Increased Albumin and Fibrinogen Synthesis in Hemodialysis Patients with Normal Nutritional Status

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Abstract. This study compared the rates of whole-body protein turnover in and albumin and fibrinogen synthesis of seven hemodialysis patients (HD) with those of seven normal matched control subjects (C). HD patients had a normal nutritional and inflammatory status and serum albumin levels >3.5 g/dl. Endogenous leucine flux, albumin and fibrinogen fractional synthesis rate (FSR), and absolute intravascular synthesis rate (ASR) of albumin and fibrinogen all were evaluated by a primed/continuous infusion of 5,5,5-D3-L-leucine. Plasma volume was determined by the Evans blue dye dilution method. Endogenous leucine flux was significantly increased in HD (3.31 ± 0.6 g/1.73 m² per d, P < 0.05) compared with C (2.17 ± 0.07 g/1.73 m² per d, P < 0.05). Serum albumin concentrations were similar in HD and C. Plasma fibrinogen levels were significantly increased in HD compared with C (P < 0.05).

Plasma volume was greater in HD than in C (P < 0.05). As a result, total intravascular pool of both albumin (141 ± 7 versus 114 ± 3 g/1.73 m², P < 0.05) and fibrinogen (11.7 ± 1 versus 6.7 ± 0.5 g/1.73 m², P < 0.05) were greater in HD than in C. Albumin FSR was not significantly different in HD and C. However, albumin ASR was significantly increased in HD than in C (13.7 ± 2 versus 10.3 ± 1 g/1.73 m² per d, P < 0.05). Similarly, FSR of fibrinogen did not differ in HD and C groups, whereas ASR of fibrinogen was significantly higher in HD than in C (3.31 ± 0.6 versus 1.94 ± 0.3 g/1.73 m² per d, P < 0.05). In summary, normoalbuminemic HD patients have an increased intravascular pool with a greater absolute synthesis rate of both albumin and fibrinogen and an increased rate of whole-body leucine flux.

Hypoalbuminemia is a strong predictor of mortality in patients with end-stage renal disease (ESRD). In particular, serum albumin and creatinine levels are indices of protein status; when reduced, they have been associated with poor survival in dialysis patients (1). Several factors may affect albumin metabolism in hemodialysis patients. Maintenance of normal albumin status may require adaptive changes in the rate of hepatic synthesis. In fact, a sizable amount of amino acid and protein are lost in the dialysate; the volume of distribution of albumin and its catabolism are increased (2). Various concomitant factors such as acute illness, acid base status, dietary protein, and calorie intakes may also affect hepatic albumin synthesis (3). In addition to albumin metabolism, whole-body protein turnover is altered in ESRD (4). Furthermore, elevated fibrinogen levels have been reported in hemodialysis patients (5) and have been associated with an increased prevalence of coronary artery disease (6).

The mechanisms responsible for the increment in fibrinogen levels have not been fully understood. No studies have correlated total protein fluxes to albumin synthesis in hemodialysis patients. Most of the information available on albumin metabolism in hemodialysis patients is derived by comparison between normoalbuminemic and hypoalbuminemic patients, showing a lower rate of albumin synthesis in the latter group (3). Whole-body protein and albumin metabolism in normal subjects and hemodialysis patients have not been compared directly. Although serum concentration of total protein and albumin may be in the normal range, hemodialysis subjects may need additional compensatory factors to maintain normoalbuminemia. In addition, simultaneous evaluation of hepatic albumin and fibrinogen synthesis have not been performed in hemodialysis patients. Cross-sectional studies suggest evidence of an inverse relationship between albumin and fibrinogen levels in hemodialysis patients. In contrast, data in nephrotic syndrome show that albumin and fibrinogen synthesis may be stimulated concomitantly (7).

