Effects of glucose on nitrogen balance during high nitrogen intake in malnourished patients

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SUMMARY

1. The effects of increasing glucose intake on nitrogen balance, energy expenditure and fuel utilization were measured in 12 malnourished adult patients receiving parenteral nutrition with constant, very high nitrogen intake (500 mg of N/kg), high (105 kJ/kg) or low (30 kJ/kg) glucose intake and constant fat intake (7 kJ/kg). Each patient received each diet for 8-day periods in random order.

2. Energy balance and nitrogen balance were determined daily. Blood samples, taken at admission, during 5% (w/v) dextrose (D-glucose) infusion and at the end of days 7 and 8 of each diet, were analysed for urea, glucose, lactate, triacylglycerols, fatty acids, glyceral, 3-hydroxybutyrate, insulin and glucagon.

3. The effect of increasing glucose intake was to increase nitrogen balance by 0.60 ± 0.25 (SEM) mg/kJ. At zero energy balance, nitrogen balance was 48 mg day⁻¹ kg⁻¹. This confirms findings of previous studies: that the effects of glucose on nitrogen balance are greater at high than at low nitrogen intakes, and that, in malnourished patients, unlike in normal adults, markedly positive nitrogen balance can be achieved at zero or negative energy balances.

4. Changes in nitrogen balance were due almost entirely to changes in urea excretion.

5. The high nitrogen intake markedly increased plasma insulin and glucagon concentrations and reduced glyceral, fatty acid and 3-hydroxybutyrate concentrations, independent of any glucose effect. Glucagon concentrations were significantly decreased by added glucose intake, an effect not previously seen at low nitrogen intakes. At this high nitrogen intake, the effects of added glucose appear to be mediated by both insulin and glucagon.

6. Unlike the effects at low nitrogen intakes, added glucose caused no increase in energy expenditure (thermogenesis) or creatinine excretion, and almost no increase in glycogen stores.

Key words: energy balance, free fatty acids, glucagon, glyceral, indirect calorimetry, insulin, metabolic regulation, resting energy expenditure, total parenteral nutrition, urea.

Abbreviations: AEE, activity energy expenditure, D₂W, 5% (w/v) dextrose (D-glucose) in water; ECW, extracellular water; FFA, free fatty acids; ICW, intracellular water; REE, resting energy expenditure; RQ, respiratory quotient; TPN, total parenteral nutrition; SAP, simplified acute physiology.

INTRODUCTION

There are a number of studies in which the separate effects of varying carbohydrate or protein intake on nitrogen balance have been measured in malnourished adult hospitalized patients [1–5]. They show: (a) that the effects of carbohydrate and protein to increase nitrogen balance are synergistic; (b) that malnourished patients, unlike normal adults, may achieve markedly positive nitrogen balance at zero or even negative energy balance; (c) that minimum nitrogen requirements to reach zero nitrogen balance at zero energy balance are above
normal for malnourished patients; and (d) that inter-
subject variability is much greater in malnourished than in
normally nourished individuals.

The goal of the present study was to round out this
picture by measuring the effect on nitrogen balance of
increasing glucose intake at very high levels of protein
intake. Nitrogen balance was measured in malnourished
patients at both a high and low glucose intake and a con-
stant daily nitrogen intake of 500 mg/kg.

METHODS

Protocol

Nutritionally depleted patients (weight loss of 15% or
greater) were admitted to the study. Initially, they were
placed on intravenous 5% (w/v) dextrose (o-glucose) in
water (D2W) for 2 days and then assigned randomly to
either a low or high caloric regimen. Nutrition was pro-
vided as total parenteral nutrition (TPN). Patients were
kept on the first regimen for 8 days before being given the
other for 8 days. An extra day was added to allow a
gradual increase of intake from D2W to TPN. Blood
samples were taken from the femoral vein at 08.00 hours,
after D2W and at the end of days 7 and 8 of each TPN diet.
Samples were analysed for glucose, lactate, triacyl-
glycerols, free fatty acids (FFA), glycerol, 3-hydroxy-
butyrate, insulin and glucagon. Additional blood samples
were taken daily for urea analysis. Nitrogen and energy
balances were measured daily over the
19 days of the
study.

This study was carried out in the Surgical Metabolism
Unit, a four-bed unit specifically designed to carry out
energy and nitrogen balance studies. The nurse/patient
ratio was maintained at 1:2 per shift, allowing for
adequate care of the patient as well as accurate and com-
plete collection of metabolic data. Two research dietitians
were responsible for diet formulation and monitoring all
input and output on a daily basis throughout the study
period.

