The metabolic consequences of critical illness: acute effects on glutamine and protein metabolism


The metabolic consequences of critical illness: acute effects on glutamine and protein metabolism. Am. J. Physiol. 276 (Endocrinol. Metab. 39): E163–E170, 1999.—Net protein loss and large decreases in plasma glutamine concentration are characteristics of critical illness. We have used [2-15N]glutamine and [1-13C]leucine to investigate whole body glutamine and leucine kinetics in a group of critically ill patients and matched healthy controls. Glutamine appearance rate (Ra,Gln) was similar in both groups. However, in the patients, the proportion of Ra,Gln arising from protein breakdown was higher than in the control group (43 ± 3 vs. 32 ± 2%, P < 0.05). Glutamine metabolic clearance rate (MCR) was 92 ± 8% higher (P < 0.001), whereas plasma glutamine concentrations were 38 ± 5% lower (P < 0.001) than in the control group. Leucine appearance rate (whole body proteolysis) and nonoxidative leucine disposal (whole body protein synthesis) were 59 ± 14 and 49 ± 15% higher in the patients (P < 0.001). Leucine oxidation and MCR were increased in the patients by 104 ± 37 and 129 ± 39%, respectively (P < 0.05). These results demonstrate that critical illness is associated with a major increase in protein turnover. The acute decrease in plasma glutamine concentration and the unaltered plasma Ra,Gln suggest that the increase in proteolysis is insufficient to meet increased demand for glutamine in this severe catabolic state.

CRITICAL ILLNESS resulting from trauma, surgery, or sepsis is associated with altered metabolism characterized by an increased catabolic rate, negative nitrogen balance, wasting of lean body mass, immunosuppression, and compromised wound healing. The muscular loss is thought to be due to the mobilization of amino acids for high-priority use by organs in the splanchnic area for gluconeogenesis, oxidation, ureagenesis, and protein synthesis and also as substrates for the immune system and wound healing (18).

Glutamine is the most abundant amino acid in both plasma and the free intracellular amino acid pool in skeletal muscle (4). Because most tissues have the ability to synthesize glutamine, it is defined as a nonessential amino acid. However, free glutamine concentrations are extremely labile, and marked decreases have been reported in a variety of catabolic states (3, 37). This suggests that during serious illness a deficiency in glutamine availability may develop and has led to the idea that glutamine is a conditionally essential amino acid (24). At present, glutamine is not routinely added to parenteral nutrition solutions, but recent clinical trials suggest that glutamine supplementation improves both nitrogen balance and gut mucosal integrity and decreases the number of infections and length of hospital stay (36, 42).

The use of [1-13C]leucine as a tracer to measure rates of whole body protein breakdown and synthesis is a well-established technique that has been applied to a variety of clinical conditions (19). The measurement of whole body plasma glutamine flux by use of glutamine labeled with 15N has also been developed, allowing experimental and clinical investigations of glutamine metabolism. Healthy subjects and the effects of various catabolic hormones on glutamine metabolism have been studied (7, 10, 11, 20, 28). However, despite the current clinical interest in the benefits of glutamine supplementation, there have been very few tracer studies investigating glutamine metabolism in patient groups, particularly critically ill patients. To our knowledge there have been no published reports of studies using stable isotope tracer techniques to measure glutamine metabolism in critically ill patients soon after the onset of illness in a general intensive care unit (ICU).

The aim of the present study was to use [2-15N]glutamine and [1-13C]leucine to investigate whole body glutamine and leucine metabolism in a group of critically ill patients and a group of matched healthy controls. The importance of matching the critically ill group for age and weight was also studied by comparing glutamine and leucine kinetics in a young and an elderly control group.

METHODS

Materials

L-[2-15N]glutamine (99% AP), L-[1-13C]leucine (99% AP), and NaH13CO3 (99% AP) were purchased from Tracer Technologies (Somerville, MA). Sterile solutions of the tracers were prepared in 0.9% saline with an aseptic technique by the Pharmacy Department, Guy’s and St. Thomas’ Hospital (London, UK).

