Effect of a high protein diet in patients with the nephrotic syndrome

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SUMMARY

1. Twelve patients with the nephrotic syndrome were prescribed for 4 week periods a normal protein diet (NPD) containing 1 g of protein/kg ideal body weight. They were then prescribed for further 4 week periods in random order diets with high (HPD) and low (LPD) protein contents, respectively 2.0 and 0.5 g/kg ideal body weight.

2. Compliance was confirmed by dietary history and measurement of urinary urea excretion.

3. Serum albumin was the same on all diets. Twenty-four hour urinary protein excretion increased progressively with increasing dietary protein (LPD 6.1 g, NPD 8.2 g, HPD 9.2 g). Recumbent plasma renin activity and serum phosphate were significantly increased on HPD (plasma renin activity: LPD 5.7, NPD 4.6, HPD 8.2 pmol of angiotensin I min⁻¹ l⁻¹; serum phosphate: LPD 1.27, NPD 1.26, HPD 1.41 mmol/l).

4. There was no evidence of protein-induced hyperfiltration or hyperperfusion: [⁵¹Cr]-ethylenediaminetetraacetate and [¹²⁵I]iodohippurate clearances were similar on all three diets.

5. Since proteinuria, increased plasma renin levels and hyperphosphataemia may contribute to progression of renal failure and because HPD did not improve hypoalbuminaemia, the use of HPD in the nephrotic syndrome should be abandoned.

6. Until it can be established that LPD, which is accompanied by the least proteinuria, does not, with long-term feeding, lead to malnutrition, NPD should be used in the treatment of the nephrotic syndrome.

Key words: dietary protein, nephrotic syndrome.

Abbreviations: ⁵¹Cr-EDTA, ⁵¹Cr-ethylenediaminetetraacetate; ERPF, effective renal plasma flow; GFR, glomerular filtration rate; HPD, high protein diet; LPD, low protein diet; NPD, normal protein diet; NUN, non-urea nitrogen; PRA, plasma renin activity.

INTRODUCTION

The nephrotic syndrome is a condition characterized by proteinuria greater than 3 g in 24 h with hypoalbuminaemia and oedema. The use of a high protein diet (HPD) for the treatment of this condition, in an attempt to maintain serum albumin concentrations, was first described by Epstein in 1917 [1]. Even at that time this treatment was not universally accepted: Kahn in 1920, reporting a series of 37 cases, considered it to be "rather a risky undertaking" [2], and Farr, in 1938, noted that proteinuria increased with increasing dietary protein intake [3]. Despite these initial reservations, an HPD has remained a cornerstone of the treatment of the nephrotic syndrome [4, 5]. However, recent concern over the possible harmful effects of protein-induced glomerular hyperfiltration [6] and increased proteinuria [7–9] have stimulated a re-examination of the effect of varying the dietary protein intake in the nephrotic syndrome [10]. It has been reported that a HPD actually reduced serum albumin and plasma albumin mass in nephrotic subjects compared with a low protein diet (LPD) because the increase in albuminuria exceeded that in albumin synthesis, but this study did not include detailed renal function studies to assess possible long-term adverse effects of protein feeding from glomerular hyperfiltration [11].

The present study was designed to determine the effect of three levels of dietary protein intake, the minimum daily requirement for healthy adults, 0.5 g day⁻¹ kg⁻¹ (LPD), a 'standard' intake of 1.0 g day⁻¹ kg⁻¹ (normal protein diet, NPD) and a high intake of 2.0 g day⁻¹ kg⁻¹ (HPD), on glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) as well as on urinary protein excretion and serum albumin concentration.
were then prescribed in random order 2.0 and 0.5 periods. During these, the patients were prescribed diets containing 1.0, 2.0 and 0.5 g protein day$^{-1}$ kg$^{-1}$.

