Postburn trauma insulin resistance and fat metabolism

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Cree MG, Wolfe RR. Postburn trauma insulin resistance and fat metabolism. Am J Physiol Endocrinol Metab 294: E1–E9, 2008. First published October 23, 2007; doi:10.1152/ajpendo.00562.2007.—Hyperglycemia and insulin resistance have long been recognized in severe burn patients. More recently, it has been observed that controlling hyperglycemia, or alleviating insulin resistance, is associated with improved outcomes. This has led to a renewed interest in the etiology of insulin resistance in this population. The postinjury hyperglycemic response appears to be associated with multiple metabolic abnormalities, such as elevated basal energy expenditure, increased protein catabolism, and, notably, significant alterations in fat metabolism. The synergy of all of the responses is not understood, although many studies have been conducted. In this article we will review the present understanding of the relationship between fat metabolism and insulin resistance posttrauma, and discuss some of the recent discoveries and potential therapeutic measures. We propose that the insulin resistance is likely related to the development of “ectopic” fat stores, i.e., triglyceride (TG) storage in sites such as the liver and muscle cells. Deposition of TG in ectopic sites is due to an increase in free fatty acid delivery secondary to catecholamine-induced lipolysis, in conjunction with decreased β-oxidation within muscle and decreased hepatic secretion of fats. The resultant increases in intracellular TG or related lipid products may in turn contribute to alterations in insulin signaling.

burn trauma, glucose metabolism; intracellular triglycerides

MULTIPLE STUDIES HAVE DOCUMENTED hyperglycemia and insulin resistance posttrauma (32, 50, 109). Several studies have used hyperinsulinemic-euglycemic clamps to quantify the level of insulin resistance in trauma patients. Adult trauma patients had one-half the glucose uptake during hyperinsulinemia compared with healthy controls (68). Black et al. (12) found that, at approximately 1 wk postinjury, glucose uptake in response to four varied levels of insulin was impaired by at least one-third compared with controls. We recently found that within 1 wk postburn, insulin-stimulated glucose uptake was one-half of that in severely burned children compared with healthy children (24). The insulin resistance seen with injury is, largely, not due to the inactivity imposed by the injury, as patients undergoing surgery had decreased whole body glucose uptake and increased hepatic glucose release during a hyperinsulinemic clamp compared with healthy subjects confined to strict bed rest, although there were minor alteration in glucose metabolism following 7 days of bed rest in healthy individuals (79, 89). Therefore, severe insulin resistance in these patients is a direct consequence of the trauma.

Insulin resistance in these patients is of serious clinical concern, as several studies indicate that insulin resistance and related liver dysfunction may be implicated in increasing the morbidity and mortality of surgical and burned patients (38, 98–100, 104). Retrospective reviews have indicated that burned patients with higher plasma glucose levels over the duration of care have increased mortality (40, 48). Furthermore, the degree of hyperglycemia in the first 48 h is also correlated with mortality (48). In burn patients, higher plasma glucose levels are associated with increased graft loss and sepsis (40, 76). These outcome studies underscore the importance of a better understanding of insulin resistance in this patient population.

Fat metabolism is also altered postburn; this may be related to changes in insulin resistance. Burn patients experience increases in lipolysis, inadequate increases in the β-oxidation of fats relative to energy needs, and deposition of triglycerides in “ectopic sites,” or tissues other than adipose tissue, such as muscle and hepatic tissue (10, 73, 115). Recent studies in other models of insulin resistance, such as type 2 diabetes mellitus (T2DM), have found a strong relationship between fat and glucose metabolism (51, 83, 84). It appears that some, but not all, of the mechanisms found in this model can be found in burns. In this review, we will describe present research as it relates to muscle and hepatic insulin sensitivity and fat metabolism postburn trauma.

