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Alcohol Modulation of the Post Burn Hepatic Response

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Abstract

The widespread and rapidly increasing trend of binge drinking is accompanied by a concomitant rise in the prevalence of trauma patients under the influence of alcohol at the time of their injury. Epidemiologic evidence suggests up to half of all adult burn patients are intoxicated at the time of admission and the presence of alcohol is an independent risk factor for death in the early stages post burn. As the major site of alcohol metabolism and toxicity, the liver is a critical determinant of post burn outcome and experimental evidence implies an injury threshold exists beyond which burn-induced hepatic derangement is observed. Alcohol may lower this threshold for post burn hepatic damage through a variety of mechanisms including modulation of extrahepatic events, alteration of the gut-liver axis, and changes in signaling pathways. The direct and indirect effects of alcohol may prime the liver for the second-hit of many overlapping physiologic responses to burn injury. In an effort to gain a deeper understanding of how alcohol potentiates post burn hepatic damage, we summarize possible mechanisms by which alcohol modulates the post burn hepatic response.

Keywords

Alcohol; burn; gut-liver axis; trauma

Introduction

Alcohol is the most abused substance in the US and the third leading cause of preventable death [1], much of which is associated with unintentional injury [2,3]. Binge drinking, defined as consuming five or more drinks on one occasion, is an increasingly prevalent form of intoxication [4] and is the characteristic pattern of drinking among patients presenting with traumatic injury, including burns [5]. Nearly 50% of patients admitted for burns have a positive blood alcohol content (BAC) and these patients have worse clinical outcomes than

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individuals who sustain similar injuries not under the influence [6,7,8]. Specifically, they are twice as likely to acquire an infection, require more surgical procedures and have a longer duration of stay in the ICU than their nonintoxicated counterparts [6,8,9]. As a result of these complications, burn patients with prior alcohol exposure have been identified as a patient population at high risk for death in the early stages post burn [10]. With 1 million burn injuries in the US each year, resulting in 40,000 hospitalizations [11], this represents a substantial burden of morbidity, mortality and socioeconomic cost that is worsened by alcohol abuse. Despite the established consequences, there are currently few differences in the treatment and management of burn patients with and without prior alcohol exposure. The increased morbidity exhibited by patients with pre-injury alcohol exposure may be due to an early increased inflammatory response and subsequent immune suppression [12,13], though the inciting cells and mechanisms responsible for these phenomena remain largely unknown.

As a responsive organ with metabolic, hormonal and immune functions, the liver is central to the physiologic response to burn injury and plays a pivotal role in post burn outcome [14]. This is highlighted by the close correlation between hepatic function and post burn prognosis as seen in a national sample of 31,338 adult burn patients [15]. Correspondingly, hepatic cirrhosis, often caused by chronic alcoholism, is a high premorbid contributor to death in the setting of severe burn (3). Given the comorbidities associated with chronic alcoholism, it is not surprising that clinical and animal studies demonstrate amplified liver damage when chronic alcohol exposure precedes thermal injury. In recent years, however, the prevalence of binge drinking has increased precipitously and now represents the majority of alcohol consumed in the US [4]. Due to its high association with injury in an otherwise healthy population, binge drinking may be the more clinically relevant mode of alcohol abuse in burn patients today [5,16]. Indeed, more recent studies suggest the majority of intoxicated burn patients are now binge drinkers not chronic alcoholics [6]. Animal studies also confirm using various doses and timing before injury that the presence of intoxication at the time of injury, even at a single dose, is the key factor in the ability of alcohol to worsen post burn outcome. Therefore we focus this review on the potential mechanisms of how alcohol, consumed acutely as a binge, affects the post burn hepatic response.

The total body surface area (TBSA) affected by a burn is a major factor in determining the severity of injury, with increased TBSA correlating to increased systemic inflammation [17]. In an animal model, substantial hepatic derangements were present after a 40% TBSA burn that were absent when reduced to 20% TBSA [18]. The authors concluded from this work that increasing the severity of injury does not lead to a simple dose-dependent response but rather qualitatively different responses, though this may also suggest an injury threshold beyond which an aberrant hepatic response occurs. Work from our lab and others demonstrate significant hepatic damage in a mouse model of 15–20% TBSA burn only when intoxication precedes the injury [19,20,21,22,23]. This may indicate that alcohol lowers the threshold for an impaired post burn hepatic response. Indeed, alcohol exposure and burn injury have many overlapping physiologic effects that work in a synergistic manner to cause hepatic derangement. While burn-induced liver dysfunction may last for years after the initial injury [24], we center this review on the short term response in hopes of better characterizing the early events that may predispose to the later hypermetabolic state. We summarize below potential mechanisms of alcohol's ability to worsen post burn outcome

through extrahepatic events, direct effects on the liver and alterations in signaling pathways before discussing existing treatment regimens.