Patients

Twelve patients with gastrointestinal malfunction were
admitted to the study (Table 1). None of these patients
could maintain their body weight with oral intake alone.
All injuries and surgical procedures were remote from the
time of the study. None of these patients had metastatic
cancer, chronic liver disease, diabetes or chronic renal
disease. All of the patients were referred to the TPN
service for their clinical nutritional problem and were
studied in the Surgical Metabolism Unit. All nutritional
intake, except for some water, was administered intraven-
ously.

The protocol of the study, including risks, was
explained to the patient, usually in the presence of
members of the family, and written consent was obtained.
This protocol and the experimentation was approved by
the Institutional Review Board of Columbia University.

TPN regimens

The aim of the study was to have energy intakes with
the two TPN regimens of either 0.8 times or 1.4 times the
measured resting energy expenditure (REE). Nitrogen
was kept constant at approximately 4 mg of N/kJ REE
and provided as Aminosyn (Abbott Laboratories, North
Chicago, IL, U.S.A.). Glucose was supplied as 50% (w/v)
dextrose (o-glucose; Abbott Laboratories). Essential fatty
acids were provided as a fat emulsion (Intralipid; Cutter
Laboratories, Berkeley, CA, U.S.A.) in minimal amounts.
The amounts of nutrients actually administered are
shown in Table 2. Appropriate amounts of electrolytes,
vitamins and trace elements were provided.

Nutrients were infused continuously at a constant rate
throughout each day, except that fat emulsion was infused

Table 1. Sex, age, weight, REE, creatinine height index and diagnosis of the patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Entering weight (kg)</th>
<th>Weight loss (%)</th>
<th>Entering REE* (kJ/kg)</th>
<th>% of predicted</th>
<th>SAP score†</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>65</td>
<td>31</td>
<td>28</td>
<td>110</td>
<td>83</td>
<td>48</td>
<td>6.1</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>61</td>
<td>56</td>
<td>21</td>
<td>109</td>
<td>110</td>
<td>75</td>
<td>6.0</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>59</td>
<td>47</td>
<td>39</td>
<td>—</td>
<td>—</td>
<td>21</td>
<td>5.8</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>52</td>
<td>54</td>
<td>13</td>
<td>105</td>
<td>88</td>
<td>67</td>
<td>3.6</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>41</td>
<td>61</td>
<td>19</td>
<td>113</td>
<td>103</td>
<td>78</td>
<td>1.9</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>61</td>
<td>57</td>
<td>35</td>
<td>99</td>
<td>92</td>
<td>74</td>
<td>3.5</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>62</td>
<td>49</td>
<td>15</td>
<td>109</td>
<td>100</td>
<td>74</td>
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<td>8</td>
<td>F</td>
<td>75</td>
<td>54</td>
<td>15</td>
<td>72</td>
<td>80</td>
<td>78</td>
<td>6.8</td>
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<tr>
<td>9</td>
<td>M</td>
<td>79</td>
<td>45</td>
<td>20</td>
<td>130</td>
<td>108</td>
<td>39</td>
<td>6.7</td>
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<tr>
<td>10</td>
<td>F</td>
<td>39</td>
<td>37</td>
<td>45</td>
<td>112</td>
<td>85</td>
<td>30</td>
<td>2.9</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>61</td>
<td>58</td>
<td>24</td>
<td>98</td>
<td>88</td>
<td>44</td>
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<tr>
<td>12</td>
<td>M</td>
<td>68</td>
<td>72</td>
<td>16</td>
<td>93</td>
<td>82</td>
<td>22</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Mean ± SEM 60 ± 3 53 ± 3 24 ± 3 105 ± 4 93 ± 3 54 ± 7 4.7 ± 0.5

*Average value for first 2 days during 5% dextrose administration. Predicted values from Aub & DuBois as given by Sherman [6].
†Average value for entire study.
Effects of glucose on nitrogen balance

Table 2. Daily nutrient intakes of 12 depleted patients given high or low caloric diets

Results are means ± SEM for days 6–8 of each 8-day regimen.

