Modulation of the Hypermetabolic Response After Thermal Injury

R.Y. Fram[1,2], V.E. Watson[1,2], D.N. Herndon[1,2]

Summary

Major thermal injuries have traditionally been associated with mortality and poor outcomes. Over the past three decades, however, patient survival has improved due to greater understanding of the hypermetabolic stress response and advancements in burn care treatment. The hypermetabolic response is not only an acute phenomenon, but continues for at least 9-12 months post-injury. Circulating levels of glucagon, cortisol and catecholamines are increased leading to a catabolic state that results in loss of lean body mass and muscle wasting. An important intervention after a burn injury is attenuation of the catabolic activity occurring. Non-pharmacological interventions include early excision and grafting, control of infection, sustaining room temperatures to an ambient level of 33°C, and instituting a high carbohydrate enteral diet early in the acute setting. Pharmacological alternatives include the use of recombinant human growth hormone, insulin-like growth factor-1, insulin, oxandralone, and propranolol. The purpose of this paper is to review the mechanisms of the hypermetabolic response and the current modes of treatment to provide optimal care and improved outcomes for the severely burned patient.

Department of Surgery, [1]University of Texas Medical Branch, Galveston, [2]TX and Shriners Hospital for Children, Galveston, TX

Introduction

Traditionally, major thermal injuries have been associated with mortality and poor clinical outcomes. Predictors of mortality have been extensively studied. Age, burn size, presence of inhalation injury and delay in resuscitation have been found to increase mortality (1-3). Over the past three decades, a greater understanding of the hypermetabolic stress response that occurs with massive burns has dramatically increased patient survival. Specifically, advancements in resuscitation techniques, early identification and control of infection, appropriate nutritional support and early excision and grafting have led to improvements in survival of thermally injured patients (4-6).

Hypermetabolic Response to Thermal Injury

The hypermetabolic response that follows a thermal injury is typified by a hyperdynamic state which is associated with increases in cardiac output and basal energy expenditure (7). In addition, increases in body temperature, lipolysis and proteolysis occurs (8). The net result is a catabolic state of body protein. Energy needs become greater leading to depletion of protein stores and loss of skeletal muscle (7, 8). In a study by Chang et al, consequences associated with breakdown of lean body mass include impairments in immune function, longer wound healing times, increased incidence of pneumonia, pressure sores and mortality (9).

Although the burn wounds may be completely healed at approximately 2 months post-injury, the

catabolic state continues to persist even 9 months after the acute hospital stay (10). Predictive variables, including age, male sex, weight and height correlated with increases in the catabolic response during the acute burn hospitalization. Serum creatinine values have been shown to correlate directly with negative protein balance. Increases in burn size up to 40% TBSA was associated with a heighten degree of protein catabolism. The highest predictor of catabolism was sepsis using both the AACP/SCCM definition of sepsis and the criteria defined by the burn team (8) (Figure 1).

The phenomenon of hyperglycemia and impaired insulin sensitivity observed during the hypermetabolic response complicates the care of the thermally injured patient. These changes in glucose metabolism could be due to increased production of glucose along with a decrease in ability of the patient to clear glucose (7). Circulating levels of gluconeogenic hormones, such as glucagon, cortisol and catecholamines are elevated in response to a thermal injury (7) and can stimulate glucose production in the liver. Glucose production increases as the recycling of glucose carbons derived from lactate also increases (11,12). This recycling is largely due to the anaerobic metabolism occurring from wound healing and the net muscle protein catabolism (7). In addition, plasma free fatty acid levels are elevated in thermally injured patients and play a role in fat oxidation and substrate utilization.

A common sequelae of severe burns is hepatomegaly. On autopsy, severely burned children have liver weights ranging from 142% to 406% of their predicted normal size for age and height. Histologic findings include fatty infiltration, cholestasis and congestion (13, 14). Fatty infiltration was found in over 80% of patients at autopsy [14], thus presenting as the most common finding. One mechanism for this is the catabolism contributes to the increased breakdown in peripheral fat and lipolysis and ultimately causing hepatic steatosis (Table 1) (Figure 2).

