TITLE: REGULATION OF PROTEIN AND AMINO ACID CATABOLISM BY INSULIN IN SEPTIC OR SEVERELY BURNED PATIENTS

AUTHORS: Robert E. Shangraw, M.D. Ph.D., Farook Jahoor, Ph.D., Hiroshi Miyoshi, M.D., William A. Neff, M.D., Charles A. Stuart, M.D., and Robert R. Wolfe, Ph.D.

AFFILIATION: Department of Anesthesia, University of Pennsylvania, Philadelphia, PA 19104; Metabolism Unit, Shriners Burns Institute; and Departments of Anesthesiology, Medicine and Surgery, University of Texas Medical Branch, and Shriners Burns Institute, Galveston, Texas 77550

INTRODUCTION. Patients with sepsis or during the "flow" phase following burn injury exhibit markedly accelerated protein breakdown and peripheral release of amino acids. In addition, amino acid catabolism as measured by urea production is stimulated by 80-100%. The result is increased urinary nitrogen loss and erosion of the body protein pool. These patients simultaneously exhibit glucose intolerance associated with a so-called "insulin-resistant" state. Besides its effect on glucose metabolism, insulin regulates protein and amino metabolism, by inhibiting protein breakdown. It seems reasonable that the accelerated nitrogen loss results from a failure of insulin to restrain proteolysis, i.e. that "insulin resistance" affects protein metabolism as well as glucose metabolism in the septic or burned patient. The present study was designed to test the maximum biological effectiveness of insulin in regulating protein and amino acid degradation in septic or burned patients. Six healthy young men restricted to bed for 1 week served as controls.

METHODS. Eight septic patients and eight nonseptic burn patients were studied in the Intensive Care Unit of the University of Texas Medical Branch after written informed consent approved by the Institutional Review Board was obtained. Septic patients (sepsis score 17±1) were studied within 48 hours of diagnosis. The nonseptic burn patients had an average burn size of 63±5% total body surface, and were studied during the hypermetabolic "flow" phase, at postburn day 11±1. Postabsorptive subjects were studied during a 3 hr basal period and a 5 hr hyperinsulemic euglycemic clamp (1), using a primed-constant infusion of tracer ^{13}C-leucine and $^{15}N_2$-urea. Rates of appearance of intracellular leucine, plasma urea, and oxidation of leucine were calculated during the basal and hyperinsulinemic periods.

RESULTS.

Parameter	Group	Basal	Insulin Infusion
Ra leucine (μmol/kg.min)	Bedrest	2.66±0.13	1.59±0.05*
	Sepsis	4.08±0.22+	2.95±0.18*+
	Burns	5.16±0.23+	3.39±0.13*+
Leucine oxidation (μmol/kg.min)	Bedrest	0.55±0.02	0.28±0.02*
	Sepsis	1.14±0.10+	1.02±0.11*+
	Burns	1.58±0.13+	0.99±0.11*+
Ra urea (μmol/kg.min)	Bedrest	4.20±0.40	-----
	Sepsis	6.23±1.10+	5.49±0.99*
	Burns	8.19±0.92+	7.02±0.60*
Plasma leucine (μmol/liter)	Bedrest	91±4	39±3*
	Sepsis	114±11	45±7*
	Burns	124±14	47±5*

* statistical difference from the basal period ($p < 0.03$).
\+ difference vs controls at same circulating insulin level ($p < 0.05$)

DISCUSSION. The present study shows that protein degradation and amino acid catabolism are both stimulated in the septic or severely burned patient, confirming that the mechanism of net nitrogen loss involves activation of protein breakdown, amino acid oxidation, and ureagenesis rather than simply inhibition of protein synthesis. This study extends our knowledge further, however, by demonstrating that insulin can be used effectively to retard these pathological processes in septic or severely burned patients. Despite the significant reduction in proteolysis and ureagenesis produced by hyperinsulinemia in both septic and burned patient groups, these remained elevated relative to bedrest volunteers.

Septic and burned patients exhibited a metabolic rate which was elevated 48% and 61%, respectively, above that predicted by the Harris Benedict equation and 67% above that of bedrested controls (2). During the euglycemic clamp, insulin effectively stimulated glucose uptake and utilization in the burned patients, but not in septic patients (2). Only 42% of the septic patient's energy requirements could be met by the maximal insulin-stimulated glucose utilization, compared to 90% in the burned patients (2). The remaining energy must be supplied by oxidation of fat or from protein catabolism. Leucine oxidation in septic patients was only minimally reduced by insulin despite a reduction in protein degradation which was comparable to the burned patients. Therefore, the continued excessive leucine oxidation and concomitant urea synthesis by septic patients, in the presence of pharmacologic insulin, may reflect a failure of insulin to provide sufficient glucose to the cells as an alternate substrate. On the other hand, the continued excessive proteolysis and leucine oxidation in the nonseptic burned patients during hyperinsulinemia may represent activity of a relatively larger mass of insulin-insensitive tissue, such as directly-injured tissue. In extensive burns, a continued excessive availability of liberated leucine for oxidation cannot be reduced further because the process of protein breakdown is not fully inhibited.

In conclusion, sepsis and burn injury derange protein metabolism in slightly different manners, but the effect of each can be ameliorated by pharmacologic insulin. In both clinical states, insulin significantly retarded protein degradation, amino acid oxidation and ureagenesis. Therefore, insulin should be considered as part of the nutritional support of either septic or burned patients to circumvent erosion of the body's protein pool.

References

1. DeFronzo RA, et al: Am J Physiol 23:E214, 1979
2. Shangraw RE, et al: Anesthesiol 67:A129, 1987