<table>
<thead>
<tr>
<th>Diet</th>
<th>Protein (kJ/kg)</th>
<th>Fat (kJ/kg)</th>
<th>Carbohydrate (kJ/kg)</th>
<th>Total energy kJ/kg</th>
<th>Nitrogen mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>58 ± 2</td>
<td>7 ± 0</td>
<td>105 ± 5</td>
<td>169 ± 6</td>
<td>496 ± 18</td>
</tr>
<tr>
<td>Low</td>
<td>59 ± 2</td>
<td>6 ± 0</td>
<td>30 ± 3</td>
<td>96 ± 3</td>
<td>505 ± 20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.44 ± 0.05</td>
<td>4.21 ± 0.16</td>
</tr>
</tbody>
</table>

Plasma substrate and hormone concentrations

Femoral venous blood was drawn at 08.00 hours, centrifuged and the plasma stored at −80°C for later determinations. Plasma glucose was measured using an automated procedure (Glucose analyser; Beckman Instruments Inc., Fullerton, CA, U.S.A.). Daily plasma urea was also measured using an automated technique (BUN analyser; Beckman Instruments Inc., Fullerton, CA, U.S.A.). Plasma glycerol, triacylglycerols and 3-hydroxybutyrate were determined using semi-automated, enzymatic procedures in a fast centrifugal analyser (Multistat; Instrumentation Laboratories Inc., Lexington, MA, U.S.A.). Plasma FFA were determined using the method of Dole & Meinertz [10]. Insulin [11] and glucagon [12] were measured by radioimmunoassays in the laboratory of Dr Xavier Pi-Sunyer at the St Luke’s-Roosevelt Hospital Center, New York, U.S.A.

Calculations and estimates of error

Nitrogen balance. Daily nitrogen balance was taken to be the difference between nitrogen intake and total nitrogen output corrected for daily changes in plasma urea. Total nitrogen output included measured values in urine, stool and drainage and an estimated value of 9 mg day⁻¹ kg⁻¹ for integumental losses [2]. Nitrogen intake was calculated by multiplying the weight of Aminosyn infused by the nitrogen content supplied by the manufacturer. As discussed in detail previously [4], the estimated error (95% confidence limits) for each individual value of daily nitrogen balance is believed to be not more than ±3 mg of N day⁻¹ kg⁻¹ or 0.2 g of N/day per subject.

Energy, carbohydrate and fat balances. The measurements of gas exchange and nitrogen excretion were used with standard formulae of indirect calorimetry to calculate REE and resting values of protein, carbohydrate and fat oxidation, and of lipogenesis [2, 13, 14]. As discussed previously [4], errors in individual daily values of REE are probably less than 5% (95% confidence limits). The energy due to physical activity (activity energy expenditure) was calculated from resting carbohydrate balance. This is based on the assumption that at steady state and with a constant carbohydrate intake, there is no change in mean daily glycogen stores. Since, in ambulatory patients receiving any carbohydrate intake, resting carbohydrate balance is always positive, it is assumed to represent the carbohydrate component of intake.
activity energy expenditure (AEE), and at high carbohydrate intake (RQ > 1) to be equal to AEE, assuming no change in rates of fat oxidation or lipogenesis. In the present study, AEE was taken to be equal to steady-state (days 6–8) values of resting carbohydrate balance during the high carbohydrate intake (Fig. 1), and to be the same for each subject on the low carbohydrate intake. The difference between carbohydrate balance on days 1–5 and steady state, on each regimen, was assumed to equal deposition or utilization of glycogen stores. Conversion of nutrient intakes from g to kJ was carried out: by multiplying nitrogen intake by 6.25 to give protein intake, and then by 18.8 kJ/g; by multiplying lipid intake by 38.9 kJ/g; by multiplying glycerol by 18.0 kJ/g; and by multiplying anhydrous glucose by 15.7 kJ/g. Resting balances for total energy, carbohydrate and fat were obtained by subtracting daily expenditures from daily intakes. Energy contents were taken to be 17.4 kJ/g for glycogen and 39.7 kJ/g for fat. Protein balance was obtained by multiplying nitrogen balance by 6.25.

A more detailed description and critique of both the methods and calculations has been published previously [4].

Changes in intracellular (ICW) and extracellular (ECW) water. ICW was assumed to be equal to 3.4 × protein changes plus 3 × glycogen changes. ECW changes were assumed to equal changes in body weight minus changes in ICW, glycogen, protein and fat [15].

Creatinine height index. Creatinine height index was obtained from the ratio of creatinine excretion to the patient’s body height, divided by predicted values of Bis-trian et al. [16] and multiplied by 100.

Simplified acute physiology (SAP) score. Evaluations of SAP score [17] were made daily throughout the study period for each patient.

Statistics

Statistical analyses were performed using Student’s t-test for either paired or unpaired data and linear regression when appropriate [18]. Values are given as means ± SEM.