Table 1: Liver weight per body weight for normal vs. burned patients (2 mos. to 15 years of age)

	Full-Thickness Burn (%)	**Livenwgt/BW (gm/kg)**	**Weight Increase (%)**
Normal (n = 14)	0	34.3±1.1	-
Burn (n = 14)	76±5	75.6±6.0*	120

Burn Size and Liver Weight Rations = Bady Weight
*Significant Difference at p<.001

- Burn
  - At least 3 of the following:
    - T>38.5 or <36.5°C
    - Progressive tachycardia
    - Progressive tachypnea
    - WBC > 12,000 or <4,000
    - Refractory hypotension
    - Thrombocytopenia
    - Hyperglycemia
    - Enteral Feeding Intolerance
  - AND
    - Pathologic tissue source identified
- Modified ACCP/SCCM
  - At least 2 of the following:
    - T>38.5 or <36.5°C
    - HR>20% above NL for age
    - RR>20% above NL for age or PaCO2<32 torr
    - WBC > 12,000 or <4,000
  - AND
    - Bacteremia or fungemia
    - Pathologic tissue source identified

Figure 1: Definition of sepsis.

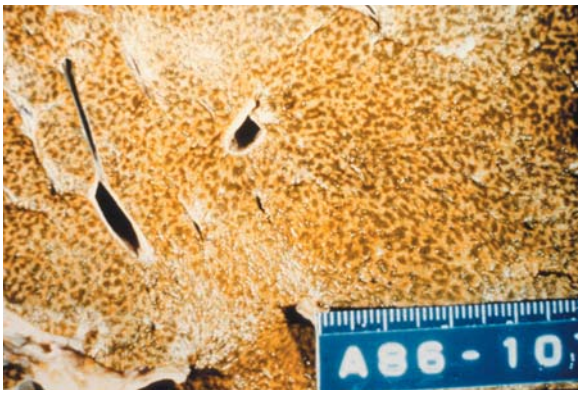

Figure 2: Effect of burn injury on the liver

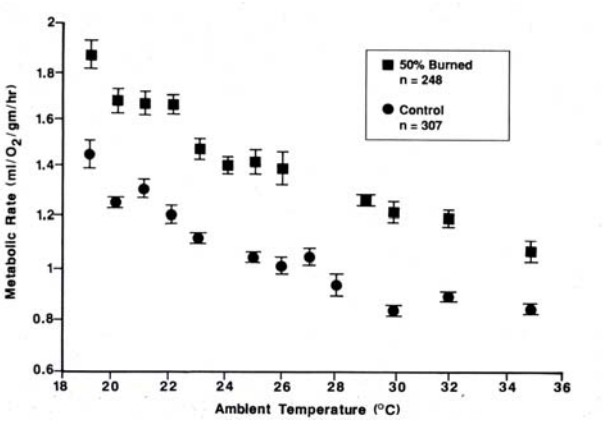

Figure 3: Effect of ambient temperature on metabolic rate.

Reducing the Hypermetabolic Response

Effect of Environmental Temperature

Severe burns disrupt the integrity of the skin leading to alterations in skin permeability. Heat is lost through vaporization, and metabolic rates increase by 30% above percent predicted (15). The higher metabolic rate allows the body to raise skin and core temperatures 1.7-2° C higher than normal (16). Herndon previously studied the effect of environmental manipulation with the burn rat model and found that burned rats had metabolic rates 40% higher than non-burned rats (17) (Figure 3). Other research has found that by treating patients with a room environment of 33ºC, as compared to 22ºC, metabolic rates decreased in patients with burns over 60% TBSA (16).

Nutritional Support

Early nutritional support is fundamental to the acute care of the burn patient. Patients with burns that are greater than 40% of their total body surface area can lose up to 25% of their preadmission weight within three weeks of their injury (18). A number of formulas have been established to estimate the energy requirements of adult and pediatric patients with severe burns. Traditionally, continuous enteral or parental nutrition giving 25 kcal (0.105 MJ)/kg per day plus 40 kcal per % burn in area per day in adults (19, 20), and 1800 kcal (7.56 MJ)/m2 per day plus 2200 kcal per m2 of burn area per day in children (21) will maintain body weight throughout the acute stay. However, the nutritional requirements estimated from these formulas often provided 35-45% more calories than actually needed to maintain weight. Thus, 1500 kcal/m2 body surface area per day plus 1500 kcal/m2 burn is currently used to provide adequate calories for weight maintenance (22). Parenteral feeding is reserved only for patients with prolonged ileus or intolerance to enteral feedings. Yet, a combination of parenteral feeding with maximally tolerated enteral nutrition can be used to reach the caloric delivery requirements. This combination of nutritional support should be used with caution since research has found that parenteral feeding has been linked to increased mortality, impaired liver function and immunocompromise (23).