**Experimental design**

Weight and height were measured without shoes, wearing light indoor clothing. After remaining recumbent for 120 min venous blood was drawn for measurement of aldosterone, plasma renin activity (PRA), plasma creatinine, urea and electrolytes, and serum albumin. Lying and standing blood pressure were measured with a Hawksley random zero sphygmononometer. After 120 min mobilization a further sample of venous blood was drawn for repeat measurements of PRA and aldosterone. GFR and ERPF were both measured using a single injection isotope technique [12–14]. $^{51}$Cr-Ethlenediaminetetraacetate ($^{51}$Cr-EDTA; 2.2 MBq) for determination of GFR and $^{125}$Iodohippurate (1 MBq) for estimation of ERPF were administered into a forearm vein. Samples of venous blood were taken from the contralateral arm at 10, 20, 30, 44, 60, 120 and 240 min after injection. Patients rested after injection to avoid the effect of exercise on ERPF.

**Analytical methods**

Plasma and urine creatinine were measured by the Jaffé reaction on a Beckman Astra 8 autoanalyser. Plasma and urinary sodium and potassium were measured by flame photometry. Serum and urinary phosphate were measured spectrophotometrically using the acid ammonium molybdate reaction. Urinary protein concentration was measured using the Lowry method [15]. PRA was measured by the estimation of angiotensin I generation [16] (RIANEN Angiotensin I kit, New England Nuclear), with intra-assay and inter-assay coefficients of variation of 9.2% and 14.2%, respectively. Aldosterone was measured by a solid-phase radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA, U.S.A.); for a sample containing 560 pmol/l, intra-assay and inter-assay coefficients of variation were 3.6% and 4.0%, respectively. $^{51}$Cr-EDTA and $^{125}$Iodohippurate plasma activity were measured simultaneously on a Philips Automatic Gamma Counter and a cross-over correction was applied. Dilution spaces of injected $^{51}$Cr-EDTA at 120 and 240 min were calculated and used in the formula of Morgan et al. [12], previously validated in our laboratory. ERPF was calculated from bi-exponential analysis of the plasma disappearance curve of $^{125}$Iodohippurate using the 44–60 min data for obtaining the residual slope.

**Assessment of dietary compliance**

Dietary compliance was checked after 2 weeks of each diet by telephone interview to encourage adherence to the diet. Quantitative assessments of compliance were obtained at the end of the 4 week period on each diet from a 4 day food record, using household measures [17], and measurement of urinary urea excretion. A dietary interview was conducted after a 4 day food record and dietary protein intake was calculated from this. Two 24 h urine collections were also obtained at the end of each dietary period and the urea and protein concentrations were measured. The rate of urea nitrogen production is equal to the 24 h urea nitrogen excretion assuming that there is no change in the body urea nitrogen pool during the collection period. Loss of nitrogen in the form of protein was calculated from the 24 h urinary excretion assuming that, on average, 1 g of nitrogen is found in 6.25 g of protein. Non-urea nitrogen (NUN) excretion was estimated using an assumed NUN excretion of 31 mg day$^{-1}$ kg$^{-1}$ [18]. It was thus possible to estimate total nitrogen output from urea nitrogen plus urinary protein nitrogen and NUN. In a steady-state condition nitrogen output should equal nitrogen intake and thus an estimate of dietary protein intake can be made.

**Table 1. Clinical details of the patients studied**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Primary renal disease</th>
<th>Ideal body weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>58</td>
<td>Membranous GN</td>
<td>116</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>63</td>
<td>Mesangio-capsillary GN</td>
<td>124</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>62</td>
<td>Membranous GN</td>
<td>118</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>44</td>
<td>Amyloid</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>46</td>
<td>Minimal change GN</td>
<td>110</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>66</td>
<td>Minimal change GN</td>
<td>102</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>71</td>
<td>Hypertension</td>
<td>102</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>66</td>
<td>Mesangio-capsillary GN</td>
<td>104</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>69</td>
<td>Membranous GN</td>
<td>106</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>65</td>
<td>Membranous GN</td>
<td>106</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>52</td>
<td>Membranous GN</td>
<td>117</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>43</td>
<td>Mesangio-capsillary GN</td>
<td>111</td>
</tr>
</tbody>
</table>

