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Fenofibrate Does Not Affect Burn-Induced Hepatic Endoplasmic Reticulum Stress

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Abstract

Background—Burn injury causes major metabolic derangements such as hypermetabolism, hyperlipidemia, and insulin resistance and is associated with liver damage, hepatomegaly, and hepatic endoplasmic reticulum (ER) stress. Although the physiological consequences of such derangements have been delineated, the underlying molecular mechanisms remain unknown. Previously, it was shown that fenofibrate improves patient outcome by attenuating post-burn stress responses.

Methods—Fenofibrate, a peroxisome proliferator-activated receptor (PPAR)- agonist, regulates liver lipid metabolism and has been used to treat hypertriglyceridemia and hypercholesterolemia for many years. The aim of the present study is to determine the effects of fenofibrate on burn-induced hepatic morphologic and metabolic changes. We randomized rats to sham, burn injury, and burn injury plus fenofibrate. Animals were sacrificed and livers were assessed at 24 or 48 hours post-burn.

Results—Burn injury decreased albumin and increased alanine transaminase ($p = 0.1$ vs. sham), indicating liver injury. Fenofibrate administration did not restore albumin or decrease alanine transaminase. In addition, ER stress was significantly increased after burn injury both with and without fenofibrate ($p < 0.05$ vs. sham). Burn injury increased fatty acid metabolism gene expression ($p < 0.05$ vs. sham), downstream of PPAR. Fenofibrate treatment increased fatty acid metabolism further, which reduced post-burn hepatic steatosis (burn vs. sham $p < 0.05$, burn +fenofibrate vs. sham not significant).

Conclusions—Fenofibrate did not alleviate thermal injury induced hepatic ER stress and dysfunction but reduced hepatic steatosis by modulating hepatic genes related to fat metabolism.

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Keywords

burn; liver metabolism; fenofibrate; steatosis; endoplasmic reticulum stress; apoptosis

1. INTRODUCTION

Severe burn injury causes hepatic metabolic and structural changes resulting in major metabolic derangements such as hypermetabolism, insulin resistance, and lipolysis, which are closely linked with each other [1–4]. It is well established that burn injury induces hepatic acute phase responses and decreases albumin production and that these conditions persist over a prolonged period of time [1–5]. In addition, burn-induced upregulation of hepatic ER stress [3, 4, 6–8] leads to hepatic metabolic alterations such as insulin resistance and lipolysis [2, 9–13], but furthermore to apoptosis that can be detrimental to recovery [4, 5, 7]. Our group hypothesizes that attenuating these processes may not only improve hepatic function but also hepatic glucose and lipid metabolism and subsequently improve post-burn morbidity and mortality.

An agent that has been shown to affect lipid metabolism as well as glucose metabolism is fenofibrate. Recently, it has been shown that fenofibrate improves patient outcome by attenuating post-burn stress responses such as insulin resistance [14, 15]. Fenofibrate is a peroxisome proliferator-activated receptor (PPAR) agonist which regulates liver lipid metabolism and improves insulin resistance, and is used clinically to reduce plasma cholesterol and triglyceride levels [16]. There are numerous clinical, in vivo, and in vitro studies concerning fenofibrate including “The Fenofibrate Intervention and Event Lowering in Diabetes” (FIELD) trial that consisted of nearly 10,000 patients with type II diabetes [17]. In a study with Zucker rats, fenofibrate treatment led to a ~60% reduction in liver triglyceride content after 14 weeks and approximately 20% reduction after 21 weeks [18]. In another study, fenofibrate treatment of mice with hepatic steatosis led to a ~80% reduction in liver triglyceride content after 15 weeks [19]. However, in both cases, the mechanism of action appears to be activation of expression of genes involved in fatty acid turnover.

As fenofibrate appears to be an ideal agent to alleviate post-burn glucose and lipid metabolism, the aim of our present study was to determine the effects of fenofibrate in post-burn rat livers. We hypothesize that burn causes hepatic lipogenesis, which leads to hepatic steatosis, resulting in increased insulin resistance and increased morbidity; and that fenofibrate prevents poor outcomes by preventing lipogenesis.

2. MATERIALS AND METHODS

Animals and treatments

All procedures were in accordance with current NIH guidelines and were approved by the University of Texas Medical Branch Institutional Animal Care and Use Committee. All animals were housed in wire bottom cages with a 12-hour light-dark cycle and received food and water *ad libitum*.

A well-established method [20] was used to induce a 60% total body surface area (TBSA) scald burn in adult male Sprague-Dawley rats (approximately 350 g). Rats received analgesia (Buprenorphine, 0.05 mg/kg, intramuscular) and were anesthetized with Ketamine-Xylazine mixture (40 mg/kg and 5 mg/kg, respectively, intraperitoneally) prior to burn. Areas to receive the scald burn were shaved. The rats were then secured in a protective mold and the exposed skin was immersed in 96–100°C water (10 seconds back, 1.5 second front) to induce third-degree burn. After receiving thermal injury, rats were resuscitated with

Ringer's Lactate (60 ml/kg intraperitoneally). Analgesia was administered every 12 hours. Sham animals received the same treatment except for the scald burn. Fenofibrate (450 mg/kg, po; Sigma, St. Louis, MO) was administered immediately post-burn, every 12 hours. Animals (n=8–10 per group per time point) were sacrificed at 24 or 48 hours post-burn, and livers were rapidly removed, frozen, and stored in -80°C until further processing.