Indirect calorimetry provides an accurate measurement of caloric needs through the calculation of resting energy expenditure (REE). This noninvasive technique is performed at the bedside and measures oxygen consumption and carbon dioxide production. REE can then be calculated with these values using the Harris-Benedict equation. At our institution, total energy expenditure in burned children was measured using the stable isotope technique with doubly-labeled water. TEE was 1.2 times higher than REE, and optimal nutritional support will be achieved by multiplying REE by an activity factor of 1.2 (24). Of significance, caloric delivery greater than 1.2 times REE has resulted in increased fat mass without changes in lean body mass (25). Some studies have shown that enteral nutrition delivering a high carbohydrate diet (3% fat, 82% carbohydrate and 15% protein) improves

endogenous insulin production and lean body mass compared to a high-fat enteral diet (44% fat, 42% carbohydrate and 14% protein) (26). Sufficient protein intake is vital in maintaining lean body mass. Severely burned patients oxidize amino acids at rates 50% higher than healthy fasting individuals. Therefore, severely burned adults may need increased protein delivery from 1.0 g/kg/day for healthy individuals to 1.5-2.5 g/kg/day (27). In children, Wolfe and his colleagues suggested that increasing protein intake to 1.15-3 g/kg/day did not improve the rate of muscle protein synthesis but did increase skin protein synthesis, thereby improving wound healing (28).

Pharmacological Modulation of the Hormonal Response

The persistence of the hypermetabolic response is largely due to catabolic hormones such as catecholamines and cortisol. Pharmacological management of the severe catabolism is an important means of modulating the hypermetabolic response. These treatments include: anabolic agents; such as growth hormone, insulin, insulin-like growth factor (IGF-1), IGF-1 and IGF binding protein 3 (IGFBP-3), oxandrolone and testosterone; and anticatabolic agents, including propranolol and metoprolol.

Recombinant Human Growth Hormone

Daily administration of recombinant human growth hormone (r-HGH) (0.2 mg/kg) increased serum IGF-1 levels, decreased donor site healing times by 25% and reduced length of hospital stay for an adult with burns averaging 60% TBSA [29, 30]. Acutely, patients treated with r-HGH showed no difference in scarring as compared with patients who did not receive treatment. However, one to two years post-burn, scarring improved in patients receiving r-HGH at 0.2 mg/kg/day (31). Long- term, severely burned children, when given a daily dose of growth hormone at 0.05 mg/kg, showed improvements in height velocities, weight gain, lean body mass composition and bone mineral content and left ventricular ejection fraction (32, 33). These outcomes continued up to 3 years post-injury (34, 35). Growth hormone also decreased the acute phase response that occurs with thermal injury by decreasing C reactive protein, serum amyloid-A, tumor necrosis factor-_ and IL-1; and increasing serum retinol binding protein (36). However, r-HGH is not without adverse side effects. One double-blind, randomized, controlled study found that adults given r-HGH during their acute intensive care stay had higher mortality rates, longer length of stays and increased number of days on the ventilator (37). The safety of human growth hormone in the severely burned pediatric population was reviewed for similarities in morbidity and mortality as seen in adults. At our institution, mortality was not different among those patients receiving human growth hormone vs. placebo (2% for both groups). No differences were observed in cardiac, renal or septic events, as well as the number of days requiring ventilatory support. On the other hand, the incidence of hyperglycemia was higher in the r-HGH patients as compared to placebo, and a higher percentage of children receiving r-HGH required exogenous insulin to maintain euglycemia (38).

