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METABOLIC CHANGES IN BURNS: A REVIEW

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ABSTRACT

Stress due to burn injury results in major changes in body metabolism. The degree depends on the degree of the burn insult. This response leads to potentially deleterious changes in body composition, and a hypermetabolic state. Significant alterations in both glucose and fat metabolism occur followed by burn trauma. Hyperglycemia due to increased hepatic gluconeogenesis and peripheral insulin resistance is common. Free fatty acid (FFA) cycling is increased up to three fold, and triglyceride (TAG) deposition in the liver occurs. Studies in burned animals indicate that mitochondrial number and oxidative capacity are severely reduced minimizing the ATP production. Severe burns covering more than 40% of total body surface area (TBSA) typically are followed by a period of stress, inflammation, and hypermetabolism, characterized by a hyperdynamic circulatory response with increased body temperature, glycolysis, proteolysis, glycogenolysis, gluconeogenesis lipolysis, and futile substrate cycling. This article tries to assimilate the proved but less studied metabolic aspects, especially carbohydrate and lipid metabolisms and their relationship with mitochondrial ATP synthesis and their formation of a vicious cycle along with insulin resistance in burn trauma.

Key words: Metabolic Changes, Insulin Resistance, Vicious Cycle, Burn Injury

INTRODUCTION

Severe thermal injuries are typically followed by a catabolic state **[1, 2]**. Hyperglycemia that is characteristically seen in burns increases the mortality **[3, 4]**. It also increases the risk

of graft loss and sepsis **[3, 5]**. Initial 48 hours of post burn period, 'ebb period'has highest adrenaline and noradrenaline excretion (in the first 8 hours after the burn) **[6]**. Catecholamines physiologically increase metabolic rate and glycogenolysis and lipolysis at the tissue level. Hyperglycemia can also be attributed to the suppressive effect of catecholamines on insulin **[7-10]**. Lipid alterations also occur in this period but free fatty acid (FFA) levels vary (increase or decrease) depending on the existence of adipose tissue before injury and resuscitation methods **[11]**.

Second phase is 'flow phase'which extends to a few weeks to a few months following burn injury. Reduced glucose uptake by the cells **[12]**, doubled insulin release in response to glucose **[13, 14]** unable to bring down the glucose levels suggests the state of 'insulin resistance' in this phase. Heightened lipolysis occurs because of adrenergic activity **[15, 16]**. Hormone sensitive lipase is stimulated by catecholamines, which breaks down TGs and releases FFAs.But oxidation of FFAs is decreased because of the inhibition of Carnitine Palmitoyl Transferase-1(CPT-I) by glucose via malonyl CoA.FFAs undergo re-esterification forming TGs **[11, 17]**. Albumin levels diminish due to the third space loss and availability for binding of FFAs falls which contributes to the excessive re-esterification of FFAs **[18, 19]**. This forms a futile cycle, because of which lipids get deposited in extra adipose tissues as well as reincorporated in adipocytes **[19-21]**.

We review the burns induced changes on mitochondrial functions, carbohydrate and lipid metabolisms in detail.

Impact of Burn Trauma on Mitochondrial Electron Transport Chain

Burns produce significant mitochondrial damage in multiple tissues. It has been found that there is a substantial decrease in the mitochondrial oxidative capacity of both pyruvate and palmitate **[22]**. Experiments on rats have demonstrated a substantial burn caused a 43% decrease in ATP production in skeletal muscle **[23]**. Gene expression of many mitochondrial enzymes involved in respiratory chain, TCA cycle and fatty acid oxidation were down regulated in these animals. These enzymes are cytochrome *c*, citrate synthase, and CPT-1respectively **[23]**. Many components of the mitochondrial electron transport chain are down-regulated , including subunits of NADH ubiquinone dehydrogenases (complex I), succinate dehydrogenase complex (complex II), subunits of cytochrome *c* oxidase (complex IV), and ATP synthase (F1F0 ATPase or complex V). This finding substantiate the fact

that burn trauma results in reduced ATP synthesis by mitochondria. Genes involved in mitochondrial protein production and activation within skeletal muscle were also down regulated in post burn period in rats **[24]**. The mitochondrial dysfunction seen in post injury was associated with increased skeletal muscle apoptosis **[25]**.

Several genes are down-regulated after burn trauma like those encoding glycolytic enzymes and transporters, as well as Pyruvate dehydrogenase (PDH) multi enzyme complex. This fact suggests that the muscle has decreased glucose levels, which could in turn result in an increased demand for fatty acid oxidation to fulfill its energy requirements. But FFAs cannot meet the energy need because of inhibition of their oxidation by the CPT-1, transporter of acetyl CoA **[26]**.

