**Objective:** To determine if the anabolic effects of intravenous insulin on protein kinetics could be exploited in the enterally fed trauma victim.

**Design:** Randomized, crossover control protocol.

**Setting:** Level I trauma center.

**Patients:** Ten trauma patients with an Injury Severity Score higher than 20. Exclusion criteria included diabetes mellitus, pregnancy, steroid use, and aged younger than 18 years or older than 65 years.

**Interventions:** Within the first 24 hours of admission to the intensive care unit, each patient had a transpyloric feeding tube inserted radiographically. Enteral nutrition was provided with a protein supplement (Ensure, Ross Laboratories, Columbus, Ohio) and Promod, supplemented with protein powder to supply 1.5 g/kg per day of protein and 156.9 kJ/kg per day. Intravenous insulin was provided at 0.043 U/kg per hour beginning on the second or fourth day.

**Main Outcome Measures:** Urinary nitrogen balance and 3-methylhistidine excretion rates were measured at the end of the third and fifth days. Plasma glucose, insulin, and C-peptide levels were obtained at these same times.

**Results:** Urinary nitrogen balance was not significantly different with or without the administration of insulin (−4.58 ± 50.1 mg/kg per day vs −9.38 ± 50.9 mg/kg per day, respectively). 3-Methylhistidine excretion rates did not change significantly with or without the administration of insulin (5.77 ± 0.67 µmol/kg per day vs 6.15 ± 0.43 µmol/kg per day, respectively). Serum insulin levels did not differ significantly when exogenous infusions were added (57.8 ± 17.9 µU/mL vs 82.1 ± 44.9 µU/mL), but serum C-peptide levels did decrease significantly when exogenous insulin was added (5.11 ± 3.2 µU/mL vs 10.28 ± 3.5 µU/mL; P = .04). Serum glucose levels decreased significantly when insulin was administered (5.8 ± 0.4 mmol/L [104.6 ± 7.2 mg/dL] vs 7.7 ± 0.4 mmol/L [138.1 ± 7.4 mg/dL]; P = .004).

**Conclusion:** The anabolic effect of intravenous insulin on protein kinetics is not evident when nutrition is provided enterally in the trauma victim.

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**EARLY NUTRITIONAL support is an integral part of the care of the acutely injured patient. Enteral feeding is the preferred method of providing nutrition to the victims of major trauma because it maintains the integrity of the gut mucosal barrier by directly providing the enterocyte with necessary nutrients. Equally important, early nutritional support provides the necessary components for wound healing and for ameliorating muscle wasting during convalescence. Providing more protein to the catabolic patient to attain a more favorable nitrogen balance has its advantages. However, there should be concern as to the effect of high protein intake on renal function. Therefore, until the body becomes more efficient in the retention of protein during the convalescent period, the use of anabolic hormones should be contemplated to stimulate nitrogen assimilation.**

Insulin has been shown to increase skeletal muscle protein synthesis and to decrease it degradation in numerous in vitro and in vivo studies when amino acids are provided intravenously, but to our knowledge, no studies have been published regarding its effect when nutrition is provided enterally. Using human skeletal muscle in vitro, Lundholm and Schers demonstrated a decrease in protein degradation and an increase in protein synthesis. Human in vivo studies across a muscle bed have produced conflicting re-
PATIENTS, MATERIALS, AND METHODS

After obtaining informed consent, 10 victims of blunt trauma were enrolled in this randomized, crossover controlled protocol that had been approved by our institutional review board. Patients aged 18 to 65 years were eligible, and diabetes mellitus, pregnancy, steroid administration, or an Injury Severity Score (ISS) of less than 20 were exclusion criteria. Each patient underwent standard evaluation and treatment at our level I trauma center and was admitted to the intensive care unit (ICU). Within 24 hours of admission to the ICU, each patient was administered enteral nutrition through a radiographically placed transpyloric feeding tube. Nutrition consisted of Ensure (Ross Laboratories, Columbus, Ohio) supplemented with Promod protein powder (Ross Laboratories) to provide 1.5 g/kg per day of protein and 156.9 kJ/kg per day. After 1 day of incrementally increasing the rate to the desired level, each patient was maintained at this rate for 4 additional days. Beginning on either the second or fourth day of the protocol, each patient was given intravenous regular insulin at 0.043 U/kg per hour. After 48 hours of insulin infusion, the patient was crossed over into the other limb of the protocol, either to receive insulin or to discontinue its use.