IGF-1

Many of the effects of r-HGH are mediated through IGF. Continuous infusion of IGF alone in burned patients has been shown to improve muscle protein synthesis with fewer incidents of hyperglycemia as seen with r-HGH (39). Furthermore, a combination of IGF with its binding protein, IGFBP-3 was given by continuous infusion to evaluate for enhanced attenuation of the hypermetabolic stress response. The results showed improvements in net balance and muscle protein fractional synthetic rates, especially in catabolic children (39), as well as attenuation of the proinflammatory hepatic acute phase response (40).

Insulin

Intensive insulin therapy protocols have been instituted across the world after van den Berghe and colleagues found that controlling blood glucose levels between 80 mg/dl and 110 mg/dl, in critically-ill adults, have led to improvements in morbidity and mortality (41). Insulin, an anabolic peptide hormone, infused continuously, has been shown to stimulate muscle protein synthesis and improve lean body mass (42) without increasing

hepatic triglyceride production (43) in severely burned children and adults. Patients were given continuous insulin infusion titrated to maintain plasma insulin levels of 400-900 μU/ml over seven days with the addition to intravenous dextrose to maintain euglycemia to study the effects of insulin on wound healing. Donor site healing time was reduced by approximately 2 days (7 days for placebo vs. 5 days for treatment) (44) (Figure 4). Submaximal doses of insulin were given to adult burn patients at a rate of 2.6 mU/kg/min which raised plasma insulin concentrations to approximately 241.9μU/ml. Euglycemia was maintained with intravenous administration of 20% dextrose. Net amino acid balance as well as skeletal muscle protein synthesis was significantly improved as compared to the control group (45). Administration of insulin at lower infusion rates, such as 1.5 μU/kg/min to maintain plasma glucose values between 100 to 140 mg/dl, improved lean body mass and bone mass, as well as, decreased length of hospital stay (46).

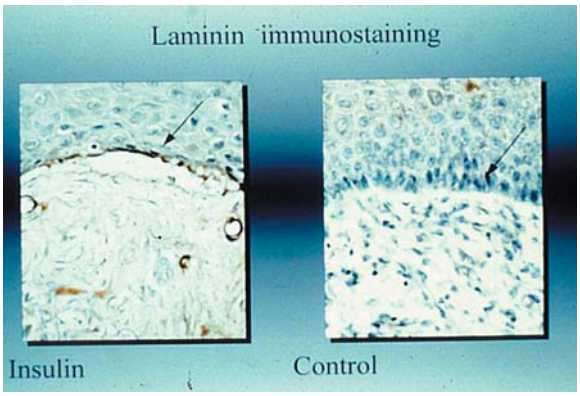

Figure 4: The effects of insulin on wound healing.

Oxandrolone

Thermal injury leads to decreases in testicular hormone production. Restoration of testosterone in healthy, young burned males caused a two-fold increase in protein synthetic efficiency and a two-fold decrease in protein breakdown, resulting in net amino acid balance of approximately zero (47). Although testosterone effectively improves net protein catabolism, oxandrolone, a synthetic analog, offers only 5% of the masculinizing effects of testosterone, and is the preferable choice, especially for prepubertal males and females. When oxandrolone was given to healthy, non-burned men, the fractional synthetic rate of skeletal muscle protein increased by 44% leading to improvements in net balance (48). Thermally-injured patients benefit from administration of testosterone, as well. Improvements in weight gain and physical endurance (49), as well as net balance without evidence of hirsutism, acne or behavioral change (50) were found in patients treated with oxandralone (0.1 mg/kg twice daily).

Catacholamine antagonist

Endogenous catecholamines have been attributed as the primary mediators of the hypermetabolic response after injury (51). Immediately following injury, there is a 10-fold increase in plasma catecholamine concentrations (52). This leads to a hyperdynamic circulation, increases in basal energy expenditure and catabolism of skeletal muscle protein (51, 53). Increased lipolysis, a characteristic feature of burn patients, is caused by stimulation of the β2-adrenergic receptor for catecholamines (54, 55). Blocking the effects of elevated concentrations of catecholamines in burned patients has been found to improve catabolism. Severely burned patients, who were treated with continuous infusion (2 mg/kg) of propranolol for 5 days were found to have reductions in thermogenesis, tachycardia, myocardial work load and resting energy expenditure (56). Long term use of propranolol during the acute burn care setting, at a dose titrated to reduce heart rate by 20%, lowered cardiac work load (57), and reduced fatty infiltration of the liver (14). Propranolol lowers hepatic steatosis by decreasing the release of free fatty acids from adipose tissue and increasing the efficiency of the liver in secreting fatty acids (58). Propranolol decreased peripheral lipolysis (59) and lowered the rates of fatty acid oxidation and triacylglycerol secretion, thus reducing the storage of hepatic fat (60). Moreover, stable isotope and serial body composition studies have shown that propranolol improves net-muscle protein balance during the acute burn hospitalization by enhancing the availability of free amino acids for muscle protein synthesis (61).

