

Insulin and the burned patient

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Severe burns lead to insulin resistance, which is associated with hyperglycemia and muscle wasting. Investigators showed relatively recently that control of hyperglycemia with intensive insulin treatment is associated with improved outcomes for those in the intensive care unit, including patients with severe burns. In this article, we review the actions of insulin in terms of glycemic

control and muscle metabolism, biochemical and clinical effects of insulin treatment in the severely burned, and the vagaries of glucose control. (Crit Care Med 2007; 35[Suppl.]:S524–S530)

KEY WORDS: burns; insulin resistance; muscle wasting; glycemic control; muscle metabolism

The discovery of insulin in 1921 by Banting and others was a landmark event in the management and treatment of diabetes due to hyperglycemia. Since then, insulin has become one of the most widely studied of modern therapeutic agents, and research continues at a feverish pace in multiple fields of medicine. A PubMed search done today using *insulin* as a keyword returned 205,335 articles in total; by contrast, adding *burn* returned a mere 414 publications (0.2%); our understanding of the role of insulin in the severely burned patient is in its infancy.

Hyperglycemia due to acute trauma was first described in 1877 (1). Treatment was expectant until recently due to the belief that this was a beneficial “fight or flight” response and should not be disturbed, as the risks (hypoglycemia) outweighed the benefits. In 2001, Van den Berghe and others (2) demonstrated a marked reduction in mortality in patients treated with intensive insulin to control hyperglycemia, and since then the role of insulin in the management of critical illness has become a topic of intense scrutiny and debate. A dialogue has emerged

between those who believe that glucose control (avoidance of hyperglycemia) is primary in conferring survival benefit and others who contend that insulin’s pharmacologic effects, including those other than glucose disposal, also contribute to improved outcomes; determining whether the latter has validity is particularly important to burn surgeons, who battle the ravaging effects of hypercatabolism and accelerated protein and lean body mass loss. The origins of this debate can be traced 3 decades back in the search to define the role of insulin in protein balance and the maintenance of lean body mass in severely burned patients.

In 1975, Hessman and Thoren (3) reported improvement in muscle glycogen storage in burned rats after administration of exogenous insulin. In this study, they produced a 20% total body surface area burn in rats of which some were given exogenous insulin immediately after injury. The authors found that glycogen stores decreased by 20% in the liver and 40% in muscle 30 mins after burn, which was sustained 20 hrs after injury. Insulin treatment improved glycogen abundance in the muscle but had no effect in the liver. The authors speculated that the overall findings of glycogen utilization in liver and muscle might be due to absolute or relative insulin deficiency; however, in an article published the same year, Hessman and Adolfsson (4) noted that serum insulin concentrations in burned rats were unchanged compared with controls, suggesting that insulin resistance was the culprit. Later, it was recognized that increased proteolysis after injury was not diminished with in-

creased glucose infusion (5) or increased protein delivery (6). Further studies demonstrated that fasting levels of growth hormone in burned subjects were significantly elevated despite fasting hyperglycemia compared with controls. Conversely, the growth hormone response to hypoglycemia was lessened (7). From this, it was postulated that an insulin resistance probably exists following severe injury.

The early 1980s saw new research that refined the understanding of insulin action in burned tissue and also systemically in burned patients. Investigators demonstrated in a rat model that muscle from burned limbs takes up glucose and amino acid at a higher rate than muscle from unburned limbs either in the same animal or in unburned controls. Insulin treatment increased glucose and amino acid uptake in the unburned limb and in controls but not in the muscle of the burned limb, again suggesting insulin resistance that in this instance was localized (8). Severe burn was also shown to cause an increase in both uptake of amino acids and catabolism of intracellular proteins. Later studies using a model that included a more severe burn demonstrated that all tissues (injured or not injured) exhibit similar catabolism and changes in substrate uptake in the face of major burn (9). In either case, exogenous insulin was not found to increase uptake of amino acids in burned tissue; however, the hormone did mitigate protein degradation. The net result was a decrease in expected lean body mass losses following severe burn with insulin treatment.

Muscle loss continues to be one of the most significant long-term components

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of severe burn and one of the most difficult to treat, with very few effective therapies available. Even of those therapies shown to have a physiologic rationale, none have been shown to confer actual clinical benefit. An explosion in the field of burn and trauma research along multiple avenues has failed to find a single magic bullet in the fight against muscle wasting; however, several drugs have shown promise, including oxandrolone, propranolol, and insulin. The latter continues to gain prominence in the critical care literature as new research demonstrates its usefulness not only as an anabolic agent but also in reducing morbidity and mortality in the intensive care unit; this review will summarize what is known about the actions of insulin and its receptor, with a focus on its role in burns.