Whole Body Changes in Glucose and Fat Metabolism Postburn

Studies in burn trauma patients and animals have long indicated that there appear to be two distinct patterns of metabolic regulation following injury (111). The first phase occurs within the first 48 h from injury and has classically been called the “ebb phase” (28, 111). This phase of the response appears to be related to the magnitude of the trauma and the acute response hormones, including norepinephrine, epinephrine, dopamine, glucagon, and cortisol (33, 94, 95, 98, 116). The initial rise in plasma glucose after injury is seen within 30 min in guinea pigs, 2 h in rats, and 1 h in severely burned children (23, 33, 116). During this acute period, the hyperglyc-
cemia is not accompanied by an increase in insulin, perhaps because of the suppressive effect of epinephrine on insulin release (5, 23, 108).

Plasma free fatty acid concentrations immediately following burn injury are variable and have been found to be increased, not changed, and decreased (Table 1). Early studies found that plasma free fatty acids (FFA) increased following burn in humans and animals (5, 106). Other studies found acutely decreased concentrations of FFA in animals. It was determined that the rise in plasma FFA is influenced by the existence of adipose tissue before injury and also the rate of blood flow to adipose tissue, which may vary depending on resuscitation methods (111). Despite the variable concentrations of plasma FFA following burn trauma, the overall cycling of FFA released from adipose triglyceride (TG) back into adipose TG is increased. This is due to the concurrent effects of catecholamines on hormone-sensitive lipase (HSL) to induced lipolysis and upregulated reesterification, partially stimulated by increased lactate concentrations (34, 111). This continuous cycle of breakdown and formation of TGs is often termed futile, as the FFA released are not used for energy production but rather continue to recycle through TG.

The second phase of the metabolic response, lasting several weeks after injury, has been termed the “flow phase” (28, 46, 99, 111), although more recent studies indicate that this phase may continue in children for at least a year postburn (46). Initial studies in burned animals indicated that glucose uptake in response to exogenous insulin is decreased (103). Additionally, insulin release in trauma patients during this time period was found to be twice that of controls in response to a glucose load (12, 36). In burned children, although plasma glucose decreases after the initial spike, it remains above normal levels, and insulin progressively increases over time, indicating the development of an insulin-resistant state (23). Whereas catecholamines may play a role in this response, plasma cortisol levels begin to decline shortly after the initial injury (71). The persistence of insulin resistance during the flow phase could also be due in part to the catabolic decrease in muscle mass seen with severe injury, since skeletal muscle is responsible for 70–80% of whole body insulin-stimulated glucose uptake (29). Furthermore, 7 days of bed rest was accompanied by moderate decreases in insulin sensitivity and a 1–4% decrease in muscle mass (89).

Lipolysis is increased during the second phase of post-burn injury. Increased lipolysis can be attributed to increased adrenergic activity, as lipolysis is consistently reduced in patients treated acutely with β-adrenergic blockade (47, 114). However, the rate of lipolysis and catecholamines do not always correlate postinjury (36). For example, basal plasma palmitate turnover was significantly increased in trauma patients compared with controls, yet there was no relationship between epinephrine or norepinephrine levels and palmitate turnover (36). Part of the varied relation between catecholamines and the extent of the increase in lipolysis may be due to the amount of subcutaneous fat present following the initial trauma. Lipolysis was elevated in burned children who had the majority of fat removed in the course of surgical treatment of severe burns (fascial excision), but lipolysis was not further increased by infusion of exogenous epinephrine (115). In contrast, epinephrine infusion stimulated lipolysis to an even greater extent in patients in whom subcutaneous fat was maintained in the process of skin grafting (tangential excision). These findings indicate that surgical removal of a significant portion of the body fat limited the increase in whole body lipolysis.