Marked and sustained increases in several hormones like catecholamine, glucocorticoid, glucagon, and dopamine initiate the cascade of events leading to the acute hypermetabolic response with its ensuing catabolic state **[27-32]**. Interleukins, IL-1 and IL-6, platelet-activating factor, TNF, endotoxin, neutrophil-adherence complexes, reactive oxygen species, nitric oxide, coagulation as well as complement cascades also have been implicated in regulating this response to thermal injury **[33]**. Inflammatory cytokines, including TNF, IL-6, and monocyte chemoattractant protein-1 (MCP-1) also act via direct effects on the insulin signal transduction pathway through modification of the signaling properties of insulin receptor substrates, contributing to postburn hyperglycemia via liver and skeletal muscle insulin resistance **[34-36]**. Proinflammatory cytokines contribute to postburn hyperglycemia via enhancing the release of the stress hormones **[37-40]**.

Carbohydrate Metabolism in Burns

These stress mediators oppose the anabolic actions of insulin **[41]**. They enhance adipose tissue lipolysis **[42]** and skeletal muscle proteolysis **[43]**. They increase gluconeogenic substrates, including glycerol, alanine, and lactate, thus augmenting hepatic glucose production in burn patients **[43-45]**. Circulating blood levels of these three precursors of new glucose synthesis by the liver are elevated in the early stages following severe burn injury **[46]**. A study suggests that lactate levels remain elevated in severely burned subjects during the first week of injury, while alanine, although high initially, fell rapidly to low levels by day seven and glycerol values followed a similar pattern. Hyperglycemia fails to suppress hepatic glucose release during this time **[47]**, and the suppressive effect of insulin on hepatic

glucose release is attenuated, significantly contributing to post trauma hyperglycemia **[48]**.

Catecholamines released in response to stress stimulates phosphorylation of glycogen phosphorylase and activates it, thus enhancing the hepatic glycogenolysis as well as direct sympathetic stimulation of glycogen breakdown, that can further aggravate the hyperglycemia **[44]**. Catecholamines also have been shown to alter the insulin signaling pathway and GLUT-4 translocation in muscle and adipose tissue impair glucose disposal, resulting in peripheral insulin resistance **[43, 49]**.

A study demonstrates elevated glucagon levels after the burn, emphasized the relationship of catabolism to the glucagon: insulin ratio **[50]**. Glucagon leads to increased glucose production through gluconeogenesis and glycogenolysis **[51]**. Epinephrine and glucagon have a synergistic effects on glycogenolysis **[51]**. In addition it also causes lipolysis and ketogenesis.

Retrospective studies have reported an increased mortality in burns patients with higher plasma glucose levels **[3, 4]**. Furthermore, the degree of hyperglycemia in the first 48 h is also correlated with mortality **[4]**. In burn patients, higher plasma glucose levels are associated with increased graft loss and sepsis **[3, 5]**.

The term 'insulin resistance' is used when blood glucose values are elevated despite the presence of apparently adequate insulin levels. This resistance may be both at the cellular uptake of glucose and the hepatic inhibition of gluconeogenesis. This phenomenon is seen in mild and severe burns. Insulin resistance has been thought to be caused by changes in 'the cell membrance **[52]**, in vivo data in the rat have shown contradictory evidence **[53]**.

The synthesis of glucose from non carbohydrate sources is called gluconeogenesis. The key enzymes are pyruvate carboxylase, phosphoenol pyruvate carboxy kinase, fructose 1,6 bis phosphatase and glucose 6 phosphatase. The genes coding for these enzymes are up-regulated after burn trauma through activation of transcription factors, causing hyperglycemia. Blood levels of the three precursors for gluconeogenesis , lactate, alanine and glycerol, are all elevated in the early stages following severe burn injury **[46]**.

Further glucose turnover via non-oxidative routes is enhanced ,including the peripheral degradation of glucose to lactate which is then released back into the circulation to be taken

up by the liver for resynthesis to glucose -the 'Cori cycle' **[54]**.

Glucose may be lysed to pyruvate in muscle and then may undergo transamination. Alanine, thus formed, returns to the liver where the amino group, is converted to urea and the carbon chain to glucose - the 'glucose alanine cycle' **[55, 56]**.

Genes encoding glycolysis enzymes are down regulated, including 2, 3-bisphosphoglycerate mutase, lactate dehydrogenase, enolase, and subunits of the pyruvate dehydrogenase complex, such as pyruvate dehydrogenase dihydrolipoamide *S*-acetyltransferase. Down regulation of these glycolytic enzyme genes suggests decreased glucose utilization after burn injury.