Molecular and Physiologic Effects of Insulin Resistance

Publications regarding intensive insulin therapy focus primarily on functional and clinical outcomes; however, a physiologic and molecular understanding of the hormone's effects is important to explain observed phenomena. Glucose enters cells via a family of facilitative transporters, glucose transporter (GLUT)-1 to GLUT-4, most of which are actually insulin-independent. GLUT-4 is the principal insulin-dependent glucose transporter and is located mostly in intracellular specialized vesicles within hepatocytes, muscle cells, and adipocytes (10). GLUT-4 transport is activated when insulin binds to α subunits on the extracellular portion of the insulin receptor, inducing autophosphorylation of the β unit and conformational change. This action phosphorylates insulin receptor substrate-1, activating phosphatidylinositol 3-kinase, which induces the conversion of phosphatidylinositol (4, 5) phosphate to phosphatidylinositol phosphate₃. This increases intracellular tyrosine kinase activity, specifically PDK1, Akt/PKB, and mammalian target of rapamycin (MTOR) (11). This activates multiple intersecting cell signaling pathways to induce incorporation of the GLUT-4-containing vesicles to the cell membrane, introducing channels that allow glucose into the cell. Insulin-mediated glucose uptake through GLUT-4 occurs primarily in the liver, skeletal muscle, and adipose tissue (Fig. 1). Other effects include activation of glycogen synthesis, lipid synthesis, inhibition of lipol-

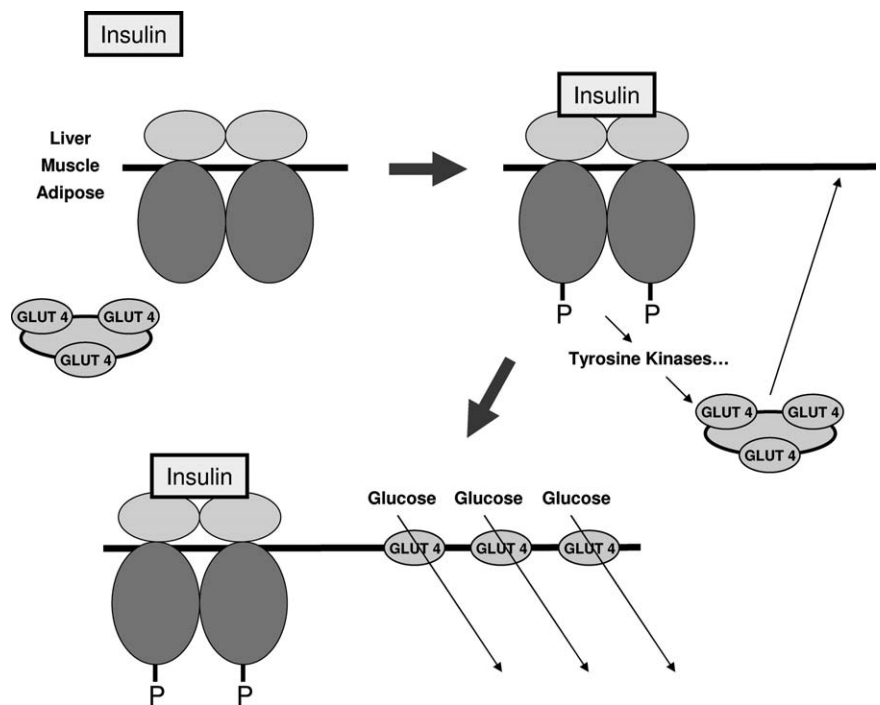


Figure 1. Insulin receptor signaling. Insulin binds the α subunits, inducing β -unit conformational change and phosphorylation. This induces an increase in tyrosine kinase activity through insulin receptor substrate/phosphatidylinositol 3-kinase/phosphatidylinositol phosphate₃ signaling. Once these signals are received, available glucose transporter (GLUT)-4 receptors are transposed onto the plasma membrane to increase inward transport of glucose.

ysis and lipocyte apoptosis, and stimulation of protein synthesis (11–15).