Extrahepatic mechanisms

Catecholamines

Immediately after burn injury, clinical studies have demonstrated a massive release of catecholamines [25] that can have detrimental effects on the liver through direct and indirect etiologies [26]. Acute alcohol intake in young men with light to moderate drinking habits has also been shown to increase plasma catecholamine levels [27]. Furthermore, intoxicated trauma patients were found to have augmented adrenergic responses which effected injury outcomes [28], though important differences may exist between injury types and the pattern of alcohol consumption. Animal studies show that chronic alcohol intake upregulates α_2 -adrenoceptors in the liver which then mediates hepatic damage [29], though the effects of binge drinking remain unexplored. The downstream consequences of the post burn adrenergic response contribute to the hyperglycemia, ischemic injury, and cytokine production that promote hepatic damage and derangement as discussed below.

Hyperglycemia

In addition to the physiological effect of adrenaline on liver glycogenolysis [27], animal studies show that catecholamines directly induce endoplasmic reticulum (ER) stress in hepatocytes [30,31] leading to JNK-dependent inhibition of the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway after burn [32], thereby promoting insulin resistance [33]. The subsequent hyperglycemia is associated with increased mortality and infectious complications in pediatric burn patients [34] and a prospective analysis of 152 burn patients demonstrated found decreased rates of pneumonia, ventilator-associated pneumonia, and urinary tract infection infections with tight glycemic control [35]. Hyperglycemia also aggravates burn-induced liver inflammation via activating nuclear factor- κ B (NF- κ B) signaling in hepatocytes as demonstrated in a rat model [36]. Alcohol consumption can have paradoxical effects on plasma glucose levels depending on the setting. In the context of a burn, however, animal studies reveal that a single dose of alcohol (1.1g/kg) significantly increases plasma glucose over a burn alone suggesting intoxication exacerbates post burn hyperglycemia [37]. Furthermore, the increased plasma glucose after a single intoxication event in mice corresponds to greater post burn hepatic neutrophil infiltration and NF- κ B activation [22].

Intestinal Ischemia

Animal studies demonstrate catecholamine-mediated vasoconstriction of the splanchnic vasculature makes the intestines particularly susceptible to ischemic injury after burn [38]. Decreased cardiac output in the early phases post burn [39] worsens circulating blood flow, leading to intestinal damage and a loss of barrier function [40,41] in rodents. A single intoxication event with alcohol prior to a burn injury in mice enhances intestinal damage leading to greater dissociation of tight junction complexes in the intestinal epithelium [42,43,44] and resultant permeability [45,46] compared to either insult alone. The mechanism for alcohol's ability to exacerbate post burn intestinal damage may stem from its

action on the post burn hemodynamic response and tissue oxygen requirements. Recent evidence revealed that alcohol given as a single oral gavage (1.1 g/kg) potentiates post burn bradykinin signaling in mice, leading to greater extravasation of fluid from the vascular compartment [47]. This adds a degree of hypovolemia into a scenario in which organs supplied by the splanchnic vasculature are already at risk for ischemic injury [41]. Likewise, clinical data demonstrate intoxicated burn patients require more aggressive fluid resuscitation than do their non-intoxicated counterparts [6], also indicating a shift in fluid compartments. Choudhry et al. demonstrated that a BAC of 100mg/dl before burn injury in rats decreases blood flow and oxygen delivery to the intestines and liver [48]. Additionally, animal studies indicate that within 90 minutes of drinking, a single dose of alcohol increases oxygen demand in the liver by 48% [49] with oxygen consumption rate doubling in the liver after 2.5 hours of alcohol exposure [50]. While this does not rule out the influence of other effects of alcohol in post burn remote organ ischemia, it points towards the ability of alcohol to enhance post burn third spacing of fluid while creating a hypermetabolic state, widening the disparity between oxygen delivery and requirement in the intestines and liver.