The present study was performed to investigate (1) the mechanism by which albumin homeostasis is maintained in normoalbuminemic hemodialysis patients and (2) the relationship between albumin and fibrinogen synthesis in this patient population.
Materials and Methods

**Patient Population**

Seven healthy, normal volunteers (four men, three women; controls) and seven patients with end-stage renal failure (four men, three women) maintained on hemodialysis treatment participated in the study protocol. Control subjects were matched for age, gender, body mass index, ideal body weight, fat-free mass, and serum albumin levels. Eligibility criteria of hemodialysis patients included age of 20 to 50 yr, ideal body weight of 90 to 115%, body mass index < 25 kg/m², serum albumin concentration within the range of 3.5 to 4.5 g/dl during the last 3 mo before the study, and no evidence of endocrine or other major organ system disease, as determined by medical history, physical examination, and routine laboratory tests. Study population characteristics are shown in Table 1. In maintenance hemodialysis patients, the duration of replacement therapy was 38 ± 9 mo and their hemodialysis adequacy was assessed by Kt/V of urea, which was 1.25 ± 0.1. In these patients, an adequate ingestion of protein was shown by a protein catabolic rate of 1.34 ± 0.1 g/kg per d, which was stable for at least 3 mo before the study. At the time of the study, in hemodialysis patients, predialysis laboratory tests showed blood urea nitrogen of 65 ± 7 mg/dl, serum creatinine of 10.7 ± 1 mg/dl, serum sodium of 140.4 ± 1 mEq/L, serum potassium of 5.7 ± 0.4 mEq/L, serum calcium of 9.8 ± 0.4 mg/dl, and serum phosphate of 7.3 ± 0.7 mg/dl. Arterial pH, bicarbonate levels, and PaCO₂ were close to normal and averaged 7.37 ± 0.02, 22.9 ± 1.2 mEq/L, and 39.7 ± 0.9 mmHg, respectively. Acute-phase reactant proteins: serum total α-2-globulin concentrations (0.70 ± 0.4 versus 0.73 ± 0.5 g/dl), C-reactive protein levels (0.32 ± 0.02 versus 0.33 ± 0.02 mg/dl), and α-2-macroglobulin levels (0.18 ± 0.01 versus 0.21 ± 0.02 g/dl) were similar in control subjects and hemodialysis patients, respectively. The hemodialysis treatment (Drake Willock, System 1000, Althin Medical, Inc., Miami, FL) was administered three times a week, and each session lasted 210 to 240 min. Polysulphone capillary dialyzers (Fresenius low flux series, model F6, F7, F8; Fresenius Medical Care, Bad Homburg, Germany) were used and no filter was reused. During hemodialysis, blood flow was maintained at 250 to 300 ml/min, while dialysate flow was 500 ml/min. Other than vitamins, erythropoietin, bicarbonate, and phosphate binder supplemetations in the uraemic group, patients were not taking any medication. The cause of renal failure in the uraemic group was as follows: chronic glomerulonephritis (n = 2), membranous nephropathy (n = 2), interstitial nephritis (n = 1), polycystic kidney disease (n = 1), and unknown (n = 1). All patients consumed a weight-maintaining diet that provided approximately 35 to 38 cal/kg per d and contained approximately 55%, 30%, and 15% carbohydrate, fat, and protein, respectively; compliance with the diet was verified with a dietary diary for 7 d before the study. The purpose and potential risks of the study were explained to all participants, and their voluntary written consent was obtained before their participation.

**Experimental Protocol**

All tests were performed in the postabsorptive state after a 12-h overnight fast. In hemodialysis patients, the study was performed during the interdialytic day. An 18-gauge polyethylene catheter was inserted into an antecubital vein for the infusion of all test substances, and a second catheter was placed retrogradely into a wrist vein for blood sampling. The hand was kept in a heated box at 60°C to ensure arterialization of the venous blood. Shunt arm was not used for analytical purposes. At 08:00, a prime (0.6 mg/kg bolus) continuous (1.2 mg/kg per h) infusion of 5,5,5-D3-L-leucine (Mass Trace, Woburn, MA) was begun and continued for 5 h by a Harvard syringe pump (Harvard Apparatus, Ealing, South Natick, MA). Ten ml of blood were collected at −15, 0, 180, 210, 240, 270, and 300 min to measure the plasma concentration and enrichment of leucine, α-ke-toisocaproic acid (KIC), and the enrichment of D3-leucine bound to albumin and fibrinogen. At the end of the leucine continuous infusion period, plasma volume was determined by the Evans blue dye dilution method. Briefly, a bolus of approximately 4 ml of 0.9% NaCl solution containing 5 mg/ml sterile, pyrogen-free Evans blue dye (BDH Laboratory Supplies, England) was injected into an antecubital vein. Blood was drawn every 10 min from 10 to 60 min for measurement of Evans blue dye in the serum.