**Methodology**

Subjects

Twelve patients participated in the study (Table 1). Inclusion criteria were: age between 21 and 75 years, urinary protein excretion greater than 3 g/24 h, serum albumin concentration less than 34 g/l and serum creatinine less than 500 pmol/l. The exclusion criteria were: coexisting hepatic, gastrointestinal or systemic disease and steroid treatment within the previous 6 months. The experimental protocol was approved by the Joint Ethics Committee of the University of Newcastle upon Tyne and the Newcastle Health Authority.

Experimental design

The study consisted of three consecutive 4 week periods. During these, the patients were prescribed diets containing 1.0, 2.0 and 0.5 g protein day$^{-1}$ kg$^{-1}$ ideal body weight. All patients started on 1.0 g day$^{-1}$ kg$^{-1}$ and were then prescribed in random order 2.0 and 0.5 g day$^{-1}$ kg$^{-1}$. At the end of each dietary period the patients were admitted to the Metabolic Investigation Unit after a 10 h overnight fast. On each occasion they were asked to bring two 24 h urine collections from the previous 48 h.

**Analytical methods**

Plasma and urine creatinine were measured by the Jaffé reaction on a Beckman Astra 8 autoanalyser. Plasma and urinary sodium and potassium were measured by flame photometry. Serum and urinary phosphate were measured spectrophotometrically using the acid ammonium molybdate reaction. Urinary protein concentration was measured using the Lowry method [15]. PRA was measured by the estimation of angiotensin I generation [16] (RIANEN Angiotensin I kit, New England Nuclear), with intra-assay and inter-assay coefficients of variation of 9.2% and 14.2%, respectively. Aldosterone was measured by a solid-phase radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA, U.S.A.); for a sample containing 560 pmol/l, intra-assay and inter-assay coefficients of variation were 3.6% and 4.0%, respectively. $^{51}$Cr-EDTA and $^{125}$Iodohippurate plasma activity were measured simultaneously on a Philips Automatic Gamma Counter and a cross-over correction was applied. Dilution spaces of injected $^{51}$Cr-EDTA at 120 and 240 min were calculated and used in the formula of Morgan et al. [12], previously validated in our laboratory. ERPF was calculated from bi-exponential analysis of the plasma disappearance curve of $^{125}$Iodohippurate using the 44–60 min data for obtaining the residual slope.

**Assessment of dietary compliance**

Dietary compliance was checked after 2 weeks of each diet by telephone interview to encourage adherence to the diet. Quantitative assessments of compliance were obtained at the end of the 4 week period on each diet from a 4 day food record, using household measures [17], and measurement of urinary urea excretion. A dietary interview was conducted after a 4 day food record and dietary protein intake was calculated from this. Two 24 h urine collections were also obtained at the end of each dietary period and the urea and protein concentrations were measured. The rate of urea nitrogen production is equal to the 24 h urea nitrogen excretion assuming that there is no change in the body urea nitrogen pool during the collection period. Loss of nitrogen in the form of protein was calculated from the 24 h urinary excretion assuming that, on average, 1 g of nitrogen is found in 6.25 g of protein. Non-urea nitrogen (NUN) excretion was estimated using an assumed NUN excretion of 31 mg day$^{-1}$ kg$^{-1}$ [18]. It was thus possible to estimate total nitrogen output from urea nitrogen plus urinary protein nitrogen and NUN. In a steady-state condition nitrogen output should equal nitrogen intake and thus an estimate of dietary protein intake can be made.