The gut-liver axis

The high baseline bacterial content of the intestines represents an enormous potential reservoir for systemic infections and sepsis after injury [51,52,53]. Trauma, such as a burn, causes a disruption in normal peristalsis leading to bacterial overgrowth in the intestine and this bacterial load is even greater when alcohol ingestion precedes the injury in rats [46]. While the exact mechanism by which alcohol enhances post burn bacterial growth in the intestine remains unknown, experimental evidence points to modulation of hormonal control [54], shifts in intestinal flora population [55], and the promotion of adynamic ileus [56] as possible causes, as reviewed elsewhere [57]. Animal models report that after disruption of intestinal barrier integrity, bacteria and bacterial products such as lipopolysaccharide (LPS) translocate from the lumen of the intestine into the lymphatic [58,59] and portal [60] systems. The number of bacteria found in the mesenteric lymph nodes is directly proportional to the degree of increased bacterial growth in the intestines after injury [46], suggesting important roles for both the luminal bacterial burden and the degree of intestinal permeability. As both bioload and permeability are exacerbated with the combined injury it is befitting that many animal studies report up to 10 times greater amounts of bacterial translocation when alcohol precedes a burn than after a burn alone [19,42,43,45,47,61]. Much of the translocated bacteria and LPS will pass through the liver, which receives 75% of its blood supply from the portal system [14] and is therefore sensitive to portal system hemodynamic changes and content. As the largest reticular endothelial system organ and the first to encounter portal blood, the liver plays an important role in clearing live intestinal bacteria and LPS. The relationship between intestinal microbiota and the liver is known as the “gut-liver axis” and is proposed to regulate a myriad of human diseases such as nonalcoholic fatty liver disease, primary sclerosing cholangitis, celiac disease, and others [62,63,64,65,66]. This interaction is prominent after burn injury as seen in autopsies of burn patients where the amount of bacterial translocation correlates with the degree of steatosis [67]. We have previously reported that in mice, antecedent ethanol exposure (single dose of 1.1 g/kg) potentiates post-burn intestinal damage [19,42,61], hepatic steatosis [23,37] and IL-6 production [19,21,61,68] compared to either intoxication or a burn alone. Furthermore,

limiting crosstalk between the gut and liver after injury, either through restoration of tight junction complexes or prophylactic sterilization of the gut, attenuated hepatic derangements to the level of a burn alone [20]. This suggests that the increased hepatic damage seen when intoxication precedes a burn stems from the ability of alcohol to alter the gut-liver axis (Figure 1). In addition to increasing the delivery of LPS into the portal system after burn, alcohol also modifies the post burn hepatic response through its influence on Kupffer cells in the liver.

Intrahepatic mechanisms

Kupffer cells

Representing the body's largest tissue-fixed macrophage population, Kupffer cells continuously sample portal blood for foreign antigen and orchestrate the hepatic response to injury [69]. Kupffer cells can become activated when LPS binds to Toll-like receptor 4 (TLR4), an interaction dependent on its co-receptor, CD14 [70] and enhanced in the presence of LPS binding protein (LBP) [71]. TLR4 signaling can result in a variety of downstream signaling pathways, many of which result in pro-inflammatory cytokine production [72,73]. At low levels, cytokines, such as interleukin-6 (IL-6), are beneficial to hepatocyte survival, but exposure to levels above an acceptable threshold or for a prolonged duration can be detrimental, as seen in a mouse model [74]. Kupffer cells protect themselves from overstimulation by expressing low levels of CD14 relative to other monocytes [75]. After burn injury, Kupffer cells fulfil the role of clearing gut-derived bacteria and LPS from the portal system while avoiding over-stimulation. The importance of maintaining homeostatic Kupffer cell function in the injury setting was nicely demonstrated in a model of systemic inflammation where Kupffer cell depletion increased gut-origin septicemia but attenuated toxic symptoms associated with macrophage hyperactivity [76]. Animals studies have shown that hyperactive Kupffer cells can cause hepatic damage after many types of injury, including hemorrhagic pancreatitis [77], trauma and sepsis [78], as well as burns [79]. Burn injury causes a transient induction of CD14 in Kupffer cells, leading to enhanced TLR4 signaling and cytokine production in mice [80]. This is supported by work with CD14 knockout mice and TLR4 defective animals implicating LPS as the initial inducing agent associated with acute phase responses (APR) in the liver after burn [81]. As a part of the APR, hepatocytes increase production of LBP leading to even greater LPS binding to Kupffer cell TLR4 in rats [82]. Over-stimulated Kupffer cells contribute not only to hepatic damage and steatosis [83], but also to systemic levels of potentially damaging pro-inflammatory cytokines. It is of great clinical importance, therefore, that Kupffer cell sensitivity to post-burn LPS is significantly increased when alcohol intoxication precedes burn injury as seen in a mouse model (Chen, in preparation).