Subjects

Seven severely ill patients (age range 32–76 yr) in the ICU of St. Thomas’ Hospital were studied. Details of their clinical and metabolic characteristics are given in Table 1. The severity of illness was evaluated on the day of the study by use of the APACHE II and TISS score systems (Table 1). Five of the patients had undergone emergency abdominal surgery within 24 h before the study. Patients 3 and 5 had had previous infections, but none of the patients had evidence of...
active infection (negative blood, sputum, and urine culture) during the study period. All patients were studied after a fasting period of between 12 and 24 h. Six of the seven patients were admitted acutely and had previously been self caring and independent, responsible for their own diet. The remaining patient (patient 5) had been receiving an oral hospital diet for 19 days before the study.

A group of 12 control subjects were recruited for the study; their physical characteristics are shown in Table 2. All were in good general health. There was no recent relevant medical history, and none of the controls was on any regular medication. The healthy adults were divided into two groups on the basis of age, young (<35 yr) and elderly (>60 yr).

The protocol was approved by the Ethics Committee, Guy's and St. Thomas' National Health Service Trust. All control subjects provided informed written consent; written consent was obtained from relatives or friends of ICU patients.

**Study Protocol**

ICU patients. All ICU patients were fasted for $\geq$12 h before the start of the study. Indwelling arterial and central venous lines were used for blood sampling and for the tracer infusion, respectively. After baseline sampling, priming boluses of [1-13C]leucine (1 mg/kg) and NaH13CO3 (0.2 mg/kg) were injected, and 4-h constant infusions of [2-15N]glutamine (2.5 mg·kg$^{-1}$·h$^{-1}$) and [1-13C]leucine (1 mg·kg$^{-1}$·h$^{-1}$) were started. Blood and breath samples were taken at 210, 215, 220, 225, 230, and 240 min for steady-state measurement of plasma glutamine and α-ketoisocaproic acid enrichment, glutamine and leucine concentrations, and breath 13CO2 enrichment. Blood samples were also taken at baseline and steady state for the measurement of metabolite and hormone levels [plasma albumin, C-reactive protein, glucose, insulin, insulin-like growth factor I (IGF-I), cortisol, thyroid hormones, and amino acids]. For glutamine analysis, 0.5-ml lithium heparin plasma aliquots were mixed with 100 µl of internal standard (100 nmol/l [U-13C5]glutamine). All samples were stored at $-72^\circ$C until analysis.

The ICU patients were all sedated and mechanically ventilated (Servo 900; Siemens, Berlin, Germany). Continuous measurements of expired volume, CO2 production, and oxygen consumption were made using an on-line mass spec-

**Table 1. Clinical and metabolic characteristics of patients**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Gender</th>
<th>Age, yr</th>
<th>Weight, kg</th>
<th>BMI, kg/m²</th>
<th>Main Diagnosis</th>
<th>APACHE II</th>
<th>TISS</th>
<th>Duration Postsurgery,* h</th>
<th>Plasma Albumin, g/dl</th>
<th>Plasma CRP, mg/dl</th>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>68</td>
<td>65</td>
<td>22.2</td>
<td>GI obstruction/laparotomy</td>
<td>15</td>
<td>34</td>
<td>24</td>
<td>19</td>
<td>157</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>76</td>
<td>74</td>
<td>22.2</td>
<td>GI bleed/laparotomy, ARF</td>
<td>23</td>
<td>49</td>
<td>24</td>
<td>27</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>72</td>
<td>82</td>
<td>23.4</td>
<td>Pneumonia, GI obstruction</td>
<td>15</td>
<td>37</td>
<td>NA</td>
<td>23</td>
<td>161</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>65</td>
<td>75</td>
<td>26.0</td>
<td>GI infarction/laparotomy</td>
<td>9</td>
<td>50</td>
<td>16</td>
<td>34</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>75</td>
<td>85</td>
<td>30.1</td>
<td>ARDS/sepsis</td>
<td>19</td>
<td>38</td>
<td>NA</td>
<td>25</td>
<td>329</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>75</td>
<td>104</td>
<td>31.0</td>
<td>AAA repair</td>
<td>24</td>
<td>47</td>
<td>20</td>
<td>19</td>
<td>248</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>32</td>
<td>59</td>
<td>20.2</td>
<td>Tumor/colonic resection</td>
<td>18</td>
<td>62</td>
<td>16</td>
<td>17</td>
<td>145</td>
</tr>
</tbody>
</table>