Rehabilitation

The hypermetabolic response to injury persists beyond the acute hospitalization. Attenuation of the catabolic effects that occur is vital to the ongoing rehabilitation process. Continued use of selective anabolic agents, such as growth hormone, oxandrolone and propranolol, along with a balanced exercise program will help maintain muscle mass and growth development. Resistance and aerobic exercise training at 6 months post-burn improved strength and distance walked (62), plus increased lean body mass (63) as compared to those patients in a traditional physical therapy program. Rehabilitation from severe burns is an involved process in which great care should be taken to enhance the quality of life and future of these patients.

Conclusion

The hypermetabolic response that occurs after thermal injury is a phenomenon that has been well established in the literature. Modulation of the catabolic effects is fundamentally significant to the treatment of the acute and rehabilitative phases of severe burns. Multiple interventions are now available including environmental interventions, pharmacological alternatives and physical rehabilitation. Treatment in a specialized burn care center can improve clinical outcomes and survival so that patients can lead productive, well-adjustive lives.

References

1. Wolf, S.E., et al., Mortality determinants in massive pediatric burns. An analysis of 103 children with > or = 80% TBSA burns (> or = 70% full-thickness). Ann Surg, 1997. 225(5): p. 554-65; discussion 565-9.
2. Brusselaers, N., et al., Outcome and changes over time in survival following severe burns from 1985 to 2004. Intensive Care Med, 2005,31(12):1648-53.
3. Ryan, C.M., et al., Objective estimates of the probability of death from burn injuries. N Engl J Med, 1998. 338(6): p. 362-6.
4. Herndon, D.N., et al., Determinants of mortality in pediatric patients with greater than 70% full-thickness total body surface area thermal injury treated by early total excision and grafting. J Trauma, 1987. 27(2): p. 208-12.
5. Herndon, D.N., et al., Increased mortality with intravenous supplemental feeding in severely burned patients. J Burn Care Rehabil, 1989. 10(4): p. 309-13.
6. Tompkins, R.G., et al., Significant reductions in mortality for children with burn injuries through the use of prompt eschar excision. Ann Surg, 1988. 208(5): p. 577-85.
7. Wolfe, R.R., Review: acute versus chronic response to burn injury. Circ Shock, 1981. 8(1): p. 105-15.
8. Hart, D.W., et al., Determinants of skeletal muscle catabolism after severe burn. Ann Surg, 2000. 232(4): p. 455-65.
9. Chang, D.W., L. DeSanti, and R.H. Demling, Anticatabolic and anabolic strategies in critical illness: a review of current treatment modalities. Shock, 1998. 10(3): p. 155-60.
10. Hart, D.W., et al., Persistence of muscle catabolism after severe burn. Surgery, 2000. 128(2): p. 312-9.
11. Sedowofia, K., et al., The systemic stress response to thermal injury in children. Clin Endocrinol (Oxf), 1998. 49(3): p. 335-41.
12. Wolfe, R.R., et al., Effect of burn injury on glucose turnover in guinea pigs. Surg Gynecol Obstet, 1977. 144(3): p. 359-64.
13. Barrow, R.E., et al., Increased liver weights in severely burned children: comparison of ultrasound and autopsy measurements. Burns, 2004. 30(6): p. 565-8.
14. Barret, J.P., M.G. Jeschke, and D.N. Herndon, Fatty infiltration of the liver in severely burned pediatric patients: autopsy findings and clinical implications. J Trauma, 2001. 51(4): p. 736-9.
15. Rutan, T.C., et al., Metabolic rate alterations in early excision and grafting versus conservative treatment. J Trauma, 1986. 26(2): p. 140-2.
16. Wilmore, D.W., et al., Effect of ambient temperature on heat production and heat loss in burn patients. J Appl Physiol, 1975. 38(4): p. 593-7.
17. Herndon, D., Mediators of Metabolism. The Journal of Trauma, 1981. 21(8 Supplement): p. 701-705.
18. Newsome, T.W., A.D. Mason, Jr., and B.A. Pruitt, Jr., Weight loss following thermal injury. Ann Surg, 1973. 178(2): p. 215-7.
19. Curreri, P.W., et al., Dietary requirements of patients with major burns. J Am Diet Assoc, 1974. 65(4): p. 415-7.
20. Wilmore, D.W., et al., Supranormal dietary intake in thermally injured hypermetabolic patients. Surg Gynecol Obstet, 1971. 132(5): p. 881-6.
21. Hildreth, M.A., et al., Reassessing caloric requirements in pediatric burn patients. J Burn Care Rehabil, 1988. 9(6): p. 616-8.
22. Hildreth, M.A., et al., Caloric needs of adolescent patients with burns. J Burn Care Rehabil, 1989. 10(6): p. 523-6.