RESULTS

Clinical and nutritional status of patients

SAP scores, averaged for each patient over the entire study period (Table 1), were 4.7 ± 1.2 (sd). When only the maximal values for each patient were used they were 7.2 ± 2.3. The highest value, 11, was seen only once in one patient. There were no significant changes with time and no significant differences between values measured during the high and low carbohydrate regimens. There was no significant correlation between nitrogen balance and SAP score during administration of either diet, nor between the differences between regimens of the two parameters. There was no significant correlation between SAP scores and changes in ECW. There was a positive correlation between SAP score and plasma urea concentration, but only during the high carbohydrate regimen (r = 0.77, P < 0.01). Urea clearance, based on 24 h values, for all patients during both regimens was 45 ± 5 ml/min; four patients had values (14, 32, 34 and 38 ml/min) below the normal range of 40–68 ml/min [19]. Urea clearance showed a negative correlation with SAP score (r = -0.65, P < 0.05). All values for plasma creatinine were within the normal range (see Table 5).

The patients (Table 1) were moderately to severely malnourished with weight loss averaging 24 ± 3% of customary weight. There were no significant correlations between prior weight loss and nitrogen balance, SAP score, changes in ECW or urea concentrations. Creatinine height index averaged 54 ± 7% in keeping with severe malnutrition. REE averaged 93 ± 3% of predicted values. Nitrogen balance, not including integumental losses, during D,W infusion was −150 ± 16 mg day⁻¹ kg⁻¹, considerably more negative than the value of −100 mg day⁻¹ kg⁻¹ observed for 67 malnourished patients previously reported from this institution [20].

Nutritional intake

Nutritional intake of these patients during days 6–8, the steady-state period, for each diet is shown in Table 2. Except for carbohydrate, there were minimal differences in the nutrient intake between the two diets. The difference in energy intake was entirely due to the difference of 75 kJ day⁻¹ kg⁻¹ in carbohydrate intake.
Effects of glucose on nitrogen balance

Changes with time

There were marked changes with time during the first few days for resting values of RQ, carbohydrate balance and lipogenesis (Fig. 1); by day 4 or 5 they had all reached a steady-state plateau. There was little change in REE with either diet. With the high glucose intake nitrogen balance also reached steady state by day 4 (Fig. 2). This was not true for nitrogen balance during administration of the low carbohydrate diet, which continued to show marked changes up to day 7 (Fig. 2). In addition, there were large differences during the first 4 days between those receiving the low glucose intake first (after D$_2$W infusion) or after the high intake. For comparative purposes, days 6-8 have been taken to represent steady-state values for all parameters presented in Tables 2-4.

Nitrogen balance

Nitrogen balance was significantly higher on the high glucose than on the low glucose intake (Table 3). Most of this change was due to a decrease in urea excretion (Table 3). There were small, but not significant, decreases in urinary non-urea nitrogen and in stool and drainage nitrogen. The change in total nitrogen excretion was somewhat greater than the change in nitrogen balance because nitrogen intake was a little higher on the low than on the high glucose diet (Table 2). Intersubject variability was high: the sds were 87 mg of N day$^{-1}$ kg$^{-1}$ with the low glucose intake and 48 mg of N day$^{-1}$ kg$^{-1}$ with the high. Three subjects had slightly lower nitrogen balances on the high than on the low carbohydrate intake. The great variability of nitrogen balance in these patients contrasts with the low variability seen in normal subjects, and must be largely due to their heterogeneous nature and underlying pathology. Nevertheless, we could find no correlation between quantitative estimates of disease status, such as SAP scores, extent of prior weight loss or changes in ECW, with the variations in nitrogen balance. The increase in nitrogen balance with increasing energy balance was 0.60 ± 0.25 mg of N/kJ. Nitrogen balance at zero energy intake was 48 ± 12 mg of N day$^{-1}$ kg$^{-1}$.

Energy expenditure and energy, fat and carbohydrate balances

REE was 13% higher during TPN than during D$_2$W administration (Tables 1 and 4). There was no appreciable difference in REE between the two regimens (Table 4, Fig. 1). As measured during TPN administration, REE was not significantly different from normal predicted values. However, under these conditions, REE includes diet-induced thermogenesis, but the predicted values do not. When measured during D$_2$W administration (Table 1) when diet-induced thermogenesis was negligible, REE was 93% of predicted, significantly lower ($P<0.05$). Resting energy balance, the difference between energy intake and REE, was markedly positive on the high glucose intake and somewhat negative on the low (Table 4). However, when estimated values for AEE were considered, total energy balance was $-49$ kJ day$^{-1}$ kg$^{-1}$ with the low glucose regimen and only $+24$ kJ day$^{-1}$ kg$^{-1}$ with the high. This estimate of AEE is very approximate, based on the assumption that there is no change in rates of fat oxidation or lipogenesis (see the Calculations and estimates of error section). That it is sufficiently accurate for present purposes is supported by a study of malnourished patients, with and without pulmonary disease, in whom energy expenditure and fuel utilization were measured at rest and during low level exercise [21]. It may be calculated from their data, for six different patient-diet groups, that measured energy expenditure during exercise accounted for $99 \pm 29$ (SD) % of values predicted from the