**Analytical Determinations**

Leucine and KIC were extracted from plasma samples as described previously (8) after the addition of 50 μl/ml noreleucine (160 μmol/ml) and 20 μl/ml ketocaproate (20 μmol/ml) as internal standards. Enrichments and concentrations of plasma leucine and KIC were determined on their t-butylidimethylsilyl derivatives using gas-chromatography mass spectrometry in electron impact ionization mode (GC38000, MS Voyager Fininning, ThermoQuest Italia, Milan, Italy), monitoring the ions 302 and 305 for leucine and 301 and 304 for KIC (9). Plasma albumin and fibrinogen were purified to obtain accurate measurements of their fractional synthesis rates (FSR) as described previously in detail (10,11). To evaluate plasma volume, we used the method of Brown et al. (12). Serum samples were added with an equal volume of approximately 4000 D, polyethylene glycol (J.T. Baker, Deventer, Holland) solution (24 g/dl) for precipitation of nonalbumin proteins to avoid interference with plasma lipids. Samples and standards were vortexed and centrifuged for 10 min at 3000 × g. Supernatants from samples and standards were then read at 620 nm of wavelength (12) using a spectrophotometer (Ciba-Corning Diagnostics Limited, Halstead, Essex, England). Serum albumin concentration was determined by standard bromcresol green method (13) (ALB plus, Roche Diagnostics, Mannheim, Germany, on autoanalyzer Hitachi 747). In hemodialysis patients, bromcresol green method has been indicated to overestimate albumin levels by approximately 10% in comparison with an immunonephelometry method (14). However, this finding has not been confirmed in later studies (13). Serum C-reactive protein was measured using an immunonephelometric method (Tina-quant, Roche Diagnostics, on Hitachi). α-2-Macroglobulin was measured using a routine nephelometric method (Behringwerke AG, Marburg, Germany). Plasma chronometric determination of fibrinogen was obtained in citrate plasma using the clotting method.

**Table 1. Summary of clinical nutritional status in control and hemodialysis subjects**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls</th>
<th>Hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>(4/3)</td>
<td>(4/3)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>37 ± 3</td>
<td>38 ± 5</td>
</tr>
<tr>
<td>BW (kg)</td>
<td>68 ± 4</td>
<td>70 ± 5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24 ± 1</td>
<td>22 ± 1</td>
</tr>
<tr>
<td>IBW (%)</td>
<td>104 ± 3</td>
<td>101 ± 5</td>
</tr>
<tr>
<td>FFM (%)</td>
<td>80 ± 2</td>
<td>81 ± 2</td>
</tr>
</tbody>
</table>

* BW, body weight; BSA, body surface area; BMI, body mass index; IBW, ideal body weight; FFM, fat-free mass. No statistical differences were present between study groups, values are expressed as the mean ± SEM.
of Clauss (15) on Hemolab Fibrinomat (bioMe’rieux sa, Lyon, France). Body composition was assessed by bioelectrical-impedance analysis with a four-terminal portable impedance analyzer (Human-Im SCAN, DS Medigroup, Milan, Italy). Measurements were made while the subject was in a supine position and after lying in a stretcher with the limbs abducted from the body. Current injector electrodes were placed just below the third phalangeal-metacarpal joint of the dorsal side of the right hand and just below the third phalangeal-metatarsal of the dorsal side of the right foot. Detector electrodes were placed on the middle of the dorsal side of the right ankle joint with the foot semiflexed. Resistance (R) to the flow of 1, 5, 10, 50, and 100 kHz injected currents was measured on a 0- to 1000-Ohm scale and reactance (Xc) was measured on a 0- to 200-Ohm scale. At each frequency, the phase angle was calculated as (resistance/reactance) and impedance was calculated as (reactance² + resistance²) 0.5 (16).