RNA Isolation and Gene Expression Analysis

Total RNA was extracted from the livers using RNeasy Mini Kit (Qiagen) and was reverse transcribed using High Capacity cDNA Reverse Transcription Kit (Applied Biosystems) following the manufacturers' instructions. Quantitative real-time PCR was performed on the ABI PRISM 7000 Sequence Detection System with SYBR Green PCR Master Mix (Applied Biosystems). 18S rRNA was used as housekeeping gene to normalize expression. ER stress markers CCAAT/enhancer-binding protein homologous protein (Chop), heat shock protein 5 (Bip), DnaJ (Hsp40) homolog, subfamily B, member 9 (Dnajb9), protein disulfide isomerase family A, member 3 (Pdia3), and X-box binding protein 1 spliced (Xbp1s), and PPAR target genes carnitine palmitoyltransferase 1 (Cpt1), acyl-CoA oxidase (AOX), fatty acid transporter (CD36), fatty acid synthase (FAS) and stearoyl-CoA desaturase 1 (SCD1) were assessed. Synthesis of albumin in the liver was also measured. PCR primer sequences are available upon request.

Liver Injury Measurement

Alanine Transaminase (ALT) activity levels were determined in rat livers using enzymatic kits (Cayman Chemical). Activity was normalized to protein concentration measured by BCA Assay (Thermo Scientific) and expressed relative to sham levels.

Liver Triglyceride Content

Liver triglyceride content was measured using a saponification method described by Salmon and Flatt [21]. Briefly, livers were saponified with ethanolic KOH to hydrolyze the triglyceride and neutralized with MgCl_2 . Glycerol produced in this process was measured with Free Glycerol Reagent (Sigma, St. Louis, MO).

Statistics

All data are presented as the mean $\pm$ the standard error of the mean. Statistical significance was examined with one-way ANOVA. All data were analyzed using GraphPad Prism software.

3. RESULTS

3.1 Hepatic structure and function

To determine the effects of fenofibrate on liver function, we measured alanine aminotransferase (ALT) and albumin levels (Figure 1). Hepatic ALT levels were increased with burn injury ($p < 0.05$ at 24 hours and $p = 0.1$ at 48 hours in burn vs. sham) and this increase was not ameliorated by fenofibrate administration. Albumin mRNA levels decreased in burn livers with or without fenofibrate. These results indicate liver damage with burn injury and that fenofibrate does not alleviate this injury.

3.2 Hepatic ER stress

One of the major hallmarks of burn injury is hepatic ER stress. Our data confirm previous reports of increased hepatic ER stress with burn injury [22–24]. In the current study, we analyzed genes that are downstream of the three branches of ER stress transducers, ATF6, PERK, and IRE1. These three molecules are transmembrane proteins that sense or monitor

misfolded proteins in the ER, and the accumulation of these misfolded proteins lead to ER stress. Downstream genes include Chop, Bip, Dnajb8, Pdia3, and Xbp1s (Figure 2). Chop is a pro-apoptotic gene that is downstream of PERK. Bip, Dnajb9, and Pdia3 are ER chaperones whose expressions are induced by the spliced variant of Xbp1s, a gene activated downstream of ATF6 and IRE1. At both 24 and 48 hours post-burn, we observed a marked increase of ER stress genes in burn (black bars, $p < 0.05$ vs. sham) and a further increase with fenofibrate treatment (gray bars, $p < 0.05$ vs. sham) suggesting that PPAR activation does not diminish ER stress gene expression.

Interestingly, we found that fenofibrate increases glucose transport. Glucose transporters are downstream of PPAR and are involved in hepatic glucose flux. Gene expression of glucose transporters, Glut1 and Glut4, were measured at 24 and 48 hours post-burn, and were found significantly increased (Figure 5).

3.3 Hepatic fatty acid metabolism

PPAR agonists are known to promote fatty acid uptake, utilization, and catabolism by upregulating genes involved in fatty acid transport and β -oxidation. We hypothesized that fenofibrate would increase the expression of several key mediators of fatty acid metabolism. In agreement with previous studies that report hypermetabolism with burn injury, we observed a 3- to 35-fold increase in gene expression with burn injury (black bars, $p < 0.05$ vs. sham, Figure 3). These expressions were almost doubled with the fenofibrate administration (gray bars, $p < 0.05$ vs. sham). This indicates that the burn itself did not induce fatty-acid metabolism gene expression to maximum capacity such that fenofibrate would not have any effect, and that there is perhaps a downstream physiological or morphological effect due to this change.