Alcohol has a well described and dynamic influence on the sensitivity of macrophages to LPS, with paradoxical effects depending on the duration of exposure [84]. After a single dose of alcohol (4g/kg), rat Kupffer cells display a brief initial decrease in LPS sensitivity that is reciprocally increased by 24 hours, correlating to a 5-fold increase in CD14 expression [85]. This is supported by studies using a mouse model of acute intoxication where the activity of interleukin-1 receptor-associated kinase (IRAK), a protein downstream

of TLR4, was increased 21 hours after a single dose of alcohol [86]. In contrast to chronic alcoholics, binge drinkers experience only a minor and transient spike of LPS in portal blood [49] and therefore increased Kupffer cell CD14 has limited clinical significance. In the context of a burn however, alcohol-exposed Kupffer cells have abundant and prolonged LPS exposure leading to aberrant increases in both the co-receptor and ligand for TLR4 signaling.

Recent work from our laboratory demonstrated that a single dose of alcohol (1.1 g/kg) potentiated post-burn hepatic damage via Kupffer cell derangement in mice (Chen et al, in preparation). Specifically, Kupffer cells isolated from mice exposed to both alcohol and burn were sensitized to LPS and produced significantly greater amounts of IL-6 in a p38-dependent manner. A member of the mitogen activated protein kinase (MAPK) family, p38 has a well-established role in post burn remote organ damage [87,88,89,90,91], is altered by intoxication [92,93] and plays a role in enhanced TLR4 reactivity following injury [94]. Antecedent depletion of Kupffer cells or global p38 inhibition after intoxication and burn injury in mice attenuated hepatic and pulmonary damage to a similar extent suggesting a prominent role for Kupffer cell p38 (Chen et al, in preparation). Furthermore, both the absence of Kupffer cells and p38 inhibition decreased hepatic damage to a level seen after a burn alone, again pointing to alcohol's ability to alter the gut-liver axis as a key mechanism for worsening post burn outcome.

Cytokine production

A paramount consequence of hyperactive Kupffer cells is the excessive release of cytokines. While beneficial at appropriate levels, aberrant cytokine release is a hallmark of the Systemic Inflammatory Response Syndrome (SIRS) and a common complication after burn [95]. The multifunctional cytokine IL-6 is particularly elevated in thermally injured patients [96,97] and correlates to mortality risk after injury [23,96,98,99]. In animal models of intoxication and burn, increased systemic levels of IL-6 are found relative to either alcohol or burn alone [19,21,23] with the highest concentrations found in the liver [21]. Furthermore, systemic IL-6 decreases in the absence of Kupffer cells after intoxication and burn (Chen et al, in preparation) and other models of trauma support the idea that Kupffer cells may be the systemic source of IL-6 after injury [100]. Identifying the systemic source of IL-6 may be crucial to successful treatment of intoxicated burn patients, as recent evidence in animal models revealed excessive IL-6 is responsible for amplified pulmonary inflammation [101] and gut permeability [42,61] in this combined injury setting. These findings do not rule out the influence of other cytokines and signaling pathways which are altered by intoxication and burn, some of which are depicted in Figure 2. However, they implicate alterations in the gut-liver axis, specifically in Kupffer cell IL-6 production, as key mechanisms for the ability of alcohol to worsen post burn hepatic damage and overall outcome.

Oxidative Stress

Another factor contributing to hepatic cytokine production after alcohol or burn is oxidative stress. Hepatic aldehyde dehydrogenase (ALDH) activity is reduced after a burn injury in rats allowing for the accumulation of toxic aldehydes produced by lipid peroxidation [102].

The generated reactive oxygen species (ROS) can directly damage intracellular proteins and lead to activation of multiple inflammatory signaling pathways including MAPKs and NF- κ B [103,104]. In addition, antioxidant enzymes in rat livers are down regulated within 24 hours after a burn [105], increasing the susceptibility of the liver to oxidative stress. Alcohol directly stimulates the release of ROS in Kupffer cells within 3 hours of intoxication as seen in a study of a rat model [106]. Other animal studies implicate this ethanol-induced oxidative stress as a key regulator of Kupffer cell LPS sensitivity after a single dose of alcohol (5g/kg) [107,108]. Furthermore, a byproduct of alcohol metabolism, acetaldehyde, is an example of the aforementioned toxic aldehydes normally cleared by ALDH [102]. Not surprisingly, animal studies revealed alcohol increased post-burn hepatic oxidative stress and IL-6 production in a dose dependent manner [23].