<table>
<thead>
<tr>
<th>Table 3. Nitrogen balance and components of nitrogen excretion for days 6–8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results are means ± SEM. Significance of difference between high and low intake: *$P&lt;0.05$.</td>
</tr>
<tr>
<td><strong>Low intake</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>N balance (mg day$^{-1}$ kg$^{-1}$)</td>
</tr>
<tr>
<td>Urea N (mg day$^{-1}$ kg$^{-1}$)</td>
</tr>
<tr>
<td>Creatinine N (mg day$^{-1}$ kg$^{-1}$)</td>
</tr>
<tr>
<td>Urinary non-urea N (mg day$^{-1}$ kg$^{-1}$)</td>
</tr>
<tr>
<td>Stool and drainage N (mg day$^{-1}$ kg$^{-1}$)</td>
</tr>
<tr>
<td>Integumental N (mg day$^{-1}$ kg$^{-1}$)</td>
</tr>
<tr>
<td>Total N (mg day$^{-1}$ kg$^{-1}$)</td>
</tr>
</tbody>
</table>

*Estimated value [2].
increase in carbohydrate oxidation above resting values, assuming no changes in proportions of fat and carbohydrate oxidized. It seems unlikely that our estimate of AEE is in error by more than 50% or 12.5 kJ day\(^{-1}\) kg\(^{-1}\) (Table 4). The main purpose of estimating AEE was to arrive at a value for total energy balance (neglecting smaller thermogenic factors such as drug administration) which is needed for comparison to nitrogen balance. An error of 12.5 kJ or less in energy balance (see Fig. 3) would not change the interpretation of these findings.

It was assumed that there was no further change in glycogen stores after day 5 of each regimen; therefore the positive values for carbohydrate balance for days 6–8 on either regimen (Fig. 1) were assumed to represent glucose oxidation during physical activity. The value obtained during the high glucose intake was assumed equal to AEE (see the Calculations and estimates of error section). The difference between resting carbohydrate balance during days 1–5 and days 6–8 (Fig. 1) was assumed to be due to net glycogen deposition (+) or utilization (−). This was −0.3 g (−6 kJ)/kg on the low glucose regimen and 1.4 g (24 kJ)/kg with the high glucose regimen.

Substantial amounts of endogenous fat were oxidized during the low glucose regimen (Table 4). This was greater than the negative total energy balance, since protein balance was positive. With the high glucose regimen, fat balance was positive, mainly representing lipogenesis de novo (Table 4) since fat intake was minimal (Table 2).

### Blood substrate and hormone concentrations

Plasma urea more than doubled on both TPN regimens compared with D\(_7\)W infusion; there was no significant difference between the two diets (Table 5). Glucose and lactate concentrations did not differ significantly between both TPN regimens and D\(_7\)W infusion but were 30% higher with the high than with the low glucose regimen (Table 5). Triacylglycerol concentrations were significantly lower during high glucose administration than with either of the other regimens. Concentrations of free fatty acids, glycerol and 3-hydroxybutyrate were highest during D\(_7\)W infusion; there were reductions in all three compounds (significant for FFA and glycerol) with the low glucose TPN, and further reductions with the high glucose TPN (Table 5). Insulin concentrations nearly doubled going from D\(_7\)W infusion to the low glucose regimen, and doubled again with the high glucose intake. Glucagon concentrations were more than twice as high with the low glucose diet as during D\(_7\)W infusion. There was significant reduction in glucagon concentration with the high glucose regimen (Table 5).