Mean ± SE
Characteristics of matched controls
Mean ± SE
3M/4F 66 ± 6 78 ± 6 25.0 ± 1.6 18 ± 2 45 ± 4 20 ± 2* 23 ± 2 170 ± 35

BMI, body mass index; CRP, C-reactive protein; GI, gastrointestinal; ARF, acute renal failure; ARDS, acute respiratory distress syndrome; AAA, aortic abdominal aneurysm; NA, not applicable. * Includes data from 5 patients who had undergone emergency surgery.

**Table 2. Characteristics of the healthy volunteers**

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Gender</th>
<th>Age, yr</th>
<th>Weight, kg</th>
<th>Height, cm</th>
<th>BMI, kg/m²</th>
<th>LBM, kg</th>
<th>Fat Mass, kg</th>
</tr>
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<tbody>
<tr>
<td><strong>Young (&lt;35 yr)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>31</td>
<td>65.4</td>
<td>167</td>
<td>23.5</td>
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<td>M</td>
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<td>184</td>
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<td>3</td>
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<td>76.7</td>
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<td>10.9</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>25</td>
<td>66</td>
<td>166</td>
<td>24.0</td>
<td>45.7</td>
<td>20.3</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>29</td>
<td>62</td>
<td>171</td>
<td>21.2</td>
<td>44.8</td>
<td>17.2</td>
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<tr>
<td>6</td>
<td>M</td>
<td>34</td>
<td>68</td>
<td>170</td>
<td>23.5</td>
<td>44.1</td>
<td>23.9</td>
</tr>
<tr>
<td><strong>Mean ± SE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 ± 2</td>
<td>69.8 ± 3.0</td>
<td>173.5 ± 3.3</td>
<td>23.2 ± 0.4</td>
<td>52.7 ± 4.6</td>
<td>17.1 ± 2.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Elderly (>60 yr)** | | | | | | | |
| 7           | F      | 65      | 78.9       | 157.5      | 31.8       | 41.5    | 37.4        |
| 8           | M      | 70      | 91.5       | 174        | 30.2       | 62.8    | 28.7        |
| 9           | F      | 67      | 76.2       | 156        | 31.3       | 29.5    | 46.7        |
| 10          | M      | 65      | 86.6       | 185        | 25.3       | 69.2    | 17.4        |
| 11          | M      | 77      | 85.5       | 174        | 26.2       | 62.0    | 23.5        |
| 12          | F      | 62      | 62.8       | 170        | 21.7       | 44.0    | 18.8        |
| **Mean ± SE** | | | | | | | |
| 68 ± 2      | 80.3 ± 4.2 | 169.4 ± 4.5 | 28.1 ± 1.6 | 51.5 ± 6.3 | 28.8 ± 4.7 |

LBM, measured lean body mass.
Experimental Methods

The isotopic enrichment and concentration of glutamine were determined from the tert-butylidemethylsilyl derivative by use of a method modified from Wolfe (41). Glutamine concentration was determined by reverse isotope dilution with L-[U-13C5]glutamine (Bioquote, North Yorkshire, UK) as the internal standard. Analysis by gas chromatography-mass spectrometry (GC-MS; MSD 5971A, Hewlett-Packard, Berkshire, UK) used electron impact ionization with selected ion monitoring of the [M-butyl] + ions at mass-to-charge ratios of m/z 432, 433, and 436. The isotopic enrichment of α-ketocaproat (α-KIC) was measured as the quinoxalinol-tert-butylidemethylsilyl derivative by use of a method modified from Ford et al. (16). GC-MS analysis used electron impact ionization with selected ion monitoring of the [M-butyl] + ions at m/z 259 and 260. Plasma α-KIC enrichment is used as a measure of intracellular leucine enrichment (29). 13CO2 enrichment was measured on a SIRA series II isotope ratio mass spectrometer (VG Isotech, Cheshire, UK) modified with a Roboprep G+ inlet system (Europa Scientific, Cheshire, UK). Plasma amino acid concentrations were measured on an Alpha II + automated amino acid analyzer (Pharmacia, Hertfordshire, UK). Plasma glucose concentrations were measured on a model 23AM glucose analyzer (YSI, Hampshire, UK). Serum insulin concentrations were measured by an in-house double-antibody radioimmunoassay (34). Total IGF-1 was measured by radioimmunoassay after acid ethanol extraction. Free thyroid hormones were measured by a competitive in-house double-antibody radioimmunoassay (34). Total IGF-I was measured by radioimmunoassay after acid ethanol extraction (34).

