THE EFFECT OF CALORIC INTAKE ON NITROGEN BALANCE IN CHRONIC RENAL FAILURE

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SUMMARY

1. Nitrogen balance in uraemic patients on similar nitrogen intakes improves with increasing caloric intake in the range of 36–55 cal/kg body weight.
2. The degree of improvement in nitrogen balance is compatible with increased utilization of endogenous nitrogen probably as a result of increased dietary calories.

Key words: calories, nitrogen balance, chronic renal failure.

Giordano (1963) demonstrated that nitrogen equilibrium could be achieved in chronic renal failure on a nitrogen intake which was less than the minimal nitrogen requirement for normal subjects. His diet was mainly synthetic, and a practical diet with low-protein foods was first devised by Giovannetti & Maggiore (1964), later modified to suit British palates by Shaw, Bazzard, Booth, Nilwarangkur & Berlyne (1965). This diet contained a large proportion of high-biological-value protein providing all the essential amino acids except methionine in the amounts recommended by Rose, Wixom, Lockhart & Lambert (1955), a methionine supplement and an adequate supply of calories.

Since that time there has been considerable controversy about the minimal nitrogen requirement for equilibrium in chronic renal failure. Shaw et al. (1965) recommended 0.26 g of protein per kg/body weight, Giovannetti & Maggiore (1964) 0.3 g and Ford, Phillips, Toye, Luck & de Wardener (1969) 0.5 g. Giovannetti (1966) stated that for the diet to be successful a high caloric intake was necessary. Ford et al. (1969) concluded that caloric intake had no effect on nitrogen metabolism in chronic renal failure. However, since their experimental protocol did not compare the effects of changing caloric intakes on nitrogen balance while on isonitrogenous diets, their nitrogen intake changing over a fourfold range, no firm conclusions can be drawn. We report here the results of an investigation into the effect of caloric intake on nitrogen metabolism in chronic renal failure.

MATERIALS AND METHODS

Patients

Our observations are based on studies carried out on seven patients with different degrees of stable chronic renal failure, all of whom remained uninfected throughout the balance.

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<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Creatinine (mg/100 ml)</th>
<th>Creatinine clearance (ml/min)</th>
<th>Blood urea (mg/100 ml)</th>
<th>B.P. Haemoglobin (g/100 ml)</th>
<th>Albumin (g/100 ml)</th>
<th>Haemoglobin balance</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.T.</td>
<td>42</td>
<td>M</td>
<td>88.9</td>
<td>8.5</td>
<td>&lt;5</td>
<td>74</td>
<td>92</td>
<td>130</td>
<td>11.2</td>
<td>3.3</td>
</tr>
<tr>
<td>C.B.</td>
<td>36</td>
<td>M</td>
<td>50</td>
<td>6.0</td>
<td>18.6</td>
<td>68</td>
<td>38</td>
<td>160</td>
<td>14.4</td>
<td>5.0</td>
</tr>
<tr>
<td>J.W.</td>
<td>31</td>
<td>M</td>
<td>66.2</td>
<td>17.5</td>
<td>&lt;5</td>
<td>96</td>
<td>80</td>
<td>170</td>
<td>11.3</td>
<td>3.6</td>
</tr>
<tr>
<td>T.G.</td>
<td>57</td>
<td>M</td>
<td>62.8</td>
<td>15.5</td>
<td>3.8</td>
<td>135</td>
<td>120</td>
<td>180</td>
<td>7.6</td>
<td>3.4</td>
</tr>
<tr>
<td>M.H.</td>
<td>49</td>
<td>F</td>
<td>46.3</td>
<td>12.6</td>
<td>3.4</td>
<td>134</td>
<td>103</td>
<td>160</td>
<td>6.9</td>
<td>4.0</td>
</tr>
<tr>
<td>R.M.</td>
<td>46</td>
<td>F</td>
<td>50.8</td>
<td>13.5</td>
<td>1.5</td>
<td>190</td>
<td>150</td>
<td>140</td>
<td>5.8</td>
<td>3.0</td>
</tr>
<tr>
<td>I.H.</td>
<td>44</td>
<td>F</td>
<td>49.6</td>
<td>9.7</td>
<td>6.0</td>
<td>94</td>
<td>82</td>
<td>130</td>
<td>8.8</td>
<td>3.1</td>
</tr>
</tbody>
</table>

**Table 1.** Clinical details of seven patients with stable chronic renal failure on whom nitrogen balance studies were carried out.
Calorie intake and nitrogen balance in uraemia

Studies. None of these patients required dialysis during the observation period or had required dialysis before starting these balance studies. All were volunteers who gave informed consent to the studies after a full explanation of the protocol. The clinical details of the patients before balance are shown in Table 1.