23. Herndon, D.N., et al., Failure of TPN supplementation to improve liver function, immunity, and mortality in thermally injured patients. J Trauma, 1987. 27(2): p. 195-204.
24. Goran, M.I., et al., Total energy expenditure in burned children using the doubly labeled water technique. Am J Physiol, 1990. 259(4 Pt 1): p. E576-85.
25. Hart, D.W., et al., Energy expenditure and caloric balance after burn: increased feeding leads to fat rather than lean mass accretion. Ann Surg, 2002. 235(1): p. 152-61.
26. Hart, D.W., et al., Efficacy of a high-carbohydrate diet in catabolic illness. Crit Care Med, 2001. 29(7): p. 1318-24.
27. Wolfe, R.R., et al., Response of protein and urea kinetics in burn patients to different levels of protein intake. Ann Surg, 1983. 197(2): p. 163-71.
28. Patterson, B.W., et al., Urea and protein metabolism in burned children: effect of dietary protein intake. Metabolism, 1997. 46(5): p. 573-8.
29. Herndon, D.N., et al., Effects of recombinant human growth hormone on donor-site healing in severely burned children. Ann Surg, 1990. 212(4): p. 424-9; discussion 430-1.
30. Herndon, D.N., et al., Characterization of growth hormone enhanced donor site healing in patients with large cutaneous burns. Ann Surg, 1995. 221(6): p. 649-56; discussion 656-9.
31. Barret, J.P., et al., Effects of recombinant human growth hormone on the development of burn scarring. Plast Reconstr Surg, 1999. 104(3): p. 726-9.
32. Hart, D.W., et al., Attenuation of posttraumatic muscle catabolism and osteopenia by long-term growth hormone therapy. Ann Surg, 2001. 233(6): p. 827-34.
33. Mlcak, R.P., et al., Effects of growth hormone on anthropometric measurements and cardiac function in children with thermal injury. Burns, 2005. 31(1): p. 60-6.
34. Aili Low, J.F., et al., The effect of short-term growth hormone treatment on growth and energy expenditure in burned children. Burns, 2001. 27(5): p. 447-52.
35. Aili Low, J.F., Effect of growth hormone on growth delay in burned children: a 3-year follow-up study. The Lancet, 1999. 354: p. 1789.
36. Jeschke, M.G., R.E. Barrow, and D.N. Herndon, Recombinant human growth hormone treatment in pediatric burn patients and its role during the hepatic acute phase response. Crit Care Med, 2000. 28(5): p. 1578-84.
37. Takala, J., et al., Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med, 1999. 341(11): p. 785-92.
38. Ramirez, R.J., et al., Growth hormone treatment in pediatric burns: a safe therapeutic approach. Ann Surg, 1998. 228(4): p. 439-48.
39. Cioffi, W.G., et al., Insulin-like growth factor-1 lowers protein oxidation in patients with thermal injury. Ann Surg, 1994. 220(3): p. 310-6; discussion 316-9.
40. Jeschke, M.G., R.E. Barrow, and D.N. Herndon, Insulinlike growth factor I plus insulinlike growth factor binding protein 3 attenuates the proinflammatory acute phase response in severely burned children. Ann Surg, 2000. 231(2): p. 246-52.
41. van den Berghe, G., et al., Intensive insulin therapy in the critically ill patients. N Engl J Med, 2001. 345(19): p. 1359-67.
42. Sakurai, Y., et al., Stimulation of muscle protein synthesis by long-term insulin infusion in severely burned patients. Ann Surg, 1995. 222(3): p. 283-94; 294-7.
43. Aarsland, A., et al., Insulin therapy in burn patients does not contribute to hepatic triglyceride production. J Clin Invest, 1998. 101(10): p. 2233-9.
44. Pierre, E.J., et al., Effects of insulin on wound healing. J Trauma, 1998. 44(2): p. 342-5.
45. Ferrando, A.A., et al., A submaximal dose of insulin promotes net skeletal muscle protein synthesis in patients with severe burns. Ann Surg, 1999. 229(1): p. 11-8.
46. Thomas, S.J., et al., The effect of prolonged euglycemic hyperinsulinemia on lean body mass after severe burn. Surgery, 2002. 132(2): p. 341-7.
47. Ferrando, A.A., et al., Testosterone administration in severe burns ameliorates muscle catabolism. Crit Care Med, 2001. 29(10): p. 1936-42.
48. Sheffield-Moore, M., et al., Short-term oxandrolone administration stimulates net muscle protein synthesis in young men. J Clin Endocrinol Metab, 1999. 84(8): p. 2705-11.
49. Demling, R.H. and L. DeSanti, Oxandrolone, an anabolic steroid, significantly increases the rate of weight gain in the recovery phase after major burns. J Trauma, 1997. 43(1): p. 47-51.
50. Hart, D.W., et al., Anabolic effects of oxandrolone after severe burn. Ann Surg, 2001. 233(4): p. 556-64.
51. Wilmore, D.W., et al., Catecholamines: mediator of the hypermetabolic response to thermal injury. Ann Surg, 1974. 180(4): p. 653-69.
52. Wilmore, D.W. and L.H. Aulick, Metabolic changes in burned patients. Surg Clin North Am, 1978. 58(6): p. 1173-87.
53. Reiss, E., E. Pearson, and C.P. Artz, The metabolic response to burns. J Clin Invest, 1956. 35(1): p. 62-77.
54. Herndon, D.N., et al., Lipolysis in burned patients is stimulated by the beta 2-receptor for catecholamines. Arch Surg, 1994. 129(12): p. 1301-4; discussion 1304-5.
55. Wolfe, R.R., et al., Regulation of lipolysis in severely burned children. Ann Surg, 1987. 206(2): p. 214-21.