Calculations

The enrichments of leucine and KIC were expressed as the tracer to tracee ratio (TTR), accounting for isotopomer skewed distribution and spectra overlapping when appropriate. Whole-body leucine flux was calculated as the rate of appearance of leucine (Ra; micromoles per kg/min) as follows:

\[ Ra = \frac{I}{Ep} \]

where I is the isotope infusion rate of leucine and Ep is the plasma enrichment (TTR) of KIC. The estimates of whole-body leucine kinetics were determined on the data obtained during the last 2 h of the study (180 to 300 min) at the isotopic and metabolic steady state (17). Albumin and fibrinogen fractional synthesis rate (FSR) were calculated by dividing the slope of the increase of the enrichment of leucine bound to albumin or fibrinogen by the enrichment of plasma KIC over the last 2 h of the study. Absolute intravascular albumin and fibrinogen synthesis rate (ASR) were estimated by multiplying albumin or fibrinogen FSR by total intravascular albumin or fibrinogen content. After Evans blue dye injection, the concentration at time 0 was extrapolated. The estimated concentration at time 0 was used to calculate plasma volume by standard dilution formula:

\[ PV (\text{ml}) = \frac{\text{dose of EBD (mcg) injected}}{\text{serum concentration of EBD (mcg/ml)}} \times \frac{\text{ID rise BUN} \times 24}{\text{kg of BW}} \]

extrapolated at time 0 (12). Protein catabolic rate in hemodialysis patients was calculated by standard formula as follows:

\[ PCR = 0.22 + (0.036 \times \text{ID rise BUN} \times 24)/\text{kg of BW} \]

where ID is the interdialytic interval in hours (18). During hemodialysis, Kt/V was calculated from Daugirdas formula (18).

Statistical Analyses

All values are expressed as the mean ± SEM. Intergroup comparisons were performed using ANOVA. Comparisons between the study groups were performed using paired t test.

Results

Plasma Volume

Plasma volume in maintenance hemodialysis patients (3586 ± 262 ml/1.72 m²) was significantly increased compared with that in control subjects (2728 ± 148 ml/1.72 m², P < 0.01 versus control).

Whole-Body Leucine Flux

In control subjects, endogenous leucine flux, an index of whole-body protein turnover, was 2.17 ± 0.07 μmol/kg per min and was slightly increased in maintenance hemodialysis patients (2.64 ± 0.08 μmol/kg per min, P < 0.05 versus control; Table 2).

Albumin Metabolism

Serum albumin levels were similar in both control and hemodialysis study groups and averaged 4.18 ± 0.1 and 3.99 ± 0.2 g/dl, respectively. The total plasma albumin pool in control subjects was 114 ± 3 g/1.73 m², whereas it was significantly greater in the hemodialysis study group (141 ± 7 g/1.73 m², P < 0.01 versus control). Absolute synthesis rate of albumin was 10.3 ± 1 g/1.73 m² in control subjects and was significantly greater in maintenance hemodialysis patients (13.7 ± 2 g/1.73 m², P < 0.01 versus control). In contrast, the two study groups had a similar FSR of albumin and averaged 9.03 ± 0.5% and 9.80 ± 1.4% in control subjects and hemodialysis patients, respectively (Table 2).

Fibrinogen Metabolism

Plasma fibrinogen levels were increased in hemodialysis patients in comparison with control subjects and averaged 328 ± 30 and 245 ± 18 mg/dl, respectively. Total plasma fibrinogen pool in control subjects was 6.7 ± 0.5 g/1.73 m² and was significantly greater in maintenance hemodialysis patients, respectively (Table 2).

Table 2. Albumin, fibrinogen, and leucine metabolism in control subjects and hemodialysis patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls</th>
<th>Hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum albumin (g/dl)</td>
<td>4.2 ± 0.1</td>
<td>4.0 ± 0.2</td>
</tr>
<tr>
<td>Plasma albumin pool (g/1.73 m²)</td>
<td>114 ± 3</td>
<td>141 ± 7*</td>
</tr>
<tr>
<td>Albumin ASR (g/1.73 m² per day)</td>
<td>10.3 ± 1</td>
<td>13.7 ± 2*</td>
</tr>
<tr>
<td>Albumin FSR (%/day)</td>
<td>9.0 ± 0.5</td>
<td>9.8 ± 1.4</td>
</tr>
<tr>
<td>Plasma fibrinogen (mg/dl)</td>
<td>245 ± 18</td>
<td>328 ± 30*</td>
</tr>
<tr>
<td>Plasma fibrinogen pool (g/1.73 m²)</td>
<td>6.7 ± 0.5</td>
<td>11.7 ± 1*</td>
</tr>
<tr>
<td>Fibrinogen ASR (g/1.73 m² per day)</td>
<td>1.94 ± 0.3</td>
<td>3.31 ± 0.6*</td>
</tr>
<tr>
<td>Fibrinogen FSR (%/day)</td>
<td>28.3 ± 2</td>
<td>26.8 ± 5</td>
</tr>
<tr>
<td>Endogenous leucine flux (μmol/kg per min)</td>
<td>2.17 ± 0.07</td>
<td>2.64 ± 0.08*</td>
</tr>
</tbody>
</table>