Calculations

Measurements of leucine and glutamine metabolism were calculated using standard isotope dilution equations. Leucine appearance rate, a measure of whole body protein breakdown (Ra,Leu, in µmol·min⁻¹·kg⁻¹) was calculated as Ra,Leu = F/[A/P(KIC) - 1], where F is the isotopic infusion rate (in µmol·min⁻¹·kg⁻¹) and A/P(KIC) is the plasma α-KIC enrichment. At steady state, leucine disappearance rate (Rd,Leu) was assumed to be equal to Ra,Leu. Leucine oxidation rate (OXLeu, in µmol·min⁻¹·kg⁻¹) was calculated as OXLeu = (APE CO₂ × Ra,CO₂)/A/P(KIC), where Ra,CO₂ is the production rate of CO₂ (in mmol/min), and A/P(KIC) is the enrichment of expired CO₂. In all cases, leucine oxidation was corrected with the assumption that 80% of 13CO₂ was expired (32). Nonoxidative leucine disposal (NOLD, a measure of whole body protein synthesis) was calculated as the difference between Ra,Leu and OXLeu. Leucine metabolic clearance rate (MCRLeu; in mL·min⁻¹·kg⁻¹) was calculated as MCRLeu = Ra,Leu/[Leu], where [Leu] is the steady-state plasma leucine concentration (in µmol/L). Net protein balance was estimated using the net leucine balance (NOLD - Ra,CO₂), with the assumption of 8 g of leucine for 100 g whole body protein (21).

Glutamine Ra, Ra, and MCR values were calculated using analogous equations. Because glutamine is a nonessential amino acid, Ra,Gln is derived from both protein breakdown (BGln) and de novo synthesis (DGln). Glutamine release from protein breakdown was estimated as 0.78 × Ra,Leu (14), and DGln was calculated as DGln = Ra,Gln - BGln (21).

Statistics

All data are presented as means ± SE. Steady state for plasma glutamine enrichment and concentration was confirmed as an insignificant correlation with time (P > 0.05) by use of repeated-measures ANOVA (NCSS 6.0, Dr. J. Hintze, Kaysville, UT). Comparisons between groups were made by standard two-tailed unpaired t-tests with equal or unequal variance as necessary. The cortisol and insulin data were log transformed before analysis.

RESULTS

ICU Patients vs. Matched Controls

Table 1 shows the details of the seven ICU patients studied. The severity of the illness is indicated by the TISS and APACHE II scores (9, 23). These indexes identified the patients as being severely ill and dependent on cardiorespiratory and nutritional support. The seven healthy volunteers selected as controls were well-matched to the ICU patients for sex, age, weight, and body mass index (BMI, Table 1). Figure 1 shows the plasma glutamine enrichments and concentrations for the ICU patients and their matched controls during the final 30 min of the tracer infusion. The glutamine and leucine data for the ICU patients and their matched controls are summarized in Tables 2 and 3. Glutamine MCR was significantly higher in ICU patients compared with the matched controls (P < 0.001). There was no difference in whole body Ra,Gln (or Rd,Gln) between the two groups. However, there was a significant increase (P < 0.05) in the proportion of Ra,Gln arising from protein breakdown and a resulting decrease in the proportion arising from de novo synthesis in the critically ill patients (P < 0.05).