Steatosis

The accumulation of hepatic triglycerides, also known as steatosis, is a common finding after burn injury with the clinical significance depending on the etiology and severity [109,110]. Animal and clinical studies demonstrate that post burn β -adrenergic peripheral lipolysis increases the delivery of free fatty acids to the liver [111,112,113], which has concomitantly decreased ability for very low-density lipoprotein (VLDL)-triglyceride export [113]. The resulting hepatic fatty infiltration is associated with increased incidence of sepsis and mortality in pediatric burn patients [67], highlighting the importance of organ integrity. Steatosis is also commonly caused by alcohol consumption [114] and the degree of steatosis is substantially increased in mice with the combination of alcohol and burn over either insult alone [20,22]. Animal studies show that alcohol metabolism increases the ratio of NADH:NAD⁺ which then inhibits β -oxidation of fatty acids while increasing the rate of their esterification [115], leading to excessive triglyceride storage. Uncontrolled hyperglycemia [116], oxidative stress [117], LPS signaling [118] and Kupffer cell cytokine secretion [83] can also contribute to steatosis development. As these factors are all influenced by both alcohol and burn (Figure 3), they may represent potential mechanisms by which intoxication potentiates post burn steatosis.

Epigenetic Modification

Epigenetic regulation is a key underlying mechanism, driving many of the aberrant pathophysiological responses to alcohol consumption in the liver. In broad terms, epigenetics describes modifications to DNA, RNA, or protein resulting in altered functionality or regulation of these molecules, without altering the primary genetic sequence. Epigenetic regulation includes DNA methylation, covalent modification of histone tails, and non-coding RNAs. Age, environment, injury, disease, drugs, and toxins, like alcohol, directly influence epigenetics [119]. While the epigenetic consequences of alcohol intoxication have been studied extensively, to date, few studies have characterized the role epigenetics serves in regulating the hepatic response to burn and the combined insult remains unexplored.

Transcriptional regulation of the signaling pathways and molecular mechanisms regulating acute phase and inflammatory responses to burn injury in the liver are well described and highly complex, yet the underlying contribution of epigenetics and chromatin configuration

is generally unknown. Using a non-lethal 18% TBSA burn injury model in mice, Jeong et al. measured levels of histone covalent modifications and histone variants in liver homogenates at 3, 6, 24, and 72 hours post burn [120]. They observed modest increases in histone H4 acetylation at day 1, and marked increases in global histone H3 acetylation, di-methylation, and phosphorylation at 3 days post burn, indicating burn injury causes immediate and long-lasting alterations in histone modifications in the liver. They also demonstrated up-regulation of the variant H3-D at early time-points, suggesting it likely plays a role in chromatin assembly and gene activation following burn-mediated stress signals. Immediate induction of the replacement linker histone variant, histone H1(o), was also observed [120]. Others previously reported hormone-dependent regulation of H1(o) transcription [121], raising the possibility that post burn glucocorticoid fluctuation was responsible for the observed enhanced H1(o) levels.

The effect of alcohol consumption on epigenetic alteration in the liver is likely dependent on both the amount of alcohol consumed as well as drinking pattern. While the vast majority of *in vivo* studies have focused on chronic alcoholism, epigenetic changes in the liver have been observed in a rat model of acute binge alcohol exposure, where a single dose of ethanol diluted in sterile water (32% (v/v), 6g/kg) was used. In this study, robust increases in histone acetylation were reported in the liver 12 hours following exposure [122], demonstrating that a single exposure to alcohol can have long-lasting epigenetic consequences. Alcohol metabolism skews substrate and cofactor availability for various enzymatic reactions. For example, alcohol consumption alters methionine metabolism, resulting in reduced levels of S-adenosylmethionine (SAM), thereby diminishing the methyl substrate for DNA and histone methylation reactions [123,124,125]. This effect is amplified by decreased glutathione levels and results in regional and global DNA hypomethylation [126,127]. Ethanol metabolism also dramatically increases acetyl-CoA production, thus elevating the amount of substrate available for histone acetylation by histone acetyltransferases (HATs) [128]. The shift in redox state caused by alcohol metabolism leads to inhibition of the redox-sensitive histone deacetylase (HDAC), Sirtuin-1 (Sirt1), while enhancing the activity of the HAT, p300, thereby increasing histone acetylation patterns in rats [129,130]. Recent work from our laboratory and others, suggests HDACs are also modified by burn, making them an interesting topic of exploration in combined burn injury and alcohol intoxication models.