Fuel enters the TCA cycle mainly as acetyl-CoA, which is generated by oxidative decarboxylation of pyruvate. Burn trauma up-regulates the gene for PDH kinase. This enzyme inactivates the key multi enzyme complex, pruvatedehydrogenase (PDH) by phosphorylating it. This reduces the availability of fuel to TCA cycle. Also, downstream TCA cycle genes are down-regulated, including PDH (lipoamide), succinate dehydrogenase, and citrate synthase. Furthermore, malate dehydrogenase, the final enzyme of the TCA cycle, is down-regulated after burn **[57]**.

The glucose-6-phosphatase transport protein 1 gene and GLUT 4 are down regulated, indicating that glucose uptake is reduced after burn injury.

Several genes down-regulated after burn trauma encode glycolytic enzymes and transporters, as well as PDH complex enzymes. These results suggest decreased glucose utilization by tissues, which could in turn result in an increased demand for fatty acid oxidation to fulfill its energy requirements. However results show that fatty acid oxidation gene expression is actually reduced in a burn model. This reduction should result in triglyceride accumulation. Decreased β-oxidation of FFA's and increased circulating concentrations of plasma FFA's are both likely related to insulin resistance.

Lipid Metabolism in burns:

Burn trauma also down-regulates fatty acid oxidation genes, resulting in accumulation of excessive FFAs. Re-esterification of FFAs suggests accumulation of triglycerides. Affected genes include dodecenoyl-CoA delta isomerase; acetyl-CoA acyltransferase , adipocyte complement related protein, which acts in fatty acid oxidation; carnitinepalmitoyltransferase1, which is the rate limiting enzyme of the long-chain fatty acid oxidation pathway in muscle mitochondria; and lipoprotein lipase, which

increases the cytosolic pool of nonesterified fatty acids.

Lipid metabolism changes significantly because of the futile cycling of free fatty acids and triglycerides deposition.Fat transporter proteins are decreased in the postburn period while triglycerides and FFA are increased, which could explain the fatty infiltration of the liver and other organs at postburn **[58-62]**. Hepatic triglyceride accumulation after thermal injury is due to combined effect of an excessive delivery of fatty acids to the liver as a consequence of adrenergic mediated stimulation of lipolysis by hormone sensitive lipase **[63, 64]** and a diminished effectiveness of insulin in suppressing lipolysis **[60]**.

It has been theorized that a decrease in mitochondrial function, and thus β-oxidation, causes intracellular TAG to accumulate, thereby contributing to the development of insulin resistance **[65]**. The accumulation of tissue TAG may not only be due to a decrease in the oxidation rate of fatty acids, but also to an increase in fatty acid delivery via plasma TAG and FFA.

Early studies have found that plasma free fatty acids (FFA) were increased following burn in humans and animals **[8, 66]**. Contradictorily 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 **[11]**. Despite the variable concentrations of plasma FFA following burn trauma, the overall cycling of FFA released from adipose triglyceride (TG) back into adipose TG isincreased. This is due to the concurrent effects of catecholamines on hormone-sensitive lipase (HSL) to induclipolysis and upregulatereesterification, partially stimulated by increased lactate concentrations **[67, 11]**. 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. Accelerated delivery of fatty acids due to lipolysis resulted in hepatic uptake at a rate well in excess of the requirement for oxidation. Thus, fatty acids taken up by the liver were channeled to triglyceride synthesis at a markedly accelerated rate in both pigs and humans **[64, 68]**. The process of hepatic triglyceride deposition is accelerated when a high proportion of the diet is fat **[69]**. However, substitution of dietary fat with carbohydrate results in the stimulation of *de novo* fatty acid synthesis, which also contributes to hepatic

triglycerides **[70]**. In addition, TG is not cleared by VLDL formation **[64]**.

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 **[71]**. Uncontrolled hyperglycemia leads to fat depositionin the liver augmenting fatty infiltration of the liver post severe thermal injury **[72]**.

Burn patients experience increases in lipolysis, inadequate increases in the 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 **[73, 44, 19]**. In burn patients, the rate of FFArelease far exceeds the amount needed for energy use, so thatmuch of the FFA is recycled in the liver and resecreted asVLDL-TG **[74, 75]**.