Ra,Leu, OXLeu, MCR, Leu, and NOLD were all significantly higher in the critically ill patients (P < 0.001, P < 0.05, P < 0.05, and P < 0.001, respectively). Net 24-h protein balance (Fig. 4) was significantly more negative in the critically ill subjects (P < 0.01).

The plasma amino acid profiles are given in Table 3. Plasma threonine (P < 0.01), serine (P < 0.001), glutamine (P < 0.001), glycine (P < 0.01), alanine (P < 0.001), leucine (P < 0.05), lysine (P < 0.01), histidine (P < 0.01), and arginine (P < 0.01) concentrations were significantly lower in the patients, whereas phenylalanine (P < 0.01) and aspartate (P < 0.01) levels were significantly higher. Metabolite and hormone profiles...
are shown in Table 4. Thyroid hormone and IGF-I levels were significantly lower \( (P < 0.05) \) in the patients. There was no difference in the plasma glucose or insulin levels between the two groups. Cortisol levels were higher in the ICU patients \( (P < 0.05) \), range 242–2,393 nmol/l.

Control Subjects

The characteristics of the control subjects are shown in Table 2. They were divided into two groups on the basis of age; both groups contained three males and three females. The elderly (>60) group had a mean age of 68 ± 2 yr, whereas the young (<35) group had a mean age of 28 ± 2 yr. The mean weights of the groups were 80.3 ± 4.2 and 69.8 ± 3.0 kg, respectively \( (P = 0.068) \). BMI and fat mass were significantly higher in the elderly group, 28.1 ± 1.60 vs. 23.2 ± 0.42 kg/m\(^2\) \( (P < 0.05) \) and 28.8 ± 4.7 vs. 17.1 ± 2.2 kg \( (P < 0.05) \), respectively. Lean body mass (LBM) was not significantly different between the two groups (51.5 ± 6.3 vs. 52.7 ± 4.6 kg).

Table 5 summarizes the glutamine and leucine data from the healthy volunteers. Whole body plasma glutamine flux \( (R_{\text{a,Gln}}) \) was significantly lower in the elderly group \( (4.15 ± 0.33 \text{ vs. } 5.20 ± 0.22 \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}, P < 0.05) \), but there was no difference in the proportion of \( R_{\text{a,Gln}} \) arising from de novo glutamine synthesis or protein breakdown in the two groups. However, when the results were expressed per kilogram LBM, the difference in \( R_{\text{a,Gln}} \) was no longer evident \( (6.96 ± 0.37 \text{ vs. } 6.69 ± 0.51 \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg} \cdot \text{LBM}^{-1}) \). There were no significant differences in glutamine MCR or in any of the measurements of leucine metabolism \( (R_{\text{a,Leu}}, \text{Ox}_{\text{Leu}}, \text{MCR}_{\text{Leu}}, \text{and NOLD}) \) in the two groups of volunteers, whether the results were expressed per kilogram body weight or per kg LBM.

Table 3 shows that plasma amino acid profiles were similar in both groups of healthy volunteers, with the exception of decreased circulating serine \( (P < 0.05) \) and histidine \( (P < 0.05) \) and increased plasma cystine concentrations in the elderly subjects. Metabolite and hormone profiles are shown in Table 4. Plasma glucose levels were significantly higher \( (P < 0.05) \) in the elderly volunteers. Cortisol levels were significantly higher \( (P < 0.05) \), and IGF-I levels were significantly lower \( (P < 0.05) \) in the elderly group, but there were no differences in insulin or thyroid hormone levels.

DISCUSSION

There is currently intense clinical interest in glutamine metabolism in critical illness. Previous studies have reported whole body glutamine turnover measurements in healthy controls, burn patients (20), enterectomized patients (12), and patients with insulin-dependent diabetes (13), but there have been no studies investigating glutamine metabolism in acute critical illness. In this study we have shown that, despite a marked decrease in plasma glutamine concentration, whole body plasma glutamine flux was unchanged in critically ill patients. Measured whole body glutamine...
mine flux reflects interorgan glutamine transport rates through plasma (10).