Whereas lipolysis is increased after severe trauma, plasma FFA concentrations continue to be variable. For example, plasma FFA concentrations in adults with large burns were found to be within the normal range, although glycerol concentrations were elevated above normal for the first 20 days postburn (44). Glycerol is a direct reflection of lipolysis, because it cannot be reutilized for TG synthesis within the adipocyte once it is released. This is because the adipocyte does not contain glycerol kinase, which is necessary to convert glycerol to glycerol phosphate, which is the backbone of newly produced TG. In trauma patients, increased glycerol concentrations, but not FFA concentrations, correlated with the severity of the injury (95). Glycerol concentrations and turnover were increased significantly 6 days following total hip replacement surgery (16). Decreased plasma albumin levels following trauma may contribute to increased reesterification of fatty acids within adipocytes (64, 115). FFA are hydrophobic and are therefore bound to albumin in plasma. Because of the decreased concentrations of albumin, the ratio of FFA to albumin was elevated three- to fourfold in burned adults compared with healthy controls (44). It may be that the decreased albumin concentration limits the release of FFA, whereas glycerol can freely enter the plasma.

Intracellular FFA turnover is part of the FFA flux that comprises the futile cycle involving the breakdown of adipose and muscle TGs into FFA, their subsequent reesterification into very low-density lipoprotein (VLDL) or TG in the liver, and their ultimate reincorporation into adipocytes or muscle TG. For each intracellular TG molecule, HSL facilitates the release of one glycerol and three FFA (80). When all FFA are released and not reesterified within the cell, three FFA will be released for each one glycerol molecule. β-Adrenergic stimulation of muscle strips from burned animals increased glycerol release threefold but did not affect FFA release, indicating increased breakdown of stored TG coupled with increased FFA recycling within muscle cells (31). In burn patients, the rate of FFA release far exceeds the amount needed for energy use, so that much of the FFA is recycled in the liver and resecreted as VLDL-TG (3, 112). In healthy adults, the reesterification of FFA accounts for 65% of VLDL-TG release after 96 h of
hyperglycemia (1). After bariatric surgery, the clearance of infused TGs by the periphery in obese patients was increased twofold, and was accompanied by increased plasma glucose and insulin levels (101). Thus the futile cycling of FFA is related to hyperglycemia, yet the nature of the relationship is not clear.

**Tissue-Specific Interactions Between Glucose and Fat Metabolism**

The primary sites of glucose regulation are hepatic and muscle tissue. Both of these tissues also have important roles in fat metabolism, and it could be that understanding the interaction of glucose and fat in these tissues is key to understanding insulin resistance. Whereas adipose tissue also plays an important role in insulin resistance, very little research has been performed on this tissue in trauma. The only study of note is one in rats that found increased adipocyte apoptosis at days 3 and 7 post-scahd injury and an overall decreased fat mass at day 7 (118). Thus we will focus our discussion on muscle and hepatic metabolism.

**Hepatic metabolism.** The liver is a complex organ with multiple metabolic roles. The primary action of the liver in glucose metabolism is to help maintain steady concentrations of plasma glucose, with gluconeogenesis and glycoenolysis in the fasted state and glycogenesis in the fed state. In terms of fat metabolism, the liver utilizes FFA for ATP generation and also secretes plasma TG, VLDL, and multiple apolipoproteins found on cholesterol molecules. Hepatic insulin resistance is manifest by insulin failure to suppress glucose release and lipolysis.

Hyperglycemia immediately following burn injury appears to be due to increased gluconeogenesis and glycogenolysis in the liver, mediated in part by increased catecholamines via different mechanisms (116). Increased gluconeogenesis may be induced by the stimulation of cAMP by catecholamines. cAMP-dependent protein kinase inactivates pyruvate kinase, preventing glycolysis and causing a shift in liver metabolism toward gluconeogenesis (17). Furthermore, glucose release is not increased in isolated perfused livers from burned animals, indicating that the increased glucose output is secondary to extrahepatic signaling such as via catecholamines (18, 62). Catecholamines also stimulate p38 mitogen-activated protein kinase, causing the release of tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), which activate nuclear factor-κB (NF-κB) via IKK (19). NF-κB is also activated by saturated plasma FFA, elevated secondary to the catecholamines, via toll-like receptor-4 (57, 61). Once activated, NF-κB can cause apoptosis, and hepatocyte damage has been documented following burn trauma and serious illness (19, 53, 105). NF-κB also induces the production of IL-6, and this can cause increased hepatic glucose release and hepatic insulin resistance (54, 102). It may be that a combination of factors is necessary for increased hepatic metabolic rate in vivo, as glucagon and free radicals were necessary to induce metabolic rates similar to those seen in injury compared with either substance alone, and there are multiple pathways that could occur immediately following burn (63).