Clinical Management

The clinical and experimental evidence above suggests that the presence of alcohol intoxication at the time of injury lowers the threshold for post burn hepatic damage by altering the gut-liver axis. While targeting therapeutic approaches at restoring gut-liver interactions may warrant further investigation, there are currently few differences in the treatment of burn patients with and without alcohol on board, despite the established consequences. We summarize in the following section clinical management strategies used to treat post burn hepatic derangement and discuss any known effects of that treatment in the presence of acute or chronic alcohol consumption.

Non-selective β -blockade

The non-specific β_1 , β_2 adrenergic receptor antagonist propranolol has been widely studied in the management of hypermetabolism following severe burn in pediatric patients. Propranolol works in a dose-dependent manner, with administration ranging from 1–4 mg/kg/day within 10 days to reduce myocardial oxygen requirements and heart rate by 10–20%, without affecting oxygen delivery or resting energy expenditure [131,132,133,134]. Propranolol administration in hyperglycemic burn patients reduces total insulin requirements and attenuates ER stress [32,133]. Propranolol has also been shown to inhibit mobilization of free fatty acids from adipose tissue via β_2 adrenergic receptors, while concurrently increasing the efficiency of hepatic fatty acid excretion, resulting in decreased steatosis [135,136,137]. Poly ADP-ribose polymerase (PARP) activation, an enzyme promoting cellular skeletal muscle necrosis, is triggered following severe burn injury [138]. Not only is PARP activity lower following propranolol administration, but in one randomized controlled trial, children with burns over 40% TBSA who received an average daily dose of 2–6 mg/kg/day exhibited an increase of 82% net protein balance above baseline compared to a 27% decrease in the non-treatment arm of the study [137,138]. Safe administration of propranolol can be continued for up to 12 months after initiation and has been associated with long-term decreases in hepatomegaly, maintenance of peripheral fat mass and no change in central fat mass [139].

Evidence for non-selective β -blockade in the setting of acute and chronic alcohol consumption is limited. Carvedilol, another non-selective β -receptor antagonist, has been used in an animal model of alcoholic fatty liver disease and was found to attenuate oxidative stresses caused by the hypermetabolic state [140]. Given that non-selective beta-blockade appears to affect ER stress in both burn and alcohol exposures, administration in the setting of combined injury should also help prevent associated oxidative damage and the development of steatosis.

Non-selective β -blockade appears to be a promising therapeutic in blunting the hypermetabolic response to burn injury alone or when augmented by alcohol exposure, and has been found to be safe in the setting of concurrent infection and sepsis [141]. However, the majority of data supporting its use is in the pediatric or adolescent burn population. Further information is needed prior to generalizing its use to severely burned adults.

Insulin

The catabolic response associated with severe burn results in hyperglycemia and loss of lean body mass (LBM), both of which increase morbidity and mortality [142]. Insulin administration and glycemic control, even at submaximal dosing, have been shown to promote protein synthesis in critically ill burn patients [143]. More intensive insulin administration, with target blood glucose ≤ 120 mg/dL, in children with burns greater than 40% improves mitochondrial oxidative capacity and decreases resting energy expenditure [144]. More aggressive control results in suppression of hepatic glucose release, lower systemic glucose levels, decreased incidence of urinary tract infections and mortality when compared to conventional goals of blood glucose <215 mg/dL [145]. Animal models have demonstrated that insulin therapy decreases hepatic ER stress, attenuates expression of pro-

inflammatory mediators such as IL-6, monocyte chemoattractant protein-1 (MCP-1), and cytokine-induced neutrophil chemoattractant-1 (CINC-1), and reverses structural and functional changes in hepatocyte mitochondria [146].

Chronic alcohol consumption also produces steatosis and promotes hepatic insulin resistance, oxidative stress and injury to ER and mitochondria. The resulting generation of ceramides, a family of waxy lipid molecules, contribute to increased insulin resistance by interfering with critical phosphorylation events and activating pro-inflammatory cytokines [147,148]. Alcohol induced insulin resistance in animal models has been linked to impairment of the hypothalamus in suppression of hepatic glucose synthesis and lipolysis [149]. Insulin administration is indicated in the setting of insulin resistance secondary to chronic alcoholism.