Twenty-four-hour urine collections from the third and fifth days of the protocol were analyzed for total urinary nitrogen levels using a nitrogen analyzer (Antek Nitrogen Analyzer; Antek, Houston, Tex) and for 3-methylhistidine (3-MH) excretion using an amino acid analyzer (Beckman Automatic Amino Acid Analyzer; Beckman Instruments, Palo Alto, Calif). Serum samples were analyzed for glucose using the glucose oxidase method, and serum insulin and C-peptide levels were determined by Labcorp (Birmingham, Ala) after each 48-hour study period. Results were analyzed using the paired Student t test and are expressed as mean ± SEM. Significance was determined at P = .05.

RESULTS

The demographics and injuries of the 10 patients in this study are given in the Table. There were 6 male and 4 female patients, with an average age of 31.4 years (age range, 21-64 years). The mean ISS was 33.3 (range, 27-50). The mean weight of this group was 73.0 kg (range, 61-103 kg), and height averaged 176 cm (range, 160-185 cm). There was no mortality during the study period and no morbidity (diarrhea or hypoglycemia) related to the protocol.

Urinary nitrogen balance was not significantly different whether or not insulin was administered (−4.58 ± 50.1 mg/kg per day vs −9.38 ± 30.9 mg/kg per day, respectively). Similarly, urinary 3-MH excretion was not significantly different with or without insulin infusion (5.77 ± 0.67 µmol/kg per day vs 6.15 ± 0.43 µmol/kg per day, respectively). Serum glucose was significantly lower when insulin was administered (5.8 ± 0.4 mmol/L [104.6 ± 7.2 mg/dL] vs 7.7 ± 0.4 mmol/L [138.1 ± 7.4 mg/dL]; P = .004). Serum insulin levels did not differ significantly when exogenous infusions were added (415 ± 128 pmol/L vs 589 ± 322 pmol/L), but serum C-peptide levels did decrease significantly when exogenous insulin was added (5.11 ± 3.2 µU/mL vs 10.28 ± 3.5 µU/mL; P = .04). Serum glucose values decreased significantly when insulin was administered (5.8 ± 0.4 mmol/L [104.6 ± 7.2 mg/dL] vs 7.7 ± 0.4 mmol/L [138.1 ± 7.4 mg/dL]; P = .004).

COMMENT

Following injury, there are hypercatabolic and hypermetabolic responses that may last for days depending on the severity of the traumatic episode.11 The negative nitrogen balance due to protein catabolism seen in patients who have suffered severe trauma is detrimental in several ways, including longer recovery time, increased morbidity and mortality, decreased wound healing, and inhibition of the immune response. Nutritional intervention during convalescence has proved beneficial in decreasing muscle wasting. Although the provision of energy intake and nitrogen does have an impact on improving nitrogen balance, a positive nitrogen balance is difficult, if not impossible, to attain at the peak of the catabolic response. The catabolic response to injury is thought to be mediated by the increase in catecholamines, cortisol, and glucagon values and by the increased resistance to insulin.

That insulin plays a major role in protein metabolism is well known. Numerous in vitro studies have shown that insulin inhibits protein breakdown and increases protein synthesis.2,12,13 Fukagawa et al8 showed the availability of amino acid substrates is also vital for maximization of the anabolic effect of insulin to be maximized.15 In patients who had undergone a major operative procedure, Valarini et al15 showed that insulin further improved the positive nitrogen balance achieved with a TPN solution that contained 0.25 g/kg of nitrogen and an energy-nitrogen ratio of 150:1 but not with 0.5 g/kg of nitrogen and an energy-nitrogen ratio of 75:1, suggesting that the effect...
of amino acids on the improvement of nitrogen balance is saturable. Inculet et al,16 using an isolated forearm skeletal muscle model, showed a decrease in nitrogen balance and 3-MH excretion in patients who were given insulin and TPN after surgery. We have recently demonstrated that intravenous insulin and TPN produced a positive nitrogen balance, decreased 3-MH excretion, and facilitated whole-body protein synthesis within 5 days of major trauma.10 These findings prompted us to perform the present protocol to determine if the anabolic effect of insulin could be combined with the advantages of enteral nutrition.