During the second phase of injury, the liver continues to release glucose at an increased rate because of increased gluconeogenesis, with amino acids from protein breakdown assuming an increased role as precursors (110). Hyperglycemia fails to suppress hepatic glucose release during this time (113). Furthermore, the suppressive effect of insulin on glucose release is attenuated, so that even high concentrations of insulin fail to suppress hepatic glucose release (27, 113). We found that hepatic glucose release was only suppressed 48% during hyperinsulinemia (27). The increased glucose release during this time contributes significantly to posttrauma hyperglycemia.

The increased delivery of FFA to the liver tissue can be shunted via several different metabolic pathways. FFA can be reesterified into VLDDL and TG for secretion, oxidized for energy, or stored within hepatocytes as TG. This is due in part to decreased β-oxidation of FFA and decreased VLDDL-TG secretion (74). In the presence of hyperglycemia, hepatic FFA uptake is increased, and FFA appear to be secreted in the form of TG and VLDDL, since these increase and β-oxidation decreases (92). When these defects are coupled with the increased FFA release, hepatomegaly due to increased storage of TGs within the liver ensues. In healthy volunteers, large increases in carbohydrate feeding lead to increased fat accumulation in adipocytes, but in the liver, VLDDL-TG synthesis increases, and there is no significant de novo fat synthesis in the liver (2). Pigs with 40% burns had increased liver fat due to decreased VLDDL secretion and not to decreased oxidation or changes in FFA uptake (69).

By using spectroscopy, we found that hepatic TG (HTG) in burned children was similar to the amount we previously found in elderly subjects with insulin resistance (23, 26). Although we have not measured HTG in healthy children, it should be similar to that found in young adults, since the diagnostic criteria of steatohepatitis are the same for both ages. Thus measured HTG was likely increased three- to fourfold in children at week 1 postburn. It is possible HTG was elevated even before that time, as liver fat in pigs doubled within 4 days postburn (69). Liver size was found to nearly double in children postburn, but ultrasound was unable to determine whether this was due to fat deposition or venous congestion (11). These are the only studies performed on living children, although many autopsy studies have long documented increased hepatic TG postburn (9, 10, 67). The hepatic TG may be related to increased mortality, underlying the importance of documenting its presence in patients who recover from their injuries (72).

It may be that the increased TG within the liver is related to the inability of the liver to respond to insulin, since these two processes occur within the same time period following injury. It is likely that the mechanism is similar to that described below for muscle.

**Myocyte metabolism.** Muscle is one of the major sites of insulin resistance in T2DM. Glucose is normally transported from plasma to within the cell via glucose transporter-4 (GLUT-4). This protein relocates to the cell surface after insulin binds to the insulin receptor (IR), causing phosphorylation of the protein and initiating a signal cascade involving, but not limited to, tyrosine phosphorylation of insulin signaling receptor-1 (IRS-1), association of phosphatidylinositol 3-kinase with IRS-1, activation of AKT, and, eventually, mobilization of intracellular GLUT-4 stores. Patients with T2DM have decreased phosphorylation of the IR, decreased tyrosine phosphorylation of IRS-1, and decreased association of Akt with IRS-1 (39). Studies have shown that the IRS-1 protein...
Muscle cell signaling after insulin stimulation in T2DM vs. postburn trauma

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Defects in muscle tissue insulin signaling after exposure to insulin are identical in patients with T2DM and previously healthy patients postburn. IRS-1, insulin signaling receptor-1.