### Table 4. Energy expenditure and balance and resting values of protein balance, fat balance, and lipogenesis

<table>
<thead>
<tr>
<th></th>
<th>Low intake</th>
<th>High intake</th>
<th>High minus low</th>
</tr>
</thead>
<tbody>
<tr>
<td>REE (kJ day(^{-1}) kg(^{-1}))</td>
<td>118 ± 4*</td>
<td>119 ± 4*</td>
<td>1 ± 3</td>
</tr>
<tr>
<td>AEE (kJ day(^{-1}) kg(^{-1}))</td>
<td>25 ± 4</td>
<td>25 ± 4</td>
<td>1 ± 3</td>
</tr>
<tr>
<td>Total energy balance (kJ day(^{-1}) kg(^{-1}))</td>
<td>−24 ± 4</td>
<td>24 ± 4</td>
<td>73 ± 3</td>
</tr>
<tr>
<td>Protein balance (kJ day(^{-1}) kg(^{-1}))</td>
<td>2 ± 3</td>
<td>7 ± 1</td>
<td>5 ± 2</td>
</tr>
<tr>
<td>Fat balance (kJ day(^{-1}) kg(^{-1}))</td>
<td>−56 ± 5</td>
<td>13 ± 4</td>
<td>69 ± 3</td>
</tr>
<tr>
<td>Lipogenesis (kJ day(^{-1}) kg(^{-1}))</td>
<td>0 ± 0</td>
<td>10 ± 3</td>
<td>10 ± 3</td>
</tr>
</tbody>
</table>

* Predicted values taken from tables of Aub & DuBois as given by Sherman [6].

### Table 5. Plasma substrate and hormone concentrations in the femoral vein during D\(_7\)W administration and days 7 and 8 of high or low glucose TPN administration

<table>
<thead>
<tr>
<th></th>
<th>D(_7)W</th>
<th>Low glucose</th>
<th>High glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (mmol/l)</td>
<td>5.6 ± 1.9</td>
<td>12.1 ± 1.5***</td>
<td>11.1 ± 1.5***</td>
</tr>
<tr>
<td>Creatinine (mmol/l)</td>
<td>0.084 ± 0.011</td>
<td>0.067 ± 0.005*</td>
<td>0.072 ± 0.008</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>7.3 ± 1.0</td>
<td>6.1 ± 0.3</td>
<td>8.3 ± 1.2†</td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
<td>1.15 ± 0.15</td>
<td>0.91 ± 0.07</td>
<td>1.23 ± 0.16†</td>
</tr>
<tr>
<td>FFA (mmol/l)</td>
<td>0.61 ± 0.05</td>
<td>0.42 ± 0.04**</td>
<td>0.30 ± 0.03***††</td>
</tr>
<tr>
<td>Triacylglycerols (mmol/l)</td>
<td>1.82 ± 0.55</td>
<td>1.64 ± 0.46</td>
<td>1.25 ± 0.41***††</td>
</tr>
<tr>
<td>Glycerol (mmol/l)</td>
<td>0.110 ± 0.018</td>
<td>0.063 ± 0.004*</td>
<td>0.039 ± 0.005**††</td>
</tr>
<tr>
<td>3-Hydroxybutyrate (mmol/l)</td>
<td>0.054 ± 0.016</td>
<td>0.022 ± 0.004*</td>
<td>0.007 ± 0.002**††</td>
</tr>
<tr>
<td>Insulin (munits/l)</td>
<td>14 ± 2</td>
<td>25 ± 4*</td>
<td>53 ± 8***††</td>
</tr>
<tr>
<td>Glucagon (ng/l)</td>
<td>197 ± 119</td>
<td>557 ± 110*</td>
<td>372 ± 68††</td>
</tr>
</tbody>
</table>
Effects of glucose on nitrogen balance

Body composition

Body weight decreased by an average of 2.3% (1.2 kg) during the 16 days of the high nitrogen regimens (Table 6), all of which was lost when the patients were receiving the low carbohydrate diet. Decreases in ECW did not differ significantly between the two dietary regimens (Table 6). However, the high carbohydrate intake was accompanied by a substantial increase in ICW (Table 6) and other intracellular components (Table 4) approximately equal to the loss of ECW. The decrease in ECW in the first 8-day period, regardless of diet, was 28 ± 12 g/kg; that in the second 8-day period was 16 ± 8, smaller but not significantly different from the first period.

DISCUSSION

Clinical effects of high nitrogen and carbohydrate intakes

The only observed adverse clinical effect of the high nitrogen and carbohydrate diets used in this study was an increase in plasma urea concentration (Table 5). There were no increases (or decreases) in SAP scores, and no adverse changes in clinical status observed by the staff taking care of the patients. The decrease in ECW throughout the 16-day course of nutritional repletion, similar to previous findings [22], implies prior fluid expansion in these patients, indicating considerable underlying disease in keeping with their SAP scores. A decrease in ECW after instituting nutritional therapy is generally considered to be a beneficial response [23], although this was not reflected in the SAP scores. Above-normal plasma urea concentrations (Table 5), seen in all but one patient, reflect the very high nitrogen intakes in this study, and occurred in seven of the eight patients with normal or above-normal rates of urea clearance. Even in the patients with below-normal urea clearance, plasma urea concentrations did not exceed 26 mmol/l and creatinine concentrations were all in the normal range, suggesting that, although impaired, kidney function was adequate.