Protein is synthesized in the cell by the translation of messenger RNA (mRNA) to protein by the protein synthetic machinery. Insulin affects this process in a number of ways. Studies showed that stimulation of protein synthesis by insulin takes place at several steps: stimulation of transcription of specific genes (16, 17), increasing stability of specific mRNAs (18), promotion of mRNA translation (19, 20), increasing peptide chain elongation rate (21), and activation of preexisting enzymes necessary for the production of protein (22). Acutely, insulin stimulates protein synthesis without changing the RNA content of the cell, meaning that the first effect of insulin is enhancement of translation. A second and later effect is to increase protein synthetic capacity through increased mRNA expression (23). The effects on translation appear to be through two different pathways activated by phosphatidylinositol 3-kinase. Mammalian target of rapamycin (MTOR) pathways are responsible for 4E-BP-1 phosphorylation with insulin stimulation, which causes dissociation from eukaryotic initiation factor-4E, allowing it to form the mRNA cap structure required

for protein synthesis (24). Insulin also activates mRNA translation through glycogen synthase-3 by regulating eukaryotic initiation factor-2B, a factor that allows eukaryotic initiation factor-2 to bind guanosine triphosphate and met-transfer RNA to the 40S ribosomal subunit, which is required for every translation event (25).

The mechanism by which insulin regulates specific mRNA expression remains unclear. The current notion is that insulin regulates the initiation of gene transcription through the activation of specific nuclear DNA binding proteins, perhaps through specific activation within the mitogen-activated protein kinase pathways. The binding of such proteins to insulin-responsive elements on genomic DNA activates the transcription of target genes. The role of changes in insulin-responsive element binding in insulin-induced changes in muscle after injury *in vivo* is not known. Data from our laboratory with high-dose insulin treatment after severe burn suggest that approximately 40 genes have increased expression while 10 have decreased expression (SE Wolf, personal communication). Much more work will be required to elucidate

the role of these changes in clinical outcomes.

Some inhibition of the previously mentioned pathways after severe injury has been noted for some time; for instance, hyperglycemia was associated with traumatic injury in the 19th century (1). Insulin resistance is described in a variety of acute conditions, and the presence of this phenomenon after severe burn is well recognized by all experienced practitioners. Overall glucose cellular uptake is not decreased, primarily because of increased transport through insulin-independent GLUT transporters. However, relative uptake of glucose via activation of insulin-dependent receptors (GLUT-4) in the liver, skeletal muscle, and adipose tissue is significantly impaired despite elevated insulin levels. Substrate mobilization by glycogenolysis and gluconeogenesis is similarly up-regulated in the face of high serum glucose (26).

The complete mechanism of insulin resistance has yet to be defined; autophosphorylation and relative inactivation of insulin receptor β subunits and other effectors downstream, including Akt/PKB, occurred in rat burn models, suggesting this as a possible mechanism. In these studies, initial insulin binding to the receptor α units was preserved (26, 27). Similar findings were shown in a mouse model, as severe burn produced a marked reduction in phosphorylation of insulin receptor substrate-1 and decreased Akt kinase activity (28). Other possibilities include phosphorylation of insulin receptor substrate-1 or phosphatidylinositol 3-kinase by MTOR or other mediators, which could be viewed as feedback inhibition gone awry. Therefore, inhibiting activation of Akt/PKB regulates skeletal muscle growth or loss, providing a link between insulin resistance and catabolic muscle wasting in burns (27). Other pathways may also be involved as well. Use of an angiotensin II blocker in rats reversed burn-induced insulin resistance, suggesting that RAS plays a role in this response (29).

Effect of Severe Burn—Catabolism and Hyperglycemia

Severe burns and injury cause a hypermetabolic state associated with protein losses that can persist for up to 9 months after injury and result in significant reduction of lean body mass (30).

Both muscle protein breakdown and synthesis are increased in burn catabolism; however, degradation exceeds synthesis, resulting in net protein losses (31). The principal defect is an accelerated rate of protein breakdown with a failure of compensatory synthesis, resulting in a decrease in net protein synthesis (muscle protein synthesis minus muscle protein breakdown). The amount of protein loss and catabolism were found to be associated with body weight before injury, severity of injury (total body surface area burned), time to definitive treatment, and the development of sepsis (32). A decrease in lean body mass of 10% to 15% leads to delayed wound healing and increased infections (33); a 25% reduction of total body nitrogen is associated with higher mortality. Hyperglycemia and catabolism leading to protein losses are linked to immune dysregulation, increasing susceptibility to sepsis and multiple organ failure. After severe burn, catabolism of lean muscle protein persists for 6–9 months after injury and affects both the acute and convalescent phases. In the critical care setting, severe catabolism can produce a weakened state, delaying recovery, prolonging ventilatory dependence, and reducing mobilization (34).