Studies by Coombes *et al*., **[76]** reported an elevated serum total triglyceride, lowered serum total cholesterol and phospholipid, and by fractionation assays show elevated low density lipoprotein (LDL) and very low density lipoprotein (VLDL) triglyceride in moderate burns with peak values 5-6 days after injury. High density lipoprotein (HDL) cholesterol and phospholipid levels were low and VLDL cholesterol slightly high. Measurement of apoprotein levels revealed a marked fall in apoprotein A, a rise in apoprotein C in the more severely burned patients. There was a relatively large loss of HDL into the blister fluid of the burn area and also some loss in urine. The loss of HDL which is necessary as a receptor for apoprotein C in the conversion of VLDL to LDL may account not only for the elevated apoprotein C levels, but alsofor the high VLDL levels and hyper triglyceridaemia seen after burn injury.

Low levels of blood ketones, indicate a failure of hepatic production.Although this may be due to hormonal regulation,thecarnitine depletion **[77]** and the limited oxidation of NEFA despite high turnover rates might be responsible.

Insulin resistance is associated with the ectopic storage of TG within myocytes. Studies have found that intra myocellular triglyceride (IMTG) in rats increased at postinjury **[78]**. 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 **[79]**. IMTG levels may be increased secondary to adipocyte dysfunction and this may account for its relationship noted in patients with increased adiposity, insulin resistance **[80]**. Studies have found close associations among intracellular lipid species such as IMTG, diacylglycerol (DAG), and fatty acyl-CoA and insulin sensitivity **[81]**. These various fatty acid metabolites are thought to influence insulin signaling either directly or by increasing Protein Kinase C (PKC), which inactivates IR and IRS-1 **[81, 82]**. A study suggests that muscle insulin sensitivity in patients with severe burns was improved inassociation with increased palmitate oxidation, concentrations of intramyocyte DAG, IMTG, and fatty acyl-CoA did not change, whereas PKC decreased with increasing insulin sensitivity **[83]**. Both DAG and long chain fatty acyl CoA have been shown to disrupt the insulin signaling pathway at the level of the insulin receptor signalling-1 protein (IRS-1), preventing translocation of glucose transporter to the cell surface membrane, and thus insulin stimulated glucose uptake **[65]**.Thus deranged lipid metabolism hampers insulin sensitivity and vice versa.

The increased concentrations of intracellular lipids are due to two primary factors, increased delivery of FFA and/ordecreased 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 oxidation of FFA within muscle is increased in burn patients, yet the rate of oxidation is inadequate to meet energy needs **[83, 84]**. Furthermore, the rate of whole body palmitate oxidation correlates with the degree of insulin sensitivity in burned children **[83]**.

All these evidences suggest that a strong vicious cycle in the metabolisms in which hormones take a major role and they successfully derange carbohydrate and lipid metabolisms. The cycle starts with stress hormones which get released immediately after burn, suppress insulin. They directly hamper glucose and lipid metabolisms. Dyslipidemia in turn further contributes to insulin resistance and the cycle goes on, leading to a vicious cycle.

All these metabolic events necessitate the use of a drug which can check these derangements. Peroxisome proliferator activating receptors (PPAR) are nuclear receptors that, when stimulated by endogenous lipids, activate specific genes involved in fat metabolism. PPAR-α agonists

increase fat oxidation and improve insulin sensitivity. Significant decreases in fasting plasma glucose, insulin and TAG, with a fall in muscle and liver TAG have been reported in mice, after treatment with PPAR-α agonists **[85, 86]**. These drugs also decrease intracellular fatty acyl CoA and malonyl CoA, and increase fatty acid oxidation in rodents **[87, 88]**. PPAR-α agonist treatment in human myocytes increased β-oxidation of oleate and decrease doleate incorporation into TAG **[89]**. Despite the encouraging results in animal and in vitro studies, results of treatment in young and middle aged humans with PPAR-α agonists have not been as well defined **[90-92]**. PPAR-α agonist treatment improves both peripheral and hepatic glucose sensitivity and improves the response of the insulin signaling cascade in muscle to insulin in burns **[93]** but, the effect of PPAR-α agonism on fat metabolism has not been studied.

CONCLUSION

A peroxisome proliferator activated receptor alpha agonist like fenofibrate provides systemic regulation of lipoprotein metabolism, fatty acid oxidation, and fatty acid transport. Its action may improve insulin signaling in skeletal muscle, as well as mitochondrial function, glucose oxidation, and insulin sensitivity. The long term use of these drugs in severe burns patients may improve hyperglycemia and insulin resistance. Although a few studies substantiate above facts, extensive research in this field may throw light on the management of metabolic derangements in severe burns.These drugs may help to break the vicious cycle of release of stress hormones →suppressed insulin action → hyperglycemia,mitochondrial dysfunction → lipid derangements → insulin resistance → alterations in carbohydrate and lipid metabolisms and so on.

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