Glutamine MCR was increased in the patients, suggesting that this may be the primary mechanism for the fall in glutamine concentration. Because amino acids are removed from blood by a transporter, we would expect this removal to exhibit Michaelis-Menten kinetics (i.e., nonlinear kinetics). There will thus be an inverse relationship between clearance and concentration. Thus, if Ra decreases, concentration will fall and clearance will rise. However, glutamine Rₐ-to-Rᵯ ratio was unchanged in the ICU patients despite a fall in glutamine concentration. The increase in glutamine MCR in the ICU patients must therefore be due to a change in the transport process, e.g., an increase in efficiency.

The percentage of the glutamine flux arising from protein breakdown was increased in this patient group, but the observed decrease in plasma glutamine concentration indicates that this increase was insufficient to meet the increased demand for glutamine. Marked alterations were also observed in protein metabolism, as reflected by the increases in leucine Rₐ, NOLD, MCR, and oxidation. These changes resulted in an increased net negative protein balance in the critically ill patients.

Marked differences were observed in the circulating levels of amino acids between the patients and their matched controls. In addition to the decreased plasma glutamine concentration, the levels of the essential amino acids leucine, lysine, threonine, and histidine were lower in the patients. Similar changes have been observed in previous studies (18, 33), and it has been suggested that elevated levels of stress hormones, by increasing splanchnic amino acid uptake, may be responsible for the decreased plasma amino acid concentrations (39). The decrease in glutamine levels may indicate an inability of glutamine synthetic mechanisms to meet the increased metabolic demand of critical illness. These findings have led to the suggestion that glutamine may behave as a “conditionally essential” amino acid. In contrast, there was an increase in the plasma phenylalanine concentration. This response has been observed in previous studies, and evidence suggests that levels of phenylalanine continue to rise with continuing illness (18, 33).

The metabolic response to critical illness is an integrated process, with elevated levels of cytokines and inflammatory mediators and increased concentrations of the “catabolic” hormones (catecholamines, glucocorticoids, and glucagon) (35). Changes observed in the patients in this study included elevated plasma cortisol concentration and decreased levels of free thyroid hormones.

Previous studies have investigated the effects of catabolic hormone infusions on glutamine metabolism in healthy volunteers. These have demonstrated that elevation of plasma cortisol to levels observed after trauma resulted in a 15% increase in whole body protein breakdown and a 40% increase in glutamine flux (11). This increase in flux was primarily due to a 55% increase in de novo glutamine synthesis, and it resulted in a significant increase in the plasma glutamine concentration. More recently, this cortisol-mediated increase in flux was shown to be dose dependent (7). In contrast, a triple hormone infusion of epinephrine, cortisol, and glucagon increased whole body glutamine flux and MCR and decreased plasma glutamine concentration (20). These studies suggest that these counterregulatory hormones may regulate the rate of glutamine metabolism, possibly through effects on glutamine transporters (30); however, they cannot fully
mimic the complex changes occurring in critically ill patients.

Although there are no comparable studies in ICU patients, whole body glutamine flux has been measured in patients after burn injury by use of a similar stable isotope technique (20). Whole body glutamine flux was higher in burns patients compared with the values we obtained (7.2 ± 0.6 vs. 4.9 ± 0.3 μmol·min⁻¹·kg⁻¹). Although the decreases in plasma glutamine concentration were similar in the two studies, a significant increase (60%) in glutamine flux was reported in the burns patients compared with a control group, in contrast to the 92% increase recorded in our patient group. However, these measurements were made 2 wk after the burn injury, whereas the patients in the present study were studied within days of admission to the ICU.

The leucine kinetic data in the critically ill indicated an increase in whole body protein synthesis and breakdown of 49 and 59%, respectively, and an increase in leucine oxidation (105%), indicating use of protein as an oxidative fuel. In addition, the plasma leucine concentration was decreased as a result of the increase in leucine oxidation (105%), indicating use of protein as an oxidative fuel. In addition, the plasma leucine concentration was decreased as a result of the increased utilization of leucine (indicated by the elevated leucine MCR). Isotope tracer methodology has been used to investigate whole body protein turnover in a variety of catabolic states, with conflicting results. A study in patients with multiple organ failure, using [1-¹³C]leucine, demonstrated significant increases in protein