Becomes phosphorylated at a serine-307 site, by atypical protein kinase C (PKC), preventing tyrosine phosphorylation and decreasing the activity of IRS-1 (122). There are several PKC isoforms in muscle, and the atypical ones, named α, ε, and θ, are thought to be metabolically active in relation to insulin resistance (88).

The alterations in the insulin signaling pathway following burn are similar to those seen in T2DM and are shown in Table 2 and Fig. 1. We found that, in children 7 days postburn, there is no increase in IR or IRS-1 phosphorylation in muscle after insulin stimulation, or IRS-1-associated AKT (27). These findings are similar to those in burned animals. For example, 3 days after a scald injury, rats injected with insulin and killed had no insulin stimulation of IR tyrosine phosphorylation, IRS-1 tyrosine phosphorylation, or phosphatidylinositol 3-kinase activation compared with controls (52). These animals also had a 30% decrease in glucose uptake in the basal state and no insulin-stimulated glucose uptake compared with controls. A similar study by the same investigators found that AKT activity also was attenuated by burns (97). Serine phosphorylation of IRS-1 was increased in rat muscle 7 days postburn (123). During fasting, there is little tyrosine phosphorylation in the absence of insulin stimulation. However, rats undergoing abdominal surgery have increased fasting basal phosphorylation of the signaling cascade, despite a decrease in insulin signaling (96). The authors speculate that an increased basal level of tyrosine phosphorylation could perhaps lead to a decreased effect of insulin compared with the basal state, because of a smaller change in phosphorylation state with new phosphorylation of proteins.

Insulin resistance is sometimes, but not always, associated with the ectopic storage of TG within myocytes. We found that concentrations of intramyocellular TG (IMTG) in pediatric burn patients were similar to those measured in the healthy elderly (25, 26). However, Astrakas et al. (8) found that IMTG was increased at days 1 and 3 postinjury. Animals with increased muscle lipoprotein lipase and muscle FFA delivery have increased IMTG and decreased intracellular insulin signaling, as well as decreased whole body glucose uptake (56). On the other hand, when myotubes overexpressed carnitine transporter-1 (CPT-1) and had increased β-oxidation and insulin sensitivity, the concentrations of IMTG were unchanged compared with control cells (82).

Studies have found close associations among intracellular lipid species such as IMTG, diacylglycerol (DAG), and fatty acyl-CoA and insulin sensitivity (91). These various fatty acid metabolites are thought to influence insulin signaling either directly or by increasing PKC, which inactivates IR and IRS-1 (87, 91). However, we found that when in vivo muscle insulin sensitivity in patients with severe burns was improved in association with increased palmitate oxidation, concentrations of intramyocyte DAG, IMTG, and fatty acyl-CoA did not change, whereas PKC-β decreased with increasing insulin sensitivity (25). Similar results were reported in rats fed a high-fat diet that had overexpression of hepatic malonyl-CoA dehydrogenase (6). Malonyl-CoA dehydrogenase breaks down malonyl-CoA and presumably increases β-oxidation of fat. Muscle, fat, and whole body insulin sensitivity improved in
these animals, but IMTG did not change, and there was a trend for increased fatty acyl-CoA production. The only metabolite that did change in these animals was short chain β-hydroxybutyrylcarbmine, a mitochondrial derivative of the ketone β-hydroxybutyrate. Furthermore, in rats fed a high-fat diet, treatment with Wy-14643, a potent peroxisome proliferator-activated receptor-α (PPARα) agonist, increased long chain fatty acyl-CoAs and insulin-mediated glucose uptake and decreased intramuscular TG (121). A similar study found that chronic Wy-14643 administration in rats did not lower palmitoyl-CoA (120). These conflicting results indicate that the association between intracellular lipids and insulin sensitivity is perhaps not as clear as previously thought, and the relationships as speculated are shown in Fig. 1. A comparison of tissue lipids in burn vs. T2DM patients is shown in Table 3.