Methods

Seven nitrogen balances were carried out on seven patients in a Metabolic Ward according to the principles of Reifenstein, Albright & Wells (1945). Balances were carried out with a constant dietary intake of known nitrogen and caloric content, over 4-day periods totalling 8 days in two studies, 12 days in two studies, 16 days in one study and 24 days in two studies.

Before balance studies urinary excretion of protein, urea and electrolytes were measured on two 24 h urine specimens, with a diet closely approximating to the experimental one.

Urine was collected over 48 h periods and kept at 4°C. Faecal collections were made over 4 days by using carmine markers to delineate balance periods. Blood for urea, electrolytes, total protein, albumin and haemoglobin was taken before breakfast on day 1 and at 4-day intervals, the final specimen being taken on the morning after the end of the last balance period.

Urea was measured by the diacetyl monoxine method (A.C.P. Technical Bulletin Number 9) and creatinine by automatic colorimetry (Technicon AutoAnalyzer, method N.116). Sodium and potassium were measured by flame photometry (Technicon AutoAnalyzer, method N.21A). Serum bicarbonate was measured by the phenolphthalein method (Technicon AutoAnalyzer, method N.8B) and total serum protein by the biuret method. Albumin was measured by the Bromocresol Green method (A.C.P. Technical Bulletin Number 11). Haemoglobin was measured on a Coulter S automatic counter. Urine, faeces, and diet were analysed for total nitrogen by a micro-Kjeldahl method (Ingram, 1962).

Since urea may be utilized as a nitrogen source in chronic renal failure the net body-protein nitrogen change (B') was estimated from the external balance (B) by allowing for changes in body urea nitrogen. Urea was assumed to be distributed equally throughout total body water at the same concentration as in plasma. Total body water was taken as 65% of body weight in men and 52% in women (Edelman, Haley, Schloerb, Shalton, Friis-Hansen, Stoll & Moore, 1952) and changes in plasma urea between the beginning and end of each 4-day period were converted into changes in total body-water urea nitrogen in g per day (Δ UN). Thus B' = B − Δ UN.

Diet

A diet as close as possible to the experimental diet was taken for 1−2 weeks as an outpatient, and the experimental diet was started as an in-patient 4 days before the balance studies began except in one patient R.M. A detailed dietary history was taken from each patient and the experimental diet tailored to suit individual tastes.

The diet was designed to provide a net intake of 40−45 mg of nitrogen/kg body wt. per day in five studies and 50−54 mg/kg per day in two studies. The total required dietary nitrogen was calculated by adding the amount of urinary protein nitrogen excreted per day to the net nitrogen intake. The main source of high-biological-value protein was whole egg which was served fried (three studies) or made into a pancake with low-protein flour (two studies) or made into a waffle (one study). Milk, double cream and butter supplied the rest of the high-
<table>
<thead>
<tr>
<th>Subject</th>
<th>Balance duration (days)</th>
<th>Total protein nitrogen (g/day)</th>
<th>Urinary protein nitrogen (g/day)</th>
<th>Net protein nitrogen (g/day)</th>
<th>Calories (total) (cal/kg)</th>
<th>Urinary nitrogen (g/day)</th>
<th>Faecal nitrogen (g/day)</th>
<th>Rejects nitrogen (g/day)</th>
<th>B' = B - Δ UN Nitrogen (mg/kg per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.T.</td>
<td>8</td>
<td>3.68</td>
<td>1.17</td>
<td>2.51</td>
<td>29.0</td>
<td>3.47</td>
<td>1.44</td>
<td>-1.23</td>
<td>1.83</td>
</tr>
<tr>
<td>C.B.</td>
<td>12</td>
<td>2.72</td>
<td>0.384</td>
<td>2.34</td>
<td>46.0</td>
<td>2.84</td>
<td>1.11</td>
<td>-1.23</td>
<td>-0.91</td>
</tr>
<tr>
<td>J.W.</td>
<td>8</td>
<td>2.80</td>
<td>0.256</td>
<td>2.54</td>
<td>39.0</td>
<td>2.55</td>
<td>0.964</td>
<td>-1.24</td>
<td>-1.06</td>
</tr>
<tr>
<td>T.G.</td>
<td>16</td>
<td>2.84</td>
<td>0.36</td>
<td>2.48</td>
<td>39.4</td>
<td>2.85</td>
<td>1.23</td>
<td>-1.24</td>
<td>-1.06</td>
</tr>
<tr>
<td>M.H.</td>
<td>24</td>
<td>2.71</td>
<td>0.16</td>
<td>2.55</td>
<td>54.0</td>
<td>2.51</td>
<td>0.81</td>
<td>-0.66</td>
<td>-0.5</td>
</tr>
<tr>
<td>R.M.</td>
<td>12</td>
<td>2.10</td>
<td>0.112</td>
<td>1.99</td>
<td>38.7</td>
<td>2.14</td>
<td>0.673</td>
<td>-0.77</td>
<td>-0.36</td>
</tr>
<tr>
<td>I.H.</td>
<td>24</td>
<td>2.79</td>
<td>0.31</td>
<td>2.48</td>
<td>50.0</td>
<td>2.36</td>
<td>0.763</td>
<td>-0.34</td>
<td>-0.28</td>
</tr>
</tbody>
</table>
biological-value protein which was kept between 70% and 80% of the total protein intake. Second-class protein was contained in vegetables and fruit, low-protein bread (wheatstarch flour, Energen, Rite Diet) and crispbread (Aproten crispbread, Carlo Erba), jam, marmalade, sugar and cornflour.