56. Herndon, D.N., et al., Effect of propranolol administration on hemodynamic and metabolic responses of burned pediatric patients. Ann Surg, 1988. 208(4): p. 484-92.
57. Baron, P.W., et al., Prolonged use of propranolol safely decreases cardiac work in burned children. J Burn Care Rehabil, 1997. 18(3): p. 223-7.
58. Aarsland, A., et al., Beta-blockade lowers peripheral lipolysis in burn patients receiving growth hormone. Rate of hepatic very low density lipoprotein triglyceride secretion remains unchanged. Ann Surg, 1996. 223(6): p. 777-87; discussion 787-9.
59. Gore, D.C., et al., Propranolol diminishes extremity blood flow in burned patients. Ann Surg, 1991. 213(6): p. 568-73; discussion 573-4.
60. Morio, B., et al., Propranolol decreases splanchnic triacylglycerol storage in burn patients receiving a high-carbohydrate diet. Ann Surg, 2002. 236(2): p. 218-25.
61. Herndon, D.N., et al., Reversal of catabolism by beta-blockade after severe burns. N Engl J Med, 2001. 345(17): p. 1223-9.
62. Cucuzzo, N.A., A. Ferrando, and D.N. Herndon, The effects of exercise programming vs traditional outpatient therapy in the rehabilitation of severely burned children. J Burn Care Rehabil, 2001. 22(3): p. 214-20.
63. Suman, O.E., et al., Effects of a 12-wk resistance exercise program on skeletal muscle strength in children with burn injuries. J Appl Physiol, 2001. 91(3): p. 1168-75.