The increased concentrations of intracellular lipids are due to two primary factors, increased delivery of FFA and/or decreased β-oxidation. As has already been discussed, whereas the overall plasma concentrations of FFA are varied, the FFA flux is increased, so that the absolute delivery of FFA is increased to muscle cells. It has been demonstrated in multiple studies that the absolute rate of β-oxidation of FFA within muscle is increased in burn patients, yet the rate of oxidation is inadequate to meet energy needs (25, 114, 115). Furthermore, the rate of whole body palmitate oxidation correlates with the degree of insulin sensitivity in burned children (25). We have recently shown that, when the rate of palmitate oxidation was increased (by ingestion of the PPAR-α agonist fenofibrate), insulin sensitivity was improved in burned patients (25).

Burns produce significant mitochondrial damage in multiple tissues. We recently found that 7 days posttrauma, children had a substantial decrease in the maximal mitochondrial oxidative capacity of both pyruvate and palmitate compared with healthy children (24). In rats, substantial burn caused a 43% decrease in ATP production in skeletal muscle (81). Furthermore, gene expression of many mitochondrial genes was downregulated in these animals, including cytochrome c, citrate synthase, and CPT-1 (81). Genes involved in mitochondrial protein production and activation within skeletal muscle were downregulated at 1 and 3 days postburn in rats (8). The mitochondrial dysfunction seen within 1 h postinjury was associated with increased skeletal muscle apoptosis up to 7 days after the original injury (119). Taken together, these data clearly demonstrate that the burn injury rapidly induced damage to the muscle mitochondria.

Mitochondrial damage may not be the only cause of decreased β-oxidation in trauma patients. Hyperglycemia has been shown to inhibit muscle β-oxidation of FFA, perhaps via inhibition of the CPT-1 transporter via malonyl-CoA (93). This system has not been evaluated in muscle from trauma patients.

The cause of mitochondrial damage after burns or trauma is unclear. The damage could partially arise secondary to reactive oxygen species (ROS). Liang et al. (66) found that following burn, cardiac muscle cells experienced a large influx of calcium that was associated with mitochondrial nitric oxide synthase, although it is unclear whether a similar mechanism occurs in skeletal muscle. Nitric oxide has been shown to directly block cytochrome c activity and also causes oxidative damage to the mitochondrial membrane (13). Alternatively, the chronic damage may be induced by lipid products, as Chen et al. (20–22) found that a lipid isolated from burn eschar was able to induce the characteristic alterations in mitochondrial function seen in burn injury, decreased ATP synthesis and state 3 oxidation and decreased cytochrome b and c activity. The increased calcium flux within cardiomyocytes postburn also induced increases in phospholipase A2 concentrations (66). Phospholipase A2 has been documented to release FFA that induce mitochondrial damage and thus insulin resistance. All of these treatments have had varied success.

Small studies have been conducted trying various means to control plasma hyperglycemia directly, influence fatty acid metabolism, or improve mitochondrial function with varied success. The simplest treatment approach has been to control glucose via chronic insulin infusions. Metformin and losartan, an angiotensin receptor blocker (ARB), have been used to improve insulin sensitivity of the muscle in humans and animals, respectively (41–43, 55). PPAR-α agonists have been used to increase fat oxidation and mitochondrial function (25, 27). Finally, antioxidants such as ascorbic acid (vitamin C) or topherol (vitamin E) or anti-inflammatory agents such as TNF-α inhibitors or cyclooxygenase-2 (COX-2) inhibitors have been given in an attempt to counteract the ROS that may induce mitochondrial damage and thus insulin resistance. All of these treatments have had varied success.