Thus there appear to be no important risks associated with the rates of nitrogen and carbohydrate intake used in this study in these patients. Clearly, in patients with less adequate kidney function these high rates of nitrogen intake may be inappropriate.

Nitrogen balance related to energy balance and nitrogen intake

The present study is the last of a series of experiments by ourselves [2-4] and others [1, 5] in which the effects on nitrogen balance of varying either carbohydrate intake or protein intake, separately, have been studied. Taken together the data from these studies present a consistent picture of the interrelations of nitrogen balance with nitrogen intake and energy balance in malnourished adult hospitalized patients (Fig. 3). Increasing either nitrogen intake or energy balance increases nitrogen balance. The two effects are synergistic. Thus, at an energy balance of 100 kJ, 40% of additional nitrogen intake is retained; at zero energy balance only 20% is retained. At an intake of 150 mg of N day⁻¹ kg⁻¹ an increase in energy balance has

<p>| Table 1. Changes in body weight, ICW and ECW during administration of low or high carbohydrate regimens |
|-------------------------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Body weight (<strong>day</strong>⁻¹ kg⁻¹)</th>
<th>ICW (g/kg body wt.)</th>
<th>ECW (g/kg body wt.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low carbohydrate (8 days)</td>
<td>−28 ± 8**</td>
<td>5 ± 3</td>
</tr>
<tr>
<td>High carbohydrate (8 days)</td>
<td>4 ± 11</td>
<td>15 ± 4**</td>
</tr>
<tr>
<td>Low + high (16 days)</td>
<td>−23 ± 10*</td>
<td>21 ± 5**</td>
</tr>
</tbody>
</table>
Only a modest effect on nitrogen balance; at 450 mg of N day\(^{-1}\) kg\(^{-1}\) the effect is nearly three times greater. Unlike normal adults, positive nitrogen balance can be achieved at zero energy balance under steady-state conditions. Nevertheless, the amount of nitrogen required to maintain zero nitrogen balance at zero energy balance, about 120 mg day\(^{-1}\) kg\(^{-1}\), is about 50% higher than for normal subjects, indicating that these hospitalized malnourished patients have substantial underlying illness.

Such patients as these represent a very heterogeneous population. Notwithstanding, the results of the various studies to date are remarkably consistent. The theoretical grid of Fig. 3, represented by the light lines, was derived from only two studies [1, 3] as previously described [3]. The heavy lines and symbols with their associated numbers for nitrogen intake represent experimental data from one of these studies [3], the present study, the other studies cited above [2, 4, 5] and two individual points (for nitrogen intakes of 266 and 402 mg day\(^{-1}\) kg\(^{-1}\)) performed in this laboratory [25, 26] in which no changes were made in total energy or nitrogen intake. As discussed elsewhere [2], many other studies, in which the separate effects of nitrogen and energy intake were not measured, produced results that are in good agreement with this scheme. Despite the variety of sources, there is a very close concordance between the experimental data and the theoretical grid. The biggest discrepancy is for the present study, represented by the heavy dotted line and a nitrogen intake of 500 mg day\(^{-1}\) kg\(^{-1}\) (Fig. 3). This coincides almost exactly with the grid for intake of 350 mg of N day\(^{-1}\) kg\(^{-1}\), but should properly be above the line for 450 mg day\(^{-1}\) kg\(^{-1}\), a displacement of about 30 mg day\(^{-1}\) kg\(^{-1}\) of nitrogen balance. It seems likely that this is because the group of patients in the present study were significantly more catabolic than the average for malnourished patients generally. Measured nitrogen excretion during D\(_{2}\)W infusion in the present study averaged 150 mg day\(^{-1}\) kg\(^{-1}\) compared with 100 mg day\(^{-1}\) kg\(^{-1}\) for 67 other malnourished patients [20], which includes those from all the other studies from this institution [2-4, 25, 26] whose data are included in Fig. 3. Thus despite this discrepancy, the present study serves to confirm the validity of the scheme shown in Fig. 3 and, in particular, the observation of Plough et al. [1], based on only three patients, that the size of the effect of increasing carbohydrate intake to increase nitrogen balance is dependent on the level of nitrogen intake.

