<tr>
<td>Phosphorus supply (mg/kg/day)</td>
<td>5.5–6.5</td>
</tr>
<tr>
<td>Cholesterol supply very low or absent</td>
<td></td>
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</tbody>
</table>

Table 1. The composition of the low-protein diets for diabetic patients with severe (A diet) or moderate (B diet) chronic renal failure, and of the supplements (EAA and KA mixture)

The mean rate of decline of creatinine clearance observed in the 32 diabetic patients during the 1.8±1.6 year follow-up period on free or uncontrolled low protein diet was 0.9±0.62 ml/min/month, in agreement with the data from reference 5. During the 3.7±3.1 years of low protein A and B diet, the rate of decline was significantly less: 0.22±0.21 ml/min/month ($P<0.001$).

Daily urinary protein loss significantly decreased in almost all patients on both the A and B diet. Before the start of the dietary treatment, the daily urinary protein loss was 4.2±2.6 g/day while at the end it was 2.5±1.8 g/day ($P<0.01$). Fasting serum glucose significantly decreased on the A and B diet, from 174±58 mg/dl to 121±20 mg/dl ($P<0.05$). Simultaneously, the daily insulin requirement decreased significantly from 49±21 to 28±10 IU/day ($P<0.01$).

The anthropometric indexes (BW, TST and MAMC) as well as the serum concentrations of rapid turnover proteins (albumin, immunoglobulins, transferrin and complement) did not show significant changes in spite of a low or very low protein intake over an established period. These results are reported in Table 2.

### Table 2. Effects of the low protein diets on nutritional status

<table>
<thead>
<tr>
<th>Free diet or uncontrolled low protein diet</th>
<th>Low protein diets (A and B diet)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>68.7±10.1</td>
<td>67.8±8.1</td>
</tr>
<tr>
<td>TST (cm)</td>
<td>1.53±0.34</td>
<td>1.68±0.24</td>
</tr>
<tr>
<td>MAMC (cm)</td>
<td>22.6±2.9</td>
<td>23.5±4.8</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>3.7±0.4</td>
<td>3.8±0.3</td>
</tr>
<tr>
<td>IgG (mg/dl)</td>
<td>1096±232</td>
<td>1066±158</td>
</tr>
<tr>
<td>IgA (mg/dl)</td>
<td>229±78</td>
<td>240±53</td>
</tr>
<tr>
<td>IgM (mg/dl)</td>
<td>105±32</td>
<td>112±25</td>
</tr>
<tr>
<td>Transferrin (mg/dl)</td>
<td>166±72</td>
<td>162±75</td>
</tr>
<tr>
<td>C3 (mg/dl)</td>
<td>70±12</td>
<td>74±10</td>
</tr>
<tr>
<td>C4 (mg/dl)</td>
<td>29±7</td>
<td>31±5</td>
</tr>
</tbody>
</table>

EAAs and KA mixture in tablets: one tablet per 6 kg of body weight. Each tablet contains: essential amino acids [l-lysine, l-threonine, l-tyrosine, l-histidine (an essential amino acid in CRF patients)]= 249 mg; keto acids (as calcium salts) (keto-leucine, keto-isoleucine, keto-valine, keto-phenylalanine, hydroxy-methionine)= 381 mg.
Low protein diet in diabetic nephropathy with CRF

Blood pressure control

Blood pressure was measured on a monthly basis during the observation period and after the start of low protein diets, when the patients underwent routine clinical and laboratory controls. The values of mean arterial pressure (MAP) were quite similar during the follow-up period on a free or uncontrolled low protein diet and during the study period on A and B low protein diet (MAP = 112.4 ± 6.1 and 110.3 ± 5.8 mmHg, respectively; P = n.s.).

Compliance with low protein diets

The daily urinary urea (uU) excretion was used to evaluate compliance with the diets. According to the dietary protein supply, a good compliance with the A diet (uU < 5 g/day) was observed in 45% of patients, and a poor compliance (uU > 6 g/day) in 25% of patients. In the remaining 30% of patients, the compliance was intermediate, as demonstrated by an uU ranging from 6 to 7 g/day. The compliance was better with the B diet due to the use of ordinary/everyday foods (normal bread and pasta) as the main caloric source, instead of starch-based artificial foods, as in the case of A diet. In fact, a good compliance (uU < 8 g/day) was observed in 69% of patients, an intermediate compliance (uU > 8 and < 10 g/day) in 24% of cases, and a poor compliance (uU > 11 g/day) in only 7%.

Outcome

Two patients with IDDM died from cardiovascular complications during the low protein diet study period. Sixteen patients changed to haemodialysis, and one to CAPD 1–2 years after the start of the A diet. Three out of these patients died on renal replacement treatment. Thirteen are still alive and are on haemodialysis, and one of these patients received a kidney—pancreas transplant 2 years ago, with a satisfactory and stable renal function up to now. At present, 13 patients (two on the A diet and 11 on the B diet) are still on conservative dietary treatment.

Conclusions

Our results confirm previous reports of the beneficial effect of low protein diets [10–12] on the progression rate of renal damage in NIDDM and IDDM patients with CRF. In our study, products of animal origin were excluded from both A and B diets due to their high contents of protein and phosphorous. Moreover, by using products of vegetable origin only, it is easier to maintain a protein intake < 0.4 mg/kg/day and a caloric supply > 30 kcal/kg/day, as in the case of the A diet.

The B diet is a pure vegetarian diet with complement-ary proteins (from cereals and legumes) which completely cover the recommended daily intake of EAAs. The B diet supplies an adequate amount of energy and low amounts of proteins and phosphorus. For these reasons, vegetable products are to be preferred to animal products as the protein source in low protein diets. The administration of EAA and KA supplements is necessary in patients following a very low protein diet (A diet) and is of some utility in association with the B diet, to avoid the risk of protein malnutrition, mainly in the presence of heavy proteinuria.

A moderately low protein vegetarian diet, such as the B diet, should be considered the first choice dietary treatment in the early phase of CRF due to diabetic nephropathy, with the aim of slowing down the progressive decline of renal function. When creatinine clearance is < 20 ml/min, the A diet is to be preferred to delay the substitutive therapy.

The mechanism of action of the low protein diets is likely to be multifactorial, but the correction of the abnormal glomerular haemodynamics [13] is undoubtedly of great importance. The improvement in urinary protein loss observed on both the A and B diet may play an important role in the protection of the residual renal function, probably by preventing progressive glomerular sclerosis.

The main concern relating to the use of more or less severely restricted protein diets in patients with CRF is that they may cause protein and calorie malnutrition. Our group has always seriously considered this possibility in patients with CRF due to diseases other than diabetic nephropathy [14]. Our opinion, supported by > 20 years experience with low protein diets, is that this side effect does not occur provided there is good compliance with the diet and EAA and KA supplements are administered. In the diabetic patients in our study the behaviour of both the anthropometric indices and of the rapid turnover serum proteins clearly demonstrate that malnutrition does not appear, even in those patients maintained on low protein diets for > 4 years.

Finally, it is evident that low protein diets slow down but do not halt the progression of diabetic nephropathy. In most patients with severe renal failure dietary treatment may offer the possibility of delaying the beginning of substitutive therapy for months or years. More importantly, better results on the prevention of ESRD could probably be obtained by an early treatment of overt diabetic nephropathy with a combined therapy based on low protein diet, tight blood glucose control and aggressive antihypertensive treatment.

References

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