Recently, much attention has been given to controlling hyperglycemia via insulin infusion, as such treatment has been shown to significantly lower both morbidity and mortality of multiple types of critically ill patients (104). In burn patients, time spent in intensive care is dependent on the severity of the burn and the covering of burned areas with donor skin through autografting or from cadavers. Very high-level exogenous insulin administration in burn patients to maintain a plasma insulin level of 400–900 μU/ml was shown to improve the donor site wound healing from 6.5 ± 1.0 to 4.2 ± 1.2 days (85). In burned children, moderate-dose insulin therapy decreased acute-phase proteins and cytokines such as TNF-α, IL-1, and IL-6 from week 1 to week 4 postburn, whereas there was no decrease in these measures in placebo-treated burned children (117).

Although there are documented benefits, insulin therapy is not without risk. The administration of insulin requires intensive monitoring to avoid hypoglycemia. Furthermore, to meet the glucose demands during exogenous insulin administration,
caloric intake must be increased far beyond the metabolic need of the patient, contributing to increased adiposity and thus increased plasma FFA due to fat deposition (14, 45). Additionally, although insulin lowers plasma glucose levels, studies have shown that insulin resistance still exists in terms of fat metabolism. High levels of exogenous insulin given for 7 days to severely burned patients (63 ± 8% total body surface area) did not suppress the release of endogenous FFA from adipocytes (4). The combination of increased calories and high plasma FFA can lead to increases in liver size (14). Indeed, 3 days of insulin infusion in type 2 diabetics leads to decreased plasma glucose in conjunction with increased muscle and liver fat (7). Insulin also prevents the transcription of CPT-1 in the liver, which would have the potential of decreasing fat oxidation and increasing fat accumulation (75).

Given the limitations of high-dose insulin therapy, approaches that would improve insulin sensitivity are appealing. In that regard, PPAR-α agonists have been demonstrated to increase the mitochondrial oxidation of fats and improve glucose homeostasis in animals and certain human populations (35, 77). We recently studied this medication in burned patients and found that 2 wk of treatment with the PPAR-α agonist fenofibrate significantly improved insulin-stimulated glucose uptake and hepatic insulin sensitivity, in conjunction with improved insulin signaling within the muscle (27). Furthermore, fenofibrate significantly increased maximal mitochondrial pyruvate and palmitate oxidation as well as the function of cytochrome c and COX enzymes (25, 27). Finally, the whole body β-oxidation of palmitate was increased significantly following treatment (25).

Metformin has been shown to decrease hepatic glucose release as well as improve peripheral insulin sensitivity. In burn trauma patients, metformin treatment lowered plasma glucose concentrations at 24–26 h postinjury in the fasted and in the fed state (42). Decreased plasma glucose was mediated by lower rates of hepatic glucose release and increased peripheral clearance of glucose (42, 43). Plasma insulin concentrations were also higher, indicating that metformin either increased the secretion of insulin or decreased the breakdown of insulin (42). Furthermore, metformin treatment was found to increase the synthetic rate of muscle protein, and, when combined with exogenous insulin, protein synthesis was further increased (41). These promising results in a small cohort of patients need to be followed by larger studies.

Insulin resistance is often accompanied by hypertension. Kasper et al. (55) studied the effects of ARBs on postburn trauma insulin sensitivity. They found that at day 3 postburn, the burned animals treated with ARBs had similar area under the curve (AUC) measurements of glucose and insulin during an oral glucose tolerance test as sham burn animals, whereas the burn-only animals had a significantly higher AUC of glucose and insulin (55). The authors speculate that the ARBs may work by decreasing serine phosphorylation of IR and IRS-1 via decreasing PKC. More studies on the mechanism of action and studies in humans are needed to determine whether the ARBs will be a potential therapeutic drug.