The caloric intake was kept constant in any one study and ranged between 36 and 55 cal/kg per day. The percentage carbohydrate calories varied between 50% and 70%. The carbohydrate calorie sources were Hycal (Beecham's Limited), Caloreen (Scientific Hospital Supplies Limited), wheatstarch, glucose, jam, sugar, cornflour and sucrose. The fat calories were derived from butter and double cream.

A duplicate 24 h diet was analysed for total nitrogen in each 4-day period. All rejects were collected and analysed in 4-day pools. The essential amino acid content of each diet was estimated from tables prepared by Orr & Watt (1957) and met the minimal requirements as set out by Rose et al. (1955) except for methionine. No methionine supplement was given. The sodium content of the diet was based on known 24 h urine sodium excretions measured before balance. All subjects took vitamin C (75 mg/day) and compound vitamin B supplements (four tablets daily).

RESULTS

Balance data on all patients are summarized in Table 2. Balance technique was considered satisfactory in all seven studies and all patients were in a steady state throughout the balance studies. The results of a typical nitrogen balance study are shown in Fig. 1.

The nitrogen intake achieved in these patients was very close to that desired with a variation of 39–54 mg/kg body weight except in one case J.T. (29 mg/kg body weight) where proteinuria had been underestimated.
Caloric intake and nitrogen balance

Fig. 2 shows the relationship between $B'$ expressed in mg of nitrogen/kg body weight and caloric intake in cal/kg body weight. Although the net nitrogen intakes are not exactly the same a regression line shows a relationship with caloric intake. Fig. 3 shows that over the narrow range of net nitrogen intake obtained in our experiments there was no correlation between net intake and $B'$.

In Fig. 2 two points have been added from the data of Ford et al. (1969) and Herndon et al. (1958). These four results have been selected from these workers' data because the nitrogen intake corresponded closely to that used in the present study.

Urinary nitrogen, $B'$ and dietary nitrogen

Table 3 shows no correlation between urinary nitrogen and $B'$. It is of interest that urinary nitrogen is similar to total dietary intake at all values of $B'$, the urinary nitrogen/dietary nitrogen ratio approaching close to 100% (98.4 ± 11.1% SD) irrespective of $B'$.

Caloric intake, blood urea and $B'$

No relationship was found between the amount of blood urea and $B'$ nor was blood urea correlated with faecal nitrogen (B. E. B. Hyne, unpublished observations).
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Fig. 3. Variation of B' (corrected nitrogen balance) with increased net dietary nitrogen intake within the range obtained in these patients, showing no significant improvement.

Table 3. Urinary nitrogen, B' and dietary nitrogen. Note how urinary nitrogen closely approximates total nitrogen intake at all values.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Urinary nitrogen (mg/kg)</th>
<th>B' (mg/kg)</th>
<th>Total nitrogen intake (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.T.</td>
<td>40.1</td>
<td>-21.17</td>
<td>42.5</td>
</tr>
<tr>
<td>C.B.</td>
<td>56.3</td>
<td>-16.86</td>
<td>53.9</td>
</tr>
<tr>
<td>J.W.</td>
<td>37.9</td>
<td>-4.5</td>
<td>41.6</td>
</tr>
<tr>
<td>T.G.</td>
<td>45.9</td>
<td>-17.1</td>
<td>45.8</td>
</tr>
<tr>
<td>M.H.</td>
<td>54.0</td>
<td>-10.9</td>
<td>54.0</td>
</tr>
<tr>
<td>R.M.</td>
<td>41.6</td>
<td>-7.1</td>
<td>40.8</td>
</tr>
<tr>
<td>I.H.</td>
<td>47.2</td>
<td>-5.6</td>
<td>55.5</td>
</tr>
</tbody>
</table>

