EARLY PROTEIN RESTRICTION
IN CHRONIC RENAL FAILURE

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Summary

We performed a prospective randomised trial in 199 patients with various stages of renal failure. Stratified for sex, age and renal insufficiency, 105 patients were assigned to a protein (Pr)-restricted group (0.4–0.6 g/kg/BW), and 94 to a control group. Pr-restriction led to a significant reduction in the excretion of urea, phosphate and protein. Survival of renal function was significantly better in Pr-restricted patients. Median serum creatinine concentration increased in the control group (p<0.05), but remained stable in Pr-restricted patients. We conclude that Pr-restriction retards, or even halts the progression of chronic renal failure.

Introduction

Once chronic renal insufficiency has been established, progression to end-stage renal disease seems inevitable. Since the beginning of this century, it has been known that protein-restricted diets are useful in uraemic patients [1].

In animals, especially in the so-called remnant kidney model, it has been shown that protein restriction retards or even halts the progression of renal failure, apparently by means of reducing glomerular hyperfiltration and thereby preventing histological lesions in remnant glomeruli [2].

However, does an early started low protein diet influence the progression of renal failure in man? Several retrospective studies concerning this topic have been published since 1976 [3–7]. Definitive proof, however, may only be drawn from a prospective randomised trial, which is still lacking. We decided to initiate such a study in December, 1981.

Patients and methods

One hundred and ninety-nine patients visiting our nephrologic outpatient department between 1 January 1982 and 1 January 1984, with creatinine
clearances between 10 and 60ml/min/1.73m² entered the trial. Patients with SLE, PAN, Wegeners' granulomatosis and potentially lethal diseases (e.g. cancer) and those on non-steroidal anti-inflammatory drugs were excluded in advance. After stratification for sex, age and renal failure, the patients were randomly allocated to a protein (Pr)-restricted and a control group.

Altogether, 105 patients were randomly assigned to the Pr-restricted group (0.4–0.6g/kg/BW) and 94 patients to the control group. Further differentiation produced four groups:

A1 (n=57): creatinine clearance 31–60ml/min/1.73m²; no protein restriction,
B (n=57): creatinine clearance 31–60ml/min/1.73m²; 0.6g protein per kg/BW,
A2 (n=37): creatinine clearance 10–30ml/min/1.73m²; no protein restriction,
C (n=48): creatinine clearance 10–30ml/min/1.73m²; 0.4g protein per kg/BW.

At entry all patients visited the dietician for dietary history. A computerised data base of 950 variables was established. Every three months it was updated with the newest results. Patients adhering to the Pr-restricted diets consulted the dietician every three months, patients in the control groups only on indication. Non-restricted patients were advised to reduce protein intake if their serum urea exceeded 25mmol/L. All patients received supplemental vitamins and trace-elements; patients in Pr-restricted groups also received methionine. Blood pressure, serum calcium and serum phosphate were, if possible, kept within normal limits in all patients. Some patients with creatinine clearance <10ml/min/1.73m² received a cadaveric kidney transplant during the follow-up. Dialysis was initiated when creatinine clearance dropped below 4ml/min/1.73m².

Statistical analysis was performed by means of survival computation. A persistent 10 per cent increase in serum creatinine was chosen as the non-survival criterion. Increase of median serum creatinine was studied in all four groups separately by linear regression analysis. Data comparison between the groups was analysed with Mann Whitney U tests, and within the groups by Wilcoxon matched pairs signed ranks tests.

**Results**

In the first instance we created two groups: A1+A2 being the non-restricted, and B+C being the Pr-restricted patients. At the moment of randomisation we scanned all relevant variables for statistical differences between these two main groups. No difference could be established for diagnosis (see Table I), serum phosphate, serum calcium, serum alkaline phosphatase, haematocrit, body weight, blood pressure, serum urea, serum creatinine, and the 24-hour excretion values of sodium, urea, creatinine and protein.

Reliable conclusions can only be drawn if dietary compliance can be measured and we used the 24-hour excretion of urea. At randomisation, it amounted to 288nmol in the combined Pr-restricted group, against 280nmol in the combined control group (Figure 1). After three months (and persistently thereafter), a decreased urea excretion in the Pr-restricted patients proved that they actually adhered to their diets. At 18 months the values were 180 and 290mmol/24hr,
TABLE 1. Distribution of the various renal diseases over the protein-restricted and the control group. $x^2_L=15.7$, not significant

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>A1+A2</th>
<th>B+C</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. unknown</td>
<td>2</td>
<td>5</td>
<td>3.5</td>
</tr>
<tr>
<td>2. membrano-proliferative glomerulonephritis</td>
<td>2</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>3. focal glomerulosclerosis</td>
<td>9</td>
<td>14</td>
<td>11.6</td>
</tr>
<tr>
<td>4. IgA-glomerulopathy</td>
<td>6</td>
<td>3</td>
<td>4.5</td>
</tr>
<tr>
<td>5. glomerulonephritis (other types)</td>
<td>6</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>6. adult polycystic kidney disease</td>
<td>4</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>7. unilateral agenesis</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>8. uninephrectomy</td>
<td>5</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>9. hypoplasia/dysplasia</td>
<td>1</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>10. pyelonephritis</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>11. Alport’s syndrome</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>12. nephrosclerosis</td>
<td>16</td>
<td>9</td>
<td>12.6</td>
</tr>
<tr>
<td>13. analgesic nephropathy</td>
<td>14</td>
<td>9</td>
<td>11.6</td>
</tr>
<tr>
<td>14. interstitial nephritis</td>
<td>3</td>
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<td>3</td>
</tr>
<tr>
<td>15. reflux nephropathy</td>
<td>7</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>16. other urological diseases</td>
<td>6</td>
<td>3</td>
<td>4.5</td>
</tr>
<tr>
<td>17. miscellaneous (amyloidosis, diabetes, etc)</td>
<td>5</td>
<td>11</td>
<td>8</td>
</tr>
</tbody>
</table>

Figure 1. Mean 24-hour urea excretion. Open bars depict the control group, hatched bars the Pr-restricted group. The significance signs represent significant differences between the two groups. The number of patients at any moment is shown as well.