Table 5. Whole body glutamine and leucine kinetics in healthy volunteers

<table>
<thead>
<tr>
<th>Glutamine Ra</th>
<th>Leucine Ra</th>
<th>Leucine Ox</th>
<th>Leucine MCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>μmol·min⁻¹·kg⁻¹</td>
<td>μmol·min⁻¹·kg⁻¹</td>
<td>μmol·min⁻¹·kg⁻¹</td>
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<tr>
<td>5.20 ± 0.22</td>
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<td>0.22 ± 4.15</td>
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<tr>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
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</tbody>
</table>

1. IGF-I, insulin-like growth factor I.
breakdown, synthesis, and leucine oxidation compared with control subjects (2). Plasma cortisol concentration was found to be the most significant predictor of protein breakdown and leucine oxidation in these patients.

In contrast, studies of protein metabolism after elective hysterectomy have shown that both whole body protein synthesis and breakdown decrease compared with the preoperative state (8). Ribosomal analysis and tracer studies have also shown that muscle protein synthesis decreases after uncomplicated elective surgery (15, 31, 40). With use of [15N]alanine as a tracer, a 37% increase in protein synthesis and a 79% increase in protein breakdown have been reported in fed patients 3–5 days after multiple skeletal trauma compared with controls receiving a similar diet (5). More recently, it has been shown that albumin and fibrinogen synthesis increased, whereas muscle protein synthesis decreased, in fed head-trauma patients (27). It is likely that the apparently conflicting data from these studies reflect the heterogeneity of the patient populations, the severity of illness, the nutritional status, the prior health of the patients, and the timing of the studies.

The major limitation of the whole body protein measurement is that this approach reflects the average rates of protein turnover in all tissues. However, during times of severe stress, different tissues in the body may behave differently. The majority of the measured increases in proteolysis may reflect increased muscle protein breakdown, as skeletal muscle is the largest protein pool in the human body. It is likely that, in part, the increase in protein synthesis reflects the increased synthesis of acute-phase proteins by the liver, tissue repair, and the immune response (leukocyte proliferation and cytokine production). This alteration of protein balance would account for the clinical observations of lean tissue loss in ICU patients.

The importance of matching the critically ill group for age and weight was studied by comparing glutamine and leucine kinetics in a young and an old control group. Leucine MCR, oxidation rate, incorporation into and release from body protein were similar in the control groups. This is in line with previously reported data suggesting that there is no independent effect of age on the measurements of leucine metabolism in postabsorptive adults, whether the results are expressed per kilogram body weight (17) or per kilogram LBM (6, 17, 38). The $R_{a,Gln}$ value in the young control subjects was significantly lower than that in the young healthy adults in the same age range (e.g., 7, 11, 29). In contrast, the $R_{a,Gln}$ value for the elderly group of controls was significantly lower than that in the young controls. However, the increase in body weight in the elderly group resulted from an increase in fat mass, not a decrease in LBM. When the results were expressed per kilogram LBM, there was no age-associated decrease in $R_{a,Gln}$, suggesting that the apparent difference in $R_a$ is related to age-associated changes in body composition rather than altered glutamine metabolism.

It is difficult to measure body composition accurately in ICU patients. Bioelectric impedance is the most accessible method, and this was used in the controls in the present study. However, as there is some doubt about the practicality and validity of bioelectrical impedance measurements of body composition in critically ill patients (22, 26), these results suggest that matched controls are necessary when glutamine metabolism is measured in ICU patients.

The patients for our study were recruited in the ICU from patients in whom the clinical decision had been made to use parenteral nutrition. Unlike previous studies reporting glutamine metabolism and most of the studies of leucine metabolism in catabolic patients, we have studied a heterogeneous group. We chose to study these patients because they represent a group in whom there is considerable clinical interest in the potential benefits of glutamine supplementation. The study demonstrates that critical illness is associated with marked alterations in protein metabolism. The increased glutamine clearance with a normal $R_{a,Gln}$ resulted in a decrease in glutamine concentration, suggesting that the increase in protein breakdown was insufficient to meet the demand for glutamine in these catabolic patients.

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