3.4 Hepatic triglyceride content

Since fatty acid metabolism was upregulated in burn livers treated with fenofibrate, we investigated its effect by measuring fat content (Figure 4). At 24 hours post-burn, there were no significant changes in triglyceride content with burn or with fenofibrate. However, at 48 hours post-burn, there was a significant increase in liver triglyceride content, indicating hepatic steatosis with burn ($p < 0.05$ vs. sham). This increase was normalized with fenofibrate administration ($p < 0.05$), indicating that fenofibrate alters post-burn fat metabolism.

4. DISCUSSION

This study examines the effects of PPAR agonist fenofibrate on hepatic hypermetabolism in the setting of a burn injury. Although there are several reports indicating the beneficial effects of fenofibrate in burn patients [14, 15, 25] such as improved insulin sensitivity and mitochondrial function, there are no mechanistic studies specifically regarding liver metabolism. The purpose of our current study was 3-fold to determine: 1) whether fenofibrate ameliorates burn induced damages such as hepatic dysfunction and ER stress, 2) whether burn with and without fenofibrate changes hepatic fatty acid metabolic gene expression, and 3) if so, how these changes may influence liver pathophysiology.

We tested the extent of liver injury by determining hepatic ALT and albumin levels. ALT is a liver enzyme commonly measured to detect liver dysfunction, as it increases with damage. Albumin, a protein synthesized in the liver, decreases with liver damage or shock. In burn injury, both ALT and albumin levels are altered significantly indicating impaired liver function and structural damage [2, 4, 5, 7, 26] and this may determine the outcome or survival. Confirming previous studies we found that burn induced hepatic damage by

increasing ALT and decreasing albumin levels. Fenofibrate treatment did not improve hepatic dysfunction during the early phases after burn. Confirming these results, there are several reports that show that fibrates increase ALT levels clinically, in vivo, and in vitro [27–29]. The changes were mild in all cases and it was speculated that the alteration was due increased synthesis or decreased clearance. In our study we saw a signal towards increased ALT with the use of fenofibrate.

Hepatic ER stress, another hallmark of burn injury [7, 23, 24], has also been shown to influence burn outcome. Previously, we have assessed hepatic ER stress by determining protein levels of the three branches of ER stress transducers: ATF6, IRE1, and PERK. In the current study, we examined further downstream of these transducers. Chop transcription is activated by phosphorylated PERK and is associated with pro-apoptotic pathways [30]. Xbp1 is synthesized downstream of ATF6 and is spliced downstream of activated PERK [31, 32]. This spliced variant of Xbp1 sits at the promoter of chaperone genes such as Dnajb9, Bip, and Pdial3, initiating their transcription [33–35]. The expressions of these genes are indicative of ER stress [36]. As shown in the results in Figure 2, we confirmed that burn induces prominent upregulation of hepatic ER stress; some genes were upregulated up to 50-fold. Interestingly, fenofibrate further induced the expression of ER stress related genes. Although it has been reported that fenofibrate reduces palmitate-induced ER stress in vitro [37], there are no in vivo reports to our knowledge, especially in the setting of hypermetabolism. We have previously shown that insulin improves burn induced ER stress [8, 23]. Given that fenofibrate actually worsened ER stress along with reduced insulin resistance, we hypothesize that the benefits of insulin administration after burn are most likely associated with insulin per se rather than glucose modulation.

PPAR is an important regulator of cellular fatty acid uptake, transport, and oxidation. We tested the expression of genes related to fatty acid metabolism in our burn model treated with fenofibrate. Since burn induces hypermetabolism [2, 38, 39], we expected transcription of genes involved with fatty acid metabolism to increase. This was indeed the case, as shown in Figure 3. We speculate that burn injury causes massive lipolysis of the adipose tissue and releases free fatty acids [1, 40], which then become ligands of PPAR. Although it has been postulated that fatty acid gene expressions modulate with burn, to our knowledge, this is the first to report in rats. After fenofibrate treatment, we found a further upregulation of gene expression, allowing us to make a couple of inferences. First, this confirms successful administration and delivery of fenofibrate (despite decreased albumin to which fenofibrate binds during delivery). Second, since fatty acid increased after fenofibrate treatment, these results indicate that fatty acid metabolism was not maximal after burn injury alone.

The PPAR targets we studied each have different roles. Cpt1 is a rate-limiting enzyme in the mitochondrial oxidation of long chain fatty acids while AOX catalyzes the first reaction in β -oxidation. CD36 regulates cellular uptake of fatty acids. FAS and SCD1 are lipogenic genes that indicate increased synthesis of fatty acids. Although these genes are downstream targets of PPAR, it is interesting to note that glucose is utilized as a source of lipogenesis. In burn, hyperglycemia is evident in humans and rodents [22–24, 41, 42]. Given that these five PPAR targets have different roles, we then asked what would culminate from the changes in gene expression. We measured hepatic triglyceride content to determine if fenofibrate improved burn-induced steatosis. We observed increased triglyceride content 48 hours post-burn, which was reversed with fenofibrate administration (Figure 4). We postulate that there is a time-dependent accumulation of fat in the liver; 24 hours may not be sufficient time to develop steatosis but by 48 hours post-burn when there is steatosis, a whole array of enzymes is available to remedy this as a result