* ASR, absolute synthesis rate; FSR, fractional synthesis rate. Values are mean ± SEM. *, P < 0.05 versus controls.
significantly greater in hemodialysis patients (11.7 ± 1 g/1.73 m², P < 0.01 versus control). The absolute synthesis rate of fibrinogen was 1.94 ± 0.3 g/1.73 m² in control subjects and was significantly greater in maintenance hemodialysis patients (3.31 ± 0.6 g/1.73 m², P < 0.01 versus control). In contrast, in the two study groups, a similar FSR of fibrinogen was observed and averaged 28.3 ± 2% and 26.8 ± 5% in control subjects and hemodialysis patients, respectively (Table 2).

Discussion

The present data demonstrate that in normoalbuminemic hemodialysis patients, the absolute rate of albumin and fibrinogen synthesis, together with their intravascular pools, both are increased when compared with control subjects. As a result of the concomitant rise of both the intravascular pool and the absolute synthesis rate, the FSR of albumin and fibrinogen in hemodialysis patients are similar to healthy control subjects. Whole-body endogenous leucine flux is also moderately elevated in hemodialysis patients in comparison with controls.

Recently, a large body of experimental evidence has pointed to albumin and fibrinogen levels as strong predictors of morbidity and mortality in hemodialysis patients (1,6). Hyperfibrinogenemia is an important risk factor for atherosclerosis in the general population, and elevated fibrinogen levels have been found in hemodialysis patients with cardiovascular disease (6,19). Several parameters may affect albumin and/or fibrinogen metabolism in hemodialysis patients, such as nutritional status (20), chronic subclinical or overt inflammatory state (19), metabolic acidosis (21), dialysis dose (22), and types and modalities of dialysis filter use (4). To minimize the effects of these confounding factors, the present study was designed to evaluate the kinetic parameters of albumin synthesis in normoalbuminemic hemodialysis patients with no clinical evidence of recent weight loss, malnutrition, inflammatory disease, inadequate dialysis dose, and metabolic acidosis. None of the hemodialysis subjects had a positive history for cardiovascular disease or deep vein thrombosis. Data obtained on hemodialysis patients were compared with results obtained on age, gender, body mass index, ideal body weight, and fat-free mass matched healthy control subjects.

Previous investigators have described several abnormalities in whole-body protein metabolism in chronic renal failure patients (4,23). However, no data are available on the relationship between albumin and whole-body protein turnover in these patients. In addition, no single study has simultaneously compared albumin and fibrinogen kinetics in maintenance hemodialysis patients and appropriately matched healthy control subjects.