Insulin resistance following severe burn demonstrated in animal models discussed previously is present also in human patients. Altered glucose utilization due to insulin-resistant states results in persistent hyperglycemia, which in turn is associated with greater catabolism; elevated blood glucose levels increase efflux of amino acids, while insulin administration decreases this effect (35, 36). To discuss muscle catabolism after protein breakdown, the role of amino acid transport into and out of the muscle cell must be included. Amino acids in the cytosol from protein breakdown have two fates: transport out of the cell or reincorporation back into protein. After burn, amino acids from protein breakdown are transported out of the muscle cell to a relatively greater extent than they are reincorporated back into protein. Inward transport of amino acids does not increase to compensate. The increase in breakdown and outward transport of amino acids compared with decreased synthesis and inward transport results in net muscle protein loss. Using a three-pool model that measures protein synthesis, protein breakdown, and amino acid fluxes into and out of the cell, it was demonstrated that, in fact, both protein

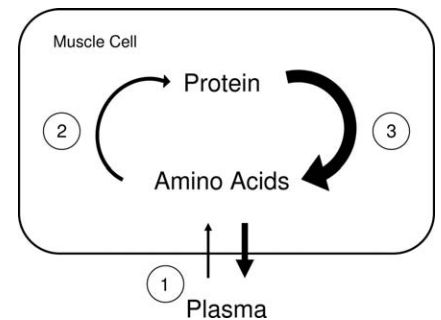


Figure 2. Changes in amino acid flux between three pools (plasma or extracellular space, free amino acids in the intracellular space, and amino acids bound in protein) after severe injury. Increased protein breakdown increases availability of free amino acids in the intracellular space, which in turn leave the cell to a greater extent than they return. To alleviate this condition, strategies would be to increase inward transport of amino acids to match outward transport, increase protein synthesis so that amino acids in the cell go back into protein rather than leave, or decrease protein breakdown.

synthesis and protein breakdown are stimulated in human muscle after severe burn (37). However, increases in breakdown outweigh increases in synthesis. The amino acids from breakdown are directed to outward transport with related ineffective compensatory synthesis.

Strategies to decrease net protein loss from muscle cells then could be directed in three fashions. The first would be to increase inward transport of amino acids (Fig. 2, 1); the second, to stimulate synthesis using amino acids released from breakdown as the principal substrate (Fig. 2, 2); and the third, to inhibit increased breakdown (Fig. 2, 3). Decreasing outward transport of amino acids is not physiologically possible with breakdown held at rates greater than synthesis.

A number of anabolic hormones have been used effectively to abrogate muscle catabolism in patients after severe injury when given over a portion of the hospital stay. These agents include insulin (37, 38), growth hormone (39), insulin-like growth factor-I (40), oxandrolone (41), and testosterone (42). Of these, insulin appears to be the best candidate for use to increase net protein synthesis during hospitalization after severe injury for several reasons. First, it is less expensive than growth hormone and insulin-like growth factor, thus providing a fiscal benefit. Second, it has a well-established side effect profile, which is limited primarily to hypoglycemia. Third, hyperglycemia is prevalent in the severely injured,

which has been shown to have deleterious effects. In fact, it was shown that hyperglycemia in burned patients was associated with increased mortality due to infection (43). Treatment with insulin, then, may have secondary benefits to improve outcomes by decreasing serum glucose levels. Fourth, insulin may have other benefits in addition to effects on muscle metabolism. In November 2001, van den Berghe and her colleagues (2) reported in the *New England Journal of Medicine* that intensive insulin therapy to maintain blood glucose <110 mg/dL reduced morbidity and mortality in critically ill patients. This study was designed to answer whether hyperglycemia and relative insulin deficiency during critical illness confer a predisposition to complications. The investigators found that of the 1,548 enrolled subjects in a surgical intensive care unit, those receiving insulin therapy had a 32% mortality risk reduction. This risk reduction was realized primarily by those in the intensive care unit for >5 days. The insulin-treated subjects also required less ventilatory support, required less renal replacement therapy, and had fewer episodes of sepsis. As a point of reference, the treated subjects (adults) received a mean of 71 units of insulin per day ($\sim 3 \mu\text{hr}$), compared with the controls, who received a mean of 33 units of insulin per day ($\sim 1.5 \mu\text{hr}$).