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respectively (p<0.001). Roughly, the mean decrease in urea excretion in the Pr-restricted groups equals 20g of protein per day.

In the Pr-restricted group, phosphate- and protein excretion also decreased; no change occurred in the control group. Serum phosphate fell significantly in

![Figure 2. Separate survival curves for group A1 versus group B (left panel) and group A2 versus group C (right panel). Dotted lines depict the Pr-restricted groups (B or C). As non-survival criterion a persistent 10 per cent increase of serum creatinine concentration at entry was chosen.](image)

![Figure 3. Relationship of median serum creatinine concentration, plotted against time, in the four groups. Open circles depict the Pr-restricted patients (B or C). Regression lines are drawn for the control groups.

A1: creat=169.50 + 2.31 * month(s); r=0.95; p<0.001.
B: creat=193.32 + 0.25 * month(s); r=0.30; not significant.
A2: creat=405.82 + 5.08 * month(s); r=0.84; p<0.05.
C: creat=357.93 - 1.36 * month(s); r=0.48; not significant.](image)
the Pr-restricted group, and patients in this group ultimately used less aluminium hydroxide. Serum urea fell immediately after institution of the Pr-restricted diet. Thereafter it remained below the starting value. In the controls, a moderate, but consistent increase was noticed. During follow-up no differences in blood pressure, haematocrit, serum alkaline phosphatase, serum albumin and 24-hour excretion of sodium developed within and between the groups.

For analysis of serum creatinine changes we used the four group divisions (A1 versus B, A2 versus C). Survival curves revealed a better survival of Pr-restricted patients (Figure 2). Moreover, it appeared that median serum creatinine concentration in the control group increased every month (Figure 3). In the Pr-restricted patients, median serum creatinine remained constant during the whole observation period.

Discussion

In this study we have shown in a prospective randomised way that early dietary protein restriction can be beneficial in patients with chronic renal failure.

From the urea excretion we concluded that the dietary compliance was sufficient, for some patients it was difficult to adhere to the low protein diet. It is our strong belief that frequent visits to a dietician are a necessary tool for maintaining patients on these diets. This idea is reinforced by the fact that the urea excretion in the combined Pr-restricted group was still decreasing after 12 months. From the dietary interviews we learned that our patients became used to their diets. There were no signs of malnutrition.

The finding of retarding progression of renal failure by low protein diets is in accordance with the hyperfiltration theory of Brenner’s group. As recently stated by Alvestrand and Bergström, amino acids (and proteins) might trigger the secretion of a liver hormone, called glomerulopressin, that reduces the tone of the afferent arteriole [8]. The resulting hyperperfusion and hyperfiltration will lead to structural changes in remnant glomeruli. The histological substrate is glomerulosclerosis.

Not all patients benefit from these diets. There are groups, for example polycystic kidney disease and nephrosclerosis, that show a steady progression to end-stage renal disease despite all efforts to retard it [9,10]. In the case of nephrosclerosis one should realise that a situation exists in which glomeruli hypofiltrate because of afferent vascular abnormalities. The same might hold true for polycystic kidney disease since this disorder is also not characterised by proteinuria. Further analysis of our data might reveal which diagnoses benefit most from the diet.

Thus, low protein diets will have a strong impact on the treatment of patients with chronic renal disease in the future.

References

Open Discussion

BROYER (Paris) What was the change in weight in the control group compared to that of the group treated by the low protein diet?

ROSMAN There was no statistical difference between the groups.

ZAKAR (Hungary) Have you seen an increase in the creatinine clearances in patients with an initial clearance of 50–60ml/min when they are given protein restriction?

ROSMAN There is an improvement in renal function in some patients in this group but others remain stable or deteriorate. Further analysis of our data will be needed to determine if this is dependent on the underlying cause of the renal failure.

ZAKAR Have you had patients with the nephrotic syndrome and chronic renal failure and what was the course of the proteinuria in such patients?

ROSMAN Unfortunately we have not looked specifically at this group.

ZAKAR In my experience a certain decrease in proteinuria is sometimes observed but not in patients with the nephrotic syndrome. It is much more commonly observed in patients with pyelonephritis. In addition in some patients there is an increase in creatinine clearance but this never exceeds 10 per cent of the starting value.

ROSMAN We believe that the reduction in proteinuria we have seen supports Brenner's hypothesis on hyperfiltration.*

BONE (Liverpool) You mentioned that there was a reduction in the phosphate excretion rate and also in the aluminium hydroxide consumption of your patients on protein restriction. Could you tell us of the magnitude of these reductions?

ROSMA\n
The 24 hour phosphate excretion shows significant differences between the groups.

BONE Was there a concomitant reduction in plasma phosphorus concentrations?

ROSMA\n
The serum phosphate decreased in protein restricted patients even though these patients used less aluminium hydroxide.