There is some concern that insulin induced release of free fatty acids and glucose delivery would predispose patients to delivery of lipid to the liver with subsequent steatosis. However, studies utilizing continuous insulin administration do not show this phenomenon [150,151]. In the acute setting, an animal model of combined burn and alcohol exposure showed attenuated steatosis following insulin administration [22]. Careful monitoring is necessary to avoid hypoglycemia in the setting of aggressive insulin therapy. According to the Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE-SUGAR) study in 2009, intensive glucose control (<180 mg/dL) in critically ill patients is associated with decreased morbidity and mortality when compared to more (81–109 mg/dL) or less (>180 mg/dL) intensive therapies [152]. While precise guidelines concerning insulin administration in patients with combined injury have not been established, a goal blood sugar range avoiding hypoglycemia is safest.

Metformin and Fenofibrate

Other agents that blunt the hypermetabolic state following burn and may be of benefit in the setting of hepatic injury include metformin and fenofibrate. Metformin has been shown to attenuate hyperglycemia in severely burned patients through decreased rates of endogenous glucose production, increased rates of glucose clearance and increased glucose oxidation without affecting arterial insulin concentrations. These patients also exhibited increases in muscle synthesis and displayed less negative net balances of alanine and phenylalanine [153]. Metformin has not, however, been shown to ameliorate hepatic ER stress in animal models, a benefit seen with insulin therapy [154]. Fenofibrate improves insulin mediated glucose disposal and decreases hepatic glucose release in severely burned children [155].

Metformin and fenofibrate have both been shown to improve hepatotoxicity following chronic alcohol exposure in animals [156,157,158,159]. In contrast, the effect of these agents on the liver of subjects exposed to alcohol on an acute or binge basis has not been investigated. A small human study with fenofibrate in individuals with chronic alcohol exposures showed significant decreases in liver function tests following administration [156]. The potential for severe metabolic acidosis following metformin administration, and rhabdomyolysis with fenofibrate administration make these agents less attractive options in the setting severe combined injury, which already predisposes patients to acidosis and muscle breakdown.

Anabolic Steroids

The use of anabolic steroids such as oxandrolone is supported in severe burn injury in both children and adults. Oxandrolone administered at 0.1 mg/kg twice daily has been shown to enhance protein synthesis and upregulate anabolic genes in acute pediatric burn patients [160], and similar benefits have also been demonstrated in adult patients [161]. Long-term benefits include increased bone mineral density and LBM up to 12 months post burn [161]. Patients who received therapy for one year post burn injury have shown benefits 5 years later with few deleterious side effects [162]. Testosterone is chronically decreased in male burn victims and therefore replacement may be indicated [163]. Like oxandrolone, testosterone supplementation utilizes intracellular amino acids derived from muscle breakdown, increasing protein synthesis [164]. Restoring serum testosterone in severely burned males significantly decreases breakdown of muscle and improves protein synthesis [165]. Anabolic steroids may be beneficial in reversing the catabolic state associated with severe burn, alcohol and subsequent hepatic injury.

Growth Hormones

Both human growth hormone (GH) and insulin-like growth factor I (IGF-I) are significantly reduced following severe thermal exposures and remain at subnormal levels even 3 years post injury [166]. Administration of recombinant human growth hormone (rhGH) improves growth and muscle mass following burn injury. Additionally, rhGH ameliorates immune function, improves wound healing, and blunts the hypermetabolic response to major stress [167,168,169,170,171], with benefits apparent 1 year after discontinuation of the drug [168,172]. Patients treated with rhGH for extended periods experienced greater weight gain, height, improved LBM, and higher bone mineral content [173]. When similar trials were performed in adults, rhGH increased mortality in severely burned patients secondary to hyperglycemia when administered at doses greater than 0.05 mg/kg/day [173]. Treatment with IGF-I alone, a mediator of growth hormone, have been shown to improve protein metabolism, although there are reports of hypoglycemic episodes [112,174]. More recent studies have shown that concomitant use of rhGH and propranolol further attenuates hypermetabolism, reduces peripheral lipolysis, and decreases inflammation, while avoiding the problematic effects of using rhGH alone [112,141]. Reduction of catabolism and peripheral lipolysis would decrease free fatty acid delivery to the liver and could theoretically improve steatosis. Interestingly, expression of IGF-I and its receptor in the brains of human alcoholics is decreased (19). This could imply a role for the administration of IGF-I in improving anabolic function following combined burn and alcohol exposure.