In our study, intravenous insulin produced no change in either urinary nitrogen balance or the excretion of 3-MH when given as a supplement to enteral nutrition. A possible explanation for a lack of effect is that the amino acids underwent modification by the liver before reaching the muscles. Some of the amino acids may have been incorporated into acute-phase reactants whose synthesis is increased after trauma. The anabolic effect of insulin has been previously evaluated mainly using an intravenous amino acid infusion model. It may be assumed that the provision of amino acids by either route would be equivalent in terms of protein synthesis. However, amino acids provided by the enteral route are first processed through the liver where it is known that this organ temporarily stores a part of the ingested amino acids as proteins, modifies the amino acid flux to muscle, and deaminates and oxidizes others as shown by McMenamy et al17 with use of a dog model. They showed a wide range in the portion of added amino acids taken up by the liver, from 90% for tryptophan and phenylalanine to approximately 20% for threonine, valine, leucine, and isoleucine. This remodeling of amino acids presented to the muscle might negate the effect of insulin that requires or favors a more appropriate blend of amino acids for protein synthesis as is present in TPN based on requirements as proposed by Rose.18 Increasing the amount of protein administered in the tube feedings to a level that could overcome the hepatic effect would likely produce undesirable side effects such as diarrhea, azotemia, and impaired renal function.

The intent of nitrogen losses should be reflected during the first 2 days of the protocol since the target rate of the enteral infusion was achieved within the first 24 hours. There should be no question that the third and fifth days are comparable to a steady nutritional state. This short equilibration time is supported by Cerra et al19 who showed urinary nitrogen losses on a constant elemental feeding to be 11.4 g of nitrogen on day 1, 12.2 g of nitrogen on day 3, and 10.6 g of nitrogen on day 7. Shronts et al20 showed nitrogen losses on a standard elemental infusion formula to be 16.0 g of nitrogen on day 1 and 18.2 g of nitrogen on day 3. On a modified enteral formula, losses were 15.8 g of nitrogen on day 1 and 18.9 g of nitrogen on day 3. Additionally, Watters et al21 began full-strength feeding via jejunostomy tubes within 6 hours of major operations and increased to the target rate of either 125% of preoperative energy expenditure or 2500 mL/d (whichever was the lesser) on the second postoperative day. Urine losses were 8.5 g of nitrogen on day 1, 8.9 g of nitrogen on day 2, and 9.3 g of nitrogen on day 3. These data also support the fact that a steady state of nitrogen dynamics is attained by day 2 and certainly by day 3 of this randomized, blinded study even when bypassing the small gastric component of digestion.

In conclusion, the route of administration of nutrition does affect insulin’s anabolic effect. Although we had previously demonstrated insulin’s ability to produce positive nitrogen balance, increase protein synthesis, and decrease protein breakdown using TPN, this effect could not be achieved with enteral feeding. We believe this is owing to the modification and use of amino acid substrates by the liver before they can reach the skeletal muscle tissue.

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REFERENCES


Depression and Risk of Coronary Heart Disease in Elderly Men and Women

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Background: Results of several recent studies suggest that depression is predictive of incident coronary disease. However, few studies have examined this relationship in the elderly, the age at which most coronary heart disease (CHD) becomes clinically manifest.

Methods and Results: Data are from the New Haven, Conn, cohort (N = 2812) of the Established Populations for the Epidemiologic Studies of the Elderly project. Baseline information on depressive symptoms and CHD risk factors was collected during an in-person interview in 1982. Nonfatal myocardial infarctions were identified through monitoring of admissions to local hospitals and were validated by medical chart review. Cause of death was obtained from death certificates for all deceased participants. Outcomes were defined as CHD deaths (n = 255) and total incident CHD events (n = 391) between January 1, 1982, and December 31, 1991. There was no association between depressive symptoms and CHD outcomes in men. Among women, depressive symptoms were associated with an age-adjusted relative risk of 1.03 (per unit increase on the symptom scale) for CHD mortality (P = .001) and total CHD incidence (P = .002). These associations were largely unaffected by adjustment for established CHD risk factors but were reduced to nonsignificant levels after additional adjustment for impaired physical function. Additional analysis showed a significant association for depressive symptoms among women who had no physical function impairments or who survived at least 3 years without an event.

Conclusion: Depressive symptoms may not be independent risk factors for CHD outcomes in elderly populations in general but may increase risk among relatively healthy older women. (1998;2341-2348)

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