In a comprehensive study, Kaysen et al. (24) evaluated albumin synthesis, fractional catabolic rate, and total body pool using (125-I) human albumin kinetics in normoalbuminemic and hypoalbuminemic dialysis patients. The estimated rate of daily albumin synthesis in normoalbuminemic subjects (14.58 ± 1.88 g/1.73 m²) was in remarkable agreement with the present data (13.7 ± 2 g/1.73 m²). Thus, the rate of synthesis of albumin is increased by approximately 30 to 35% in comparison with that observed in nutritionally matched control subjects. These data suggest that in hemodialysis patients with no additional factors that may induce hypoalbuminemia, normal serum albumin levels are maintained by a significant (30 to 35%) increase in basal rate of albumin synthesis. Several factors may affect albumin metabolism in hemodialysis patients. First, unavoidable amino acid losses in the dialysate, estimated in 6 to 10 g of amino acid per dialysis (2), and a reduced dietary protein intake may reduce the substrate availability for protein synthesis (4) and offset the long-term ability of the liver to maintain a normal albumin status. Second, a large body of experimental evidence has accumulated suggesting that hemodialysis is a chronic inflammatory state (25,26). Albumin reacts as an acute-phase inflammatory protein, and its circulating levels are diminished acutely during systemic inflammation (27). This response is mediated by lymphokines, interleukin-6, interleukin-1, and tumor necrosis factor, which induce a transcriptional inhibition of albumin synthesis and the stimulation of hepatic production of various protein, including fibrinogen, C-reactive protein, and α-2-macroglobulin. In the present study, hemodialysis patients showed normal levels of C-reactive protein and α-2-macroglobulin; therefore, it is unlikely that an inflammatory status may have affected the hepatic albumin synthesis. Acid-base disorders also affect endogenous proteolysis and albumin metabolism. However, in the present study, arterial bicarbonate levels in hemodialysis patients were 22.9 ± 1.2 mEq/L. A significant effect of correction of acidosis on albumin levels has been reported when bicarbonate levels are raised from 19 to 24 mEq/L (28). Hemodialysis-related albumin losses are approximately 1 to 2 g per dialysis (29) and may be increased only under specific, albeit rare, dialysis conditions (high-flux dialysis and filter reuse with bleach or formaldehyde sterilization). In the present study, low-flux polysulfone dialyzers were used with no filter reuse; therefore, it is unlikely that albumin losses in the dialyzer may have exceeded the 3 to 6 g per week. Increased albumin synthesis may represent a compensatory response to maintain normal intravascular oncotic pressure in patients with plasma volume expansion. Alternatively, an increased escape of albumin and fibrinogen from the vascular bed to the interstitial space is consistent with the kinetic data of the present study and may have contributed to an increased hepatic synthesis rate. In the present study, hemodialysis patients were anuric. However, if present, albuminuria may also represent a significant source of albumin losses. To this regard, it has been reported that in 78 nephrectomized rats with chronic renal failure and proteinuria, the rate of albumin synthesis is increased by 50%; and when proteinuria is prevented, no increase in albumin synthesis rate is observed (30).

Of interest, our data provide evidence that in the absence of clinical signs of inflammation, plasma fibrinogen and albumin pool and their hepatic synthesis is concomitantly increased. These results suggest a complex regulation of fibrinogen and albumin hepatic synthesis in which the enhanced synthesis of the former is not associated with the reduced synthesis of the latter. The present data are also consistent with the data of de
Sain-van der Velden et al. (7) in nephrotic patients. To this regard, the role of substrate and energy availability, hormones, and interleukin levels clearly deserves further attention. In particular, it would be of great interest to evaluate the relative change of albumin and fibrinogen synthesis in hypoalbuminemic hemodialysis patients with clinical signs of malnutrition or chronic inflammation.

Our data show that in maintenance hemodialysis patients, an increased whole-body leucine turnover is present. Because total endogenous leucine flux reflects both splanchnic and muscle protein turnover, the observed increase is consistent with the enhanced albumin and fibrinogen synthesis. Similarly, leucine turnover data are in agreement with the estimated protein catabolic rate of 1.34 ± 0.1 g/d, and in stable nonwasting hemodialysis patients reflects an elevated dietary protein intake (18). The dietary protein intake observed in the present study is slightly higher than the recommended value of 1.2 g/kg per d (29). This may be a desirable, albeit uncommon, condition in hemodialysis patients. However, the impact of a reduced protein intake on albumin and fibrinogen synthesis may deserve further attention.

In conclusion, in hemodialysis patients with a normal nutritional status, total albumin pool is increased and normal serum albumin concentration is maintained at the expense of a significant increase in the rate of hepatic albumin synthesis. In the absence of an overt sign of acute or chronic inflammation, fibrinogen and albumin synthesis and total fibrinogen pool both are elevated. Thus, in comparison with control subjects, hemodialysis patients have a concomitant rise in the absolute rate of hepatic albumin and fibrinogen synthesis, associated with a modest increment in the rate of whole-body leucine flux.

References