Several investigators have proposed that treatment with antioxidant substances, COX-2 inhibitors, or TNF-α inhibitors could counter the negative effects of ROS that may cause mitochondrial damage (49). Antioxidants are decreased in multiple tissues post-burn injury (59). Supplements of both ascorbic acid and glutathione attenuate the decrease in hepatic ATP production following burn trauma (58, 60). Others have found that high doses of ascorbic acid decreased lipid peroxidation products (70). Furthermore, cardiomyocyte ROS-associated activation of NF-κB, a molecule that induces cytokines such as TNF-α and IL-6, was reduced 24 h postburn in animals given a mixture of vitamins C, E, and A and zinc (49). However, TNF-α is an important signal in the inflammatory cascade and induces increases in several other proteins, such as fibrinogen. Thus burn patients who do not mount a robust response could be at risk for increased morbidity via hemorrhage because of an increased breakdown of fibrinogen (78). COX-2 inhibitors have been used in animal models of burn and have decreased morbidity (90). However, these studies need to be performed with glucose measurements to see whether there are any clinical implications to this work.

Alterations in operative patient care may also minimize insulin resistance. Since burn patients undergo multiple surgical procedures throughout their recovery, these studies may also be relevant to helping decrease hyperglycemia. Recent research has attempted to minimize surgical stress, and this has been shown to lower postoperative hyperglycemia (15). It may be that smaller operations will need to be balanced with the necessity for rapid coverage of open wounds. Other investigators have examined the effects of controlling intraoperative plasma glucose concentrations, administering caloric loads before surgery, and different routes of anesthesia with varied results in nontrauma patients (30, 37, 86). These approaches have yet to been investigated in trauma patients.

Overall, there are multiple approaches to increasing insulin sensitivity and decreasing hyperglycemia that may be available in the future. Further studies are needed on all of the above-mentioned medications. Furthermore, given the different mechanisms of the medications, it could be that the most beneficial treatment will be the combination of medications with complimentary actions. For example, it has already been shown that insulin and metformin increased protein synthesis more than either drug in isolation (41).

Conclusions

In conclusion, postburn insulin resistance, like the insulin resistance seen in T2DM, is complex and involves many tissues, cells, and metabolic pathways. It is clear that controlling insulin resistance is a high priority in the management of severely burned patients or patients with trauma. Understanding the mechanisms underlying the development of insulin resistance is central to formulating a rational clinical approach. Recent research indicates links among altered rates of lipolysis, impaired liver and muscle mitochondrial oxidative function, accumulation of tissue lipids, and alterations in the insulin signaling cascade that lead to insulin resistance, in terms of both the suppressive action on hepatic glucose production and stimulation of muscle glucose uptake. It is appealing to consider the stimulation of lipolysis in the absence of a corresponding increase in requirement for substrate metabolism as a starting point. Excess availability of fatty acids, coupled with impaired mitochondrial function, would lead to the accumulation of
intracellular TG and other lipid products that in turn inhibit insulin signaling. This scenario would be similar to that proposed to apply in obesity and aging (51, 91). However, available evidence fails to completely support this scenario. For example, inhibition of lipolysis in burn patients with β-adrenergic blockade does not improve insulin sensitivity, and stimulation of fatty acid oxidation with fenofibrate improved insulin action without affecting intracellular or plasma lipids. Alternatively, it is possible that the initial derangement is a stimulation of hepatic glucose production and direct inhibition of insulin action peripherally by stress hormones. The decrease in fatty acid oxidation could primarily reflect inhibition of CPT-1 by glucose via malonyl-CoA. The limitation of this scenario is that insulin resistance persists long after the acute elevations in stress hormones have been resolved.

The failure of any simplistic explanation to completely unify available data indicates that the basis for insulin resistance after trauma and burns is multifactorial. We propose that there are perhaps different mechanisms occurring during the two phases following burn injury, as shown in Fig. 1 and illustrated above. Successful treatment will only be achieved after the interactions of pathways of lipid and glucose metabolism, in relation to the insulin signaling pathway, are understood.

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REFERENCES

64. Liang WC, Tang LX, Yang ZC, Huang YS. Calcium induced the damage of myocardial mitochondrial respiratory function in the early stage after severe burns. Burns 28: 143–146, 2002.