The scheme in Fig. 3 can serve as a general guide to the interrelations between nitrogen balance and protein and carbohydrate intake in malnourished hospitalized adult patients. But this is a very heterogeneous population, and individual patients or groups of patients may show marked quantitative differences with the scheme. It should be emphasized that as yet similar experiments have not been carried out with fat.

Hormonal mediation of glucose effects on nitrogen balance

In a previous investigation [4] the protocol was almost identical to that in the present study except that nitrogen intake was 158 instead of 500 mg day\(^{-1}\) kg\(^{-1}\). On both the low and high glucose intakes, nitrogen balance was twice as high in the present study, and the increase in nitrogen balance with increasing energy balance was more than twice as great (Fig. 3). In the low nitrogen study, plasma insulin concentrations averaged 14 munits/l on the low glucose intake and 27 munits/l on the high, about 50% of the values of 23 and 48 munits/l found in the present study (Table 5). Muscle is the major site of increased protein retention during repletion therapy [27, 28], and insulin has a direct effect on muscle, both to increase protein synthesis and to decrease protein degradation. It would seem, therefore, that the effects of both glucose and amino acid infusions to increase nitrogen balance, in these two studies, can be largely explained as mediated by insulin. In both studies, the decrease in urea excretion accounted for all or almost all of the increase in nitrogen balance with the high compared with the low glucose regimen. Since insulin acts to decrease urea excretion, the increase in insulin concentration in both studies is presumably an important mediator of this decreased urea output. In the present study glucagon concentrations were very high, 557 ng/l, on the low glucose regimen, and decreased markedly, to 372 ng/l, on the high glucose regimen. Glucagon stimulates urea synthesis and gluconeogenesis in opposition to insulin, so that at the high nitrogen intake, both glucagon and insulin appear to mediate the effect of increased glucose to inhibit urea synthesis. In the previous study at a low nitrogen intake, glucagon concentrations were much lower (130 ng/l) and did not change significantly with increased glucose intake. In that study, the smaller effect of glucose to decrease urea output appeared to be mediated only by insulin with no glucagon involvement.

Energy expenditure, glycogen deposition, and creatinine excretion

In previous studies, increasing glucose intake by the amounts used in the present study increased energy expenditure by about 10% [2, 4]. In the present study the increase was less than 1%, significantly lower than the 12% (P<0.02) observed in the previous study with low nitrogen intakes [4]. Glycogen deposition in the previous study with low nitrogen intakes was 7 g (122 kJ) and - 1 (- 17 kJ) day\(^{-1}\) kg\(^{-1}\) on the high and low glucose intakes, respectively [15], compared with 1.4 g (24 kJ) and - 0.3 g (- 6 kJ) in the present study. Creatinine excretion increased by 0.8 ± 0.2 mg of N day\(^{-1}\) kg\(^{-1}\) (P<0.01) in the low nitrogen study [4] compared with 0.1 ± 0.1 mg of N day\(^{-1}\) kg\(^{-1}\) in the present study (Table 3). The increase in creatinine excretion was attributed to an increase in muscle mass due mainly to glycogen deposition [15]. Absence of an increase in creatinine excretion associated with minimal glycogen deposition in the present study is consistent with this hypothesis.

It might be postulated that these differences are due to the greater severity of illness of the patients in the present high nitrogen study than in the low nitrogen study. However, other studies [28] show that hypermetabolic, hyper-
catabolic patients have decreased rates of glucose oxidation and increased rates of glycogen deposition, just opposite to the observations reported above. Thus it appears from the present study that very high nitrogen intakes almost completely attenuate the effects of glucose loads to increase REE and glycogen stores seen at normal nitrogen intakes. The very high level of plasma glucagon in the present study might account for the inhibition of glycogen synthesis. The mechanism of the reduced thermic effect and whether the effect on thermogenesis and glycogen deposition are related remain to be clarified.

Plasma concentrations of glucose, insulin and fat metabolites

Plasma concentrations of glucose, fatty acids, glycerol and 3-hydroxybutyrate were lower during the low glucose regimen than during infusion of D5W, although the decrease for glucose was not significant. This is consistent with the higher insulin concentrations during TPN administration (Table 5). However, the increase in insulin concentrations was not due to increased glucose intake, which averaged 30 kJ day−1 kg−1 with the low glucose TPN (Table 2) and 33 during D5W infusion. Both the increase in insulin and the decrease in fat metabolites appear to be due to the increase in protein intake. The further reduction in concentrations of these fat metabolites, now accompanied by an increase in glucose concentration, with the high glucose TPN is consistent with the further increase in insulin concentration due, in this instance, to the marked increase in glucose intake.

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