Nutrition

Early enteral support reduces the hypermetabolic state caused by severe burn injury and improves survival. Nutrition should consist of appropriate amounts of carbohydrate, fat and protein, with supplementation of conditionally essential amino acids, antioxidants, vitamins and trace elements [175,176,177]. Carbohydrate serves as the principle source of calories in order to maintain LBM in burn patients, but should not exceed 7 g/kg/day, the maximal rate at which glucose assimilates in adults [177,178]. Protein provided at 1.5–2.5 g/kg/day is estimated to be adequate for counteracting catabolism in adults, while 2.5–4.5 g/kg/day in

should be sufficient for children [177]. Supplementation of with the amino acid glutamine (0.35–0.57 g/kg of body weight/d) either intravenously or via the gastrointestinal tract is associated with decreased infection rates, improved visceral protein levels, shortened length of stay, and reduced mortality [179,180]. Dietary fat should be limited as much as possible in burn patients with hepatic injuries due to the possibility of fatty infiltration. Omega-3 fatty acids have anti-inflammatory properties, therefore they are recommended by some reports in burns >30% TBSA [177,181]. Relevant vitamin deficiencies involved with hepatic metabolism in burn include vitamins A, E, and B [182,183,184]. Vitamin C, a free radical scavenger, has been suggested to be beneficial in terms of reducing microvascular permeability and may be of value in limiting the volume needed for fluid resuscitation [185]. Zinc is a trace element that is necessary for normal liver function and its deficiency has been associated with both acute and chronic liver disease [186]. Animal studies have shown that zinc deficiency associated with burn injury results in oxidative stress and mitochondrial damage and contributes to the development of insulin resistance [187,188]. Early repletion of zinc in patients with hepatic injury due to burn and alcohol exposure may limit the extent of metabolic disturbance.

HDAC inhibition

HDACs have been identified as novel targets for dampening the cytokine storm following burn and HDAC inhibitor treatments have favorable outcomes in several preclinical burn injury models. In rats, addition of the HDAC inhibitor, butyrate, to resuscitation fluid decreased systemic and lung pro-inflammatory cytokine levels and influenced several pulmonary parameters, including improved pulmonary histological changes, diminished neutrophil activation and reduced edema, compared to burned rats without butyrate supplementation [189]. Additionally, the HDAC inhibitor valproic acid (VPA), was beneficial in lethal burn models in rats and dogs. In rats, VPA treatment improved survival and gut barrier dysfunction and attenuated brain and cardiac injury [190,191]. In dogs, VPA improved survival, hemodynamics, and intestinal perfusion, and reduced circulating levels of the pro-inflammatory cytokine, TNF- α . Furthermore, blood levels of ALT, creatinine, MB isoenzyme of creatine kinase (CK-MB), and lactic acid were much lower in VPA-treated dogs, demonstrating overall improved organ function [192]. The effectiveness of HDAC inhibition in attenuating hepatic complications after burn alone or in the context of combined burn and alcohol intoxication is currently unknown though may represent a worthwhile avenue of future investigation.

Conclusions

Intoxication plays a detrimental role in traumatic injury as both a causative agent and complicating factor in recovery. This is dramatically observed in burns where high prevalence and established consequences warrant further investigation into the mechanisms by which alcohol worsens the post burn response. Furthermore, the very presence of alcohol, regardless of dependence or pre-existing hepatic sequelae, potentiates post burn hepatic damage. Clinical and animal studies suggest alcohol alters the post burn gut-liver axis in the early phases after injury which may lower the threshold for longer term hepatic derangement and hypermetabolism.

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Figure 1. Overlapping responses to burn injury and alcohol exposure alter the gut-liver axis. interleukin-6 (IL-6), Kupffer cells (KC), lipopolysaccharide (LPS), tumor necrosis factor (TNF)

Figure 2.

Potential signaling pathway alterations in Kupffer cells after alcohol and/or burn injury. activator protein-1 (AP-1), alpha-2a adrenoceptor (α_{2A} -AR), cluster of differentiation 14 (CD14), inhibitor of kappa B (I κ B), interleukin-1 receptor-associated kinase (IRAK), interleukin-6 (IL-6), endoplasmic reticulum (ER), lipopolysaccharide (LPS), LPS binding protein (LBP), nicotinamide adenine dinucleotide phosphate-oxidase (NADPH oxidase), nuclear factor kappa B (NF- κ B), Toll-like Receptor 4 (TLR4), tumor necrosis factor (TNF). Numbers in figure 2 denote associated references. *Chen et al, in preparation

Figure 3.

Mechanisms of steatosis development after burn injury and/or alcohol intoxication. Acetyl coenzyme A (acetyl CoA), glycerol 3-phosphate (glycerol 3-p), nicotinamide adenine dinucleotide (NAD), triglyceride (TG), very low-density lipoprotein (VLDL)