Discussion

Considerable experimental work has shown an inter-relation between nitrogen balance, dietary nitrogen intake and caloric intake. Calloway & Spector (1954) in a survey of the literature concluded that 'at each fixed adequate protein intake there is an individual limiting energy level beyond which increasing calories without protein or protein without calories is without
For normal men on a mixed diet with a dietary nitrogen intake of 3-4 g daily no further improvement in nitrogen balance can be achieved by increasing the daily caloric intake above 800. The nitrogen balance in such individuals was about -4 g of nitrogen daily. This implies that no further improvement in nitrogen retention can be achieved by increasing the caloric intake above 800 calories if the protein intake is not also increased. In contrast, considerably better nitrogen balance can be achieved in chronic renal failure on nitrogen intakes of about 3 g/day provided that the diet contains a high proportion of high-biological-value protein. Giordano (1963) suggested that this improvement might be due to reutilization of ammonia derived from urea by hydrolysis by gut bacteria. Work by Rose & Dekker (1956) in the rat showed that ammonia and urea could be utilized as a 'non-essential' nitrogen source.

![Graph showing the variation of B' with the caloric intake.](image)

**FIG. 4. Variation of B' with the caloric intake.** The solid line, calculated from the data of Miller & Payne (1963), represents the relationship between B' and caloric intake in normal individuals on a low-nitrogen intake of 3-4 g per day. The single points show the improvement in B' with increasing caloric intake in patients with chronic renal failure on similar low-nitrogen intakes.

○, Results from the present study; ▲, results from Ford *et al.* (1969); □, results from Herndon *et al.* (1958).

Walser & Bodenlos (1959) demonstrated recirculation of ammonia nitrogen derived from urea in normal subjects and Richards, Metcalfe-Gibson, Ward, Wrong & Houghton (1967) showed that uraemic subjects incorporated more ammonia nitrogen than normal subjects on a comparable diet. The total incorporation of ammonia nitrogen increased if a low-protein high-biological-value-protein diet was given.

Our work has confirmed the value of low-protein diets containing a high proportion of high-biological-value protein in maintaining nitrogen equilibrium in uraemic subjects. In addition we have shown that a further improvement can be obtained by increasing the caloric intake to 55 cal/kg body weight, i.e. a total daily caloric intake of 3850 cal for a 70 kg patient. This degree of improvement cannot be explained by a greater utilization of dietary nitrogen
Calorie intake and nitrogen balance in uraemia

which should be maximal at a much lower caloric intake. This is shown in Fig. 4. The solid line represents a theoretical maximum B' in normal subjects on a nitrogen intake of 3 g derived from the equations of Miller & Payne (1963) and assuming a protein source of maximum biological value. It can be seen that little improvement in B can be expected above 25 cal/kg. Additional points from studies by Ford et al. (1969) and Herndon et al. (1958) suggest that below caloric intakes of 30 cal/kg body weight a uraemic subject may utilize protein less efficiently than normal subjects. This is supported by the work of Robson, Kerr & Ashcroft (1967), who found an increased urea-production rate in patients on low-calorie low-mixed-protein diets which decreased if the caloric intake was increased or high-biological-value-protein diets used. They did not assess high-caloric intakes with high-biological-value-protein diets.

At present there is no evidence to show whether improvement continues with caloric intakes of above 55 cal/kg or if a plateau is reached in the region of 50–55 cal/kg. In any event most patients will be unable to tolerate a caloric intake of more than 60 cal/kg body weight.

It has been suggested (Shaw et al., 1965) that the main reason for the superiority of high-biological-value-protein diets over a mixed-protein diet is that the essential amino-acid requirement as defined by Rose et al. (1955) is met in this situation. However, work by Fisher, Brush & Grininger (1969) has shown that the requirement for phenylalanine and valine may be considerably decreased on a low-protein diet. Although our diets were deficient in methionine according to the requirements as set out by Rose et al. (1955) this did not prevent an improvement in B' with increasing caloric intake.

ACKNOWLEDGMENTS

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REFERENCES