Insulin treatment improves net protein synthesis in the severely burned, principally through improved muscle protein synthesis. Although controversy exists as to whether insulin is effective as an anabolic hormone through increasing protein synthesis or decreasing protein breakdown, we believe that the methods and experimental protocols used in the various studies bear consideration when evaluating this topic (44). Many of the apparent discrepancies in the literature on human subjects simply reflect the limitation of the traditional balance technique, in which the rates of muscle protein synthesis and breakdown are estimated from the arteriovenous difference of concentration and enrichment of an amino acid tracer. The general application of the limb balance method measures the rate of disappearance (R_d) of the tracer amino acid from the blood and the rate of appearance (R_a) of the tracer amino acid into the blood. When an essential amino acid is used that is neither metabolized nor produced in muscle, such as phenylalanine, R_d and R_a have some relation to muscle protein synthesis and

breakdown. However, when interpreting the results from such studies, it is important to understand that R_d and R_a are not direct measures of protein synthesis and breakdown, respectively. Rather, R_d is a reflection of protein synthesis from plasma amino acids, and R_a represents the appearance of amino acids in the plasma from protein breakdown (45). Total protein synthesis is the sum of R_d plus protein synthesis using intracellular amino acids originating from protein breakdown. Respectively, total protein breakdown is the sum of R_a plus the amino acids that were released by protein breakdown and directly reincorporated into protein (i.e., protein synthesis) before they appeared in the plasma. Therefore, the interpretation that insulin treatment improves net protein synthesis by decreasing protein breakdown ($\downarrow R_a$) may be in error because reincorporation of intracellular amino acids from stimulated protein synthesis is falsely interpreted as decreased protein breakdown (i.e., decreased R_a). These data are also consistent with what is known about intracellular insulin signaling, which has shown that insulin stimulates protein synthesis by increasing translation of mRNA through protein kinase B phosphorylation (19). No similar effects on protein breakdown pathways have been identified.

In a study in the severely burned where all the fluxes were measured in addition to R_a and R_d , maximal hyperinsulinemia with plasma insulin levels $>7.6 \text{ mU/mL}$ for 4 days in severely burned adults stimulated leg muscle protein synthesis by $>200\%$ (37), thus showing that indeed insulin treatment stimulated muscle protein synthesis. Using intracellular enrichment measurements, it seemed that the bulk of amino acids used for the stimulated rate of synthesis came from protein breakdown. However, the investigators also found an increase in inward transport of amino acids into the cell with this treatment. Curiously, insulin treatment also increased protein breakdown, but the increases in synthesis were sufficient to result in improved net protein synthesis. Thus insulin affected catabolism at these high doses by both increasing protein synthesis and increasing inward amino acid transport. A caveat to this study was that these subjects required approximately 5000 extra calories per day above calculated needs as glucose to maintain euglycemia at this very high insulin dose. It was shown that when

insulin was given at submaximal doses that required no additional calories to usual feeding regimens to maintain euglycemia, the insulin effect on stimulated protein synthesis was spared. The increase in protein synthesis was realized by greater utilization of intracellular amino acids from protein breakdown without affecting inward amino acid transport (38).

These studies serve as cornerstones to define the mechanism of insulin effects on muscle protein metabolism after severe burn. At high doses, insulin stimulated net protein synthesis with amino acid substrate from increased inward transport of amino acids and increased intracellular availability of amino acids by increased protein breakdown. At lower doses, insulin stimulated synthesis by using intracellular amino acids provided by protein breakdown, thus improving the efficiency of the protein synthetic machinery in the muscle cell. At this lower dose of insulin, amino acid transport out of the cell was abrogated by increased synthesis (with a decreased R_a), thus leaving more protein within the cell to improve net muscle protein synthesis. This notion was confirmed when insulin treatment at similar doses given throughout the hospital stay in severely burned children decreased length of hospital stay and improved lean body mass in body composition measurements (46).

In 1989, Jahoor et al. (47) used a euglycemic hyperinsulinemic clamp in combination with a leucine isotope infusion to show that increased levels of the hormone decreased protein catabolism, in agreement with the previously mentioned studies. Later, this was found to be due to insulin stimulation of protein synthesis; amino acid transport from the cell into the intracellular space decreases and export increases (31, 37, 48). Euglycemic hyperinsulinemic insulin clamps over the period of a week in the severely burned reduce muscle catabolism; however, this requires significant calories in excess of presumed metabolic requirement. One of the primary risks of overfeeding is the development of fat metabolism derangements; however, liver dysfunction appears to be prevented by the effects of insulin on hepatic fat synthesis (49). Aarsland and his colleagues (49) showed that insulin therapy increased the proportion of *de novo* synthesized fatty acid in very low density lipoprotein triglyceride, the principal export mechanism of fat from the liver, by 200% with a corre-

sponding decreased appearance of fatty acids from peripheral lipolysis. This indicates that the peripheral release of fatty acids after severe trauma represents a far greater potential for hepatic lipid accumulation in burn patients than endogenous hepatic fat synthesis, even during insulin therapy.