**Statistical analysis**

Normal probability plots were used to assess the distribution of the variables measured. Plasma urea, plasma creatinine, PRA and plasma aldosterone were all positively skewed. Log transformation normalized the distri-
Dietary protein in the nephrotic syndrome

bution of plasma urea, PRA and plasma aldosterone, but not that of plasma creatinine.

Two-way analysis of variance was used to compare the effects of the three different dietary protein intakes when the distribution of the variable was either normal or was normalized with log transformation. Plasma creatinine values at the end of the three dietary periods were compared using Friedman’s block/treatment test.

Due to unsatisfactory urine collections and food records, data were missing for some of the patients. They were therefore excluded from the appropriate analysis of variance. However, the unmatched datapoints have been shown in Figs. 4 and 5.

RESULTS

GFR and ERPF (Table 2)

There were no significant differences in GFR at the end of the three dietary periods. ERPF was lower at the end of the LPD compared with the end of the HPD and the NPD, but this did not reach statistical significance.

Urinary protein, phosphate and sodium (Table 2)

Twenty-four hour urinary protein excretion (Fig. 1) was highest at the end of the HPD and lowest at the end of the LPD (LPD, 6.1, NPD 8.2, HPD 9.2 g). The values for the HPD, NPD and LPD were all significantly different (LPD vs NPD P<0.05, NPD vs HPD P<0.05, LPD vs HPD P<0.001). Twenty-four hour urinary phosphate excretion was highest at the end of the HPD and lowest at the end of the LPD (LPD 20, NPD 25, HPD 30 mmol/l), the two values being significantly different (P<0.01). Urinary sodium excretion was highest at the end of the HPD and lowest at the end of the LPD. The values for the LPD, NPD and HPD were all significantly different from each other (LPD vs NPD P<0.01, NPD vs HPD P<0.05, LPD vs HPD P<0.001).

Serum total protein, albumin and phosphate (Table 3)

There were no significant differences in either total protein or albumin at the end of the three dietary periods. Serum phosphate (Fig. 2) was significantly higher at the end of the HPD than at the end of the LPD and the NPD (LPD 1.27, NPD 1.26, HPD 1.41 mmol/l). The three values were significantly different from each other (LPD vs NPD P<0.01, NPD vs HPD P<0.001, LPD vs HPD P<0.001).

Plasma urea and creatinine (Table 3)

There was no significant difference in plasma creatinine at the end of the three dietary periods. Plasma urea, however, was highest at the end of the HPD and lowest at the end of the LPD (LPD 9.5, NPD 11.5, HPD 15.7 mmol/l). The three values were significantly different from each other (LPD vs NPD P<0.01, NPD vs HPD P<0.001, LPD vs HPD P<0.001).

Fig. 1. Urinary protein excretion at the end of periods of dietary protein intake of 0.5 (LPD), 1.0 (NPD) and 2.0 (HPD) g/kg ideal body weight. Results are shown as means ± SEM.

Table 2. GFR, ERPF, filtration fraction, urinary protein, phosphate and sodium excretion at the end of periods of dietary protein intake of 0.5 (LPD), 1.0 (NPD) and 2.0 (HPD) g/kg ideal body weight

<table>
<thead>
<tr>
<th></th>
<th>LPD</th>
<th>NPD</th>
<th>HPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml min⁻¹ 1.73 m⁻²)</td>
<td>60</td>
<td>56</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>(45–74)</td>
<td>(42–70)</td>
<td>(44–73)</td>
</tr>
<tr>
<td>ERPF (ml min⁻¹ 1.73 m⁻²)</td>
<td>261</td>
<td>278</td>
<td>282</td>
</tr>
<tr>
<td></td>
<td>(189–333)</td>
<td>(205–351)</td>
<td>(211–369)</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>0.24</td>
<td>0.19</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>(0.16–0.31)</td>
<td>(0.14–0.23)</td>
<td>(0.16–0.22)</td>
</tr>
<tr>
<td>Urinary protein excretion (g/24 h)</td>
<td>6.1ᵃᵇᶜ</td>
<td>8.2ᵃᵇ</td>
<td>9.2ᵃᵇᶜ</td>
</tr>
<tr>
<td></td>
<td>(3–9)</td>
<td>(5–11)</td>
<td>(5–13)</td>
</tr>
<tr>
<td>Urinary phosphate excretion (mmol/24 h)</td>
<td>20ᶜ</td>
<td>25</td>
<td>30ᶜ</td>
</tr>
<tr>
<td></td>
<td>(15–25)</td>
<td>(18–33)</td>
<td>(21–39)</td>
</tr>
<tr>
<td>Urinary sodium excretion (mmol/24 h)</td>
<td>134ᵃᶜ</td>
<td>161ᵇ</td>
<td>190ᵇᶜ</td>
</tr>
<tr>
<td></td>
<td>(99–168)</td>
<td>(123–200)</td>
<td>(134–245)</td>
</tr>
</tbody>
</table>
Table 3. Serum levels of total protein, albumin and phosphate, and plasma levels of urea and creatinine at the end of periods of dietary protein intake of 0.5 (LPD), 1.0 (NPD) and 2.0 (HPD) g/kg ideal body weight

Results for total protein, albumin and phosphate are shown as means (95% confidence limits), for urea as the geometric mean (95% confidence limits) and for creatinine as the median (10–90 percentile). Values bearing the same superscript letter are significantly different from each other.

<table>
<thead>
<tr>
<th></th>
<th>LPD</th>
<th>NPD</th>
<th>HPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum total protein (g/l)</td>
<td>53</td>
<td>51</td>
<td>53</td>
</tr>
<tr>
<td>(49–58)</td>
<td>(46–56)</td>
<td>(48–58)</td>
<td></td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>29</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Serum phosphate (mmol/l)</td>
<td>1.27</td>
<td>1.26c</td>
<td>1.41bc</td>
</tr>
<tr>
<td>(1.10–1.44)</td>
<td>(1.04–1.47)</td>
<td>(1.20–1.63)</td>
<td></td>
</tr>
<tr>
<td>Plasma urea (mmol/l)</td>
<td>9.5c</td>
<td>11.5b</td>
<td>15.7bc</td>
</tr>
<tr>
<td>(3.8–15.2)</td>
<td>(5.6–17.3)</td>
<td>(7.8–23.5)</td>
<td></td>
</tr>
<tr>
<td>Plasma creatinine (μmol/l)</td>
<td>129</td>
<td>124</td>
<td>132</td>
</tr>
<tr>
<td>(104–473)</td>
<td>(102–484)</td>
<td>(98–524)</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2. Serum phosphate at the end of periods of dietary protein intake of 0.5 (LPD), 1.0 (NPD) and 2.0 (HPD) g/kg ideal body weight. Results are shown as means ± SEM.

Fig. 3. Lying (■) and standing (○) PRA at the end of periods of dietary protein intake of 0.5 (LPD), 1.0 (NPD) and 2.0 (HPD) g/kg ideal body weight. Results are shown as geometric means ± SEM. Abbreviation: ANG I, angiotensin I.

Table 4. Lying and standing PRA and aldosterone at the end of periods of dietary protein intake of 0.5 (LPD), 1.0 (NPD) and 2.0 (HPD) g/kg ideal body weight

Results for PRA are shown as the geometric mean (95% confidence limits) and for aldosterone as the mean (95% confidence limits). Values bearing the same superscript letter are significantly different from each other. Abbreviation: ANG I, angiotensin I.

<table>
<thead>
<tr>
<th></th>
<th>LPD</th>
<th>NPD</th>
<th>HPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA (pmol of ANG I min⁻¹ l⁻¹)</td>
<td>5.7d</td>
<td>12.2a</td>
<td>4.6a,b</td>
</tr>
<tr>
<td>(3.5–9.2)</td>
<td>(6.2–23.8)</td>
<td>(3.0–7.1)</td>
<td>(5.2–12.8)</td>
</tr>
<tr>
<td>Plasma aldosterone (pmol/l)</td>
<td>181a</td>
<td>340d</td>
<td>176c</td>
</tr>
</tbody>
</table>

PRA and plasma aldosterone (Table 4 and Fig. 3)

Lying PRA was significantly higher at the end of the HPD than at the end of the NPD (HPD 8.2, NPD 4.6 pmol of angiotensin I min⁻¹ l⁻¹, P<0.05). Aldosterone, lying and standing, was not significantly different at the end of the three dietary periods.

Blood pressure

Systolic/diastolic blood pressure did not change with the three diets, being on average 140/81 mmHg (18.7/10.8 kPa) at the end of the LPD, 150/89 mmHg (20.0/11.9 kPa) at the end of the NPD and 146/86 mmHg (19.5/11.5 kPa) at the end of the HPD.
Dietary compliance (Figs. 4 and 5)

Urea nitrogen appearance increased with increasing dietary protein intake (LPD 6.0, NPD 9.6, HPD 15.0 g/24 h) and the values were all significantly different (LPD vs NPD, P<0.05, NPD vs HPD, P<0.01, LPD vs HPD, P<0.001). During the LPD, the dietary history and urea excretion suggested that the patients were taking more protein than prescribed (intake calculated from dietary history 0.60 g day\(^{-1}\) kg\(^{-1}\); intake calculated from urea excretion 0.72 g day\(^{-1}\) kg\(^{-1}\)). During the NPD, the dietary history and the urinary urea excretion suggested that the subjects were staying close to the prescribed intake (intake calculated from dietary history 1.13 g day\(^{-1}\) kg\(^{-1}\); intake calculated from urea excretion 0.99 g day\(^{-1}\) kg\(^{-1}\)). During the HPD, dietary history suggested that the subjects were consuming an intake close to that prescribed, whereas the urinary urea suggested that they were consuming less than the prescription (intake calculated from dietary history 1.82 g day\(^{-1}\) kg\(^{-1}\); intake calculated from urea excretion 1.28 g day\(^{-1}\) kg\(^{-1}\)). However, the differences in protein intake on the three diets reached significance with both methods of estimation (dietary history: LPD vs NPD, P<0.001, NPD vs HPD, P<0.001, LPD vs HPD, P<0.001; urea excretion: LPD vs NPD, P<0.05, NPD vs HPD, P<0.01, LPD vs HPD, P<0.001).

DISCUSSION

We were able to achieve a satisfactory degree of compliance with the LPD, NPD and HPD each sustained for 4 weeks with significant differences in protein intake on the three diets assessed by dietary history and urinary urea excretion. Despite proven compliance with the diets, there was no increase in serum albumin on the HPD in keeping with the findings of Kaysen et al. [3, 4] using a diet of similar protein content. It may be that in order to raise serum albumin an even greater protein intake is required, since positive nitrogen balance can be achieved in nephrotic patients by increasing the protein intake further [3, 4]. However, both in the present study and that of Kaysen et al. [11] serum albumin was actually higher during the LPD than during the HPD, although the difference did not reach significance in our patients.

Urinary protein excretion was significantly increased during the HPD, as has been reported previously [3, 11], and this is of some concern since it has been suggested that proteinuria may itself contribute to the progression of renal failure [8, 9]. Urinary protein excretion was lowest during the LPD without reduction in serum albumin, suggesting that a LPD may be preferable not only to a HPD as has been suggested [11] but also to a NPD. The previous similar study to ours [11] did not include an NPD period.

An HPD increases basal GFR and ERPF in normal subjects [19] and in animals with reduced renal mass [6], raising the possibility that potentially harmful hyperfiltration may occur on an HPD in the nephrotic syndrome. It has been reported that an oral protein load acutely increases GFR and ERPF in patients with the nephrotic syndrome [20]. However, Kaysen et al. [11] found no change in 'basal' creatinine clearance with increasing dietary protein intake in patients with the nephrotic syndrome and our observations using the more reliable \(^{51}\)Cr-EDTA clearance as a measure of GFR have confirmed their finding. In addition, we have found no change in ERPF. Since the mechanism of the increase in GFR with protein feeding is not known, it is not possible to speculate on the reasons for the absence of a response in nephrotic syndrome, but mean GFR was reduced in our patients and in those of Kaysen et al. [11] to a level at which loss of renal functional reserve has been reported [21, 22]. Although 'basal' GFR and ERPF were not significantly different at the end of the three different dietary protein levels, it is possible that the change in protein...

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**Fig. 4.** Dietary protein intake estimated from dietary history during periods of dietary protein intake of 0.5 (LPD), 1.0 (NPD) and 2.0 (HPD) g/kg ideal body weight. Individual results are shown. Statistical significance: LPD vs NPD, P<0.001; NPD vs HPD, P<0.001; LPD vs HPD, P<0.001.

**Fig. 5.** Dietary protein intake estimated from urinary urea excretion during periods of dietary protein prescription of 0.5 (LPD), 1.0 (NPD) and 2.0 (HPD) g/kg ideal body weight. Individual results are shown. Statistical significance: LPD vs NPD, P<0.05; NPD vs HPD, P<0.01; LPD vs HPD, P<0.001. Some data points were not available (see the text).
excretion that we have seen reflects acute changes in the response to increased dietary protein.

PRA was increased during the HPD in nephrotic patients in keeping with our earlier observations in normal subjects [19]. This may have a long-term deleterious effect on renal function, since it may increase intraglomerular pressure through angiotensin-induced vascular constriction of the efferent arteriole. In addition, angiotensin may cause accumulation of macromolecules in the mesangium [23] and stimulate proliferation of proximal tubular cells [24] and therefore possibly other renal cells contributing to the development of glomerulosclerosis. However, these effects have as yet not been confirmed in the nephrotic syndrome in humans. The mechanism by which PRA was increased during the HPD is not clear. It did not seem to be related to sodium depletion, since urinary sodium was not reduced.

In animal models of chronic renal failure, reduction in plasma phosphate either by dietary measures or administration of phosphate binders [25, 26] has been shown to delay the progression of renal failure. In humans, a clear relationship between hyperphosphataemia and rate of progression of renal disease has not been established [27, 28]; nevertheless the rise in plasma phosphate which accompanied the HPD in our patients represents a further potential cause for concern.

Hypertension probably contributes to the progression of renal failure [29] and although there was no change in blood pressure with 4 weeks of each diet in this study, the increase in sodium excretion, indicating increased intake, which we have observed during the HPD may in the long term lead to increases in blood pressure. Thus increasing dietary protein to 2 g day$^{-1}$ kg$^{-1}$ did not improve hypoalbuminaemia in the nephrotic syndrome and although it was not accompanied by a potentially damaging increase in GFR or in blood pressure in comparison with the normal diet there was an increase in urinary protein, in PRA and in plasma phosphate, all of which may contribute to the progression of renal damage. The LPD was associated with the lowest urinary albumin excretion and serum albumin was maintained. However, it is not certain that protein malnutrition would not develop with prolonged administration of this diet [10]. Urinary protein during the NPD was significantly lower than during protein loading, although higher than during protein restriction, and as in protein restriction serum albumin was maintained and PRA was not increased.

We propose that the prescription of a HPD in the nephrotic syndrome should be abandoned and, pending the results of long-term trials of protein-restricted diets, a 'normal' diet containing 1 g of protein day$^{-1}$ kg$^{-1}$ ideal body weight should be recommended.

ACKNOWLEDGMENTS

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