Initially, insulin clamps were studied at very high doses; recent studies have shown that lower and therefore safer doses demonstrate commensurate benefits in increased protein synthesis in the muscle (38). Of late, in a rabbit model, it was found that insulin at similar doses also stimulated protein synthesis in the skin as well as muscle (50, 51). This is consistent with the earlier finding of accelerated donor site wound healing in the severely burned treated with high doses of insulin (52). This is of course of great interest in the severely burned, whose recovery is often limited by the rate of wound healing. It was also shown in the rabbit model that anabolic effects in the skin and muscle can be augmented by concurrent administration of exogenous amino acids (51). The effect of both in this study was greater than either alone.

Insulin for Glucose Regulation After Severe Burn

In the critical care literature, evidence is mounting that hyperglycemia is associated with poor outcomes, and glucose control with insulin is beneficial. Less has been done in the field of trauma and burns. Numerous publications showed that adverse outcomes are correlated with hyperglycemia; however, studies that examine the effect of tight glycemic control with insulin are limited in size and scope (53–59). Nowhere is this more true than in the field of severe burn, where work has been almost exclusively in children. Holm and others (60) published a single observational study in adults demonstrating that hyperglycemia in the first 48 hrs after injury appears to correlate with adverse outcome. In the pediatric burn literature, several studies showed that hyperglycemia is correlated with increased catabolism, bacteremia/fungemia, skin graft loss, and mortality, while intensive insulin was positively correlated with survival (35, 43, 61). Investigators demonstrated attenuation of the systemic inflammatory response syndrome with insulin therapy targeted to keep blood glucose between 120 and 180 mg/dL; compared with controls, treated subjects

had lower serum cytokine levels and exogenous albumin requirement (62). Despite the paucity of related burn research, intensive insulin protocols have become commonplace. Mortality benefits demonstrated by Van den Berghe and others are compelling (2); however, more research is needed to define benefits and risks in the burn population. Regardless, because of the findings described here and the near universal application of the conclusions of Van den Berghe and colleagues, tight control of hyperglycemia has rapidly become the standard of care in most burn units throughout the world. However, what is not yet well established is exactly how to attain and maintain euglycemia in severe burns. Second, the question remains whether the beneficial effects seen by glucose control result from the elimination of hyperglycemia or from the pharmacologic effects of insulin.

The Case for Glucose Control vs. Pharmacologic Insulin Administration

The intense scrutiny of insulin as an anabolic mediator in burn catabolism has led some to speculate whether mortality benefits seen in the Van den Berghe studies are due to the glycemic or anticatabolic functions or some combination of the two (2); given the multiplicity of metabolic pathways triggered by the hormone, discriminating between these effects in humans will not be an easy task. In an elegant rabbit burn model, Dr. Van den Berghe and colleagues (63) attempted to answer this question. Animals were randomized into one of four groups: high glucose/high insulin, high glucose/normal insulin, normal glucose/high insulin, and normal glucose/normal insulin blood levels. Mortality was higher in both hyperglycemic groups regardless of insulin level; however, myocardial systolic function was improved in the presence of high insulin and normal glucose levels. Further research is needed to determine whether similar findings are seen in human subjects.

Future Areas of Research

Insulin is one of the most intensely studied of human hormones, and new therapeutic applications continue to be found; as these are found, new questions arise. Implementation of intensive insulin protocols has led researchers to recognize that variability in serum glucose

levels is a barrier to effective glycemic control and may be prove to be a target of therapy in itself (63–66). Other barriers to intensive insulin protocols exist; current methods of bedside glucose quantification are inadequate and may be insufficiently accurate to safely achieve narrow glycemic target. Catabolic mechanisms have been described that are unique to severe burn and are not seen in sepsis or trauma; the role of insulin in attenuating burn hypermetabolism is well described, but as its use in burn intensive care units becomes commonplace, further research is needed to define risks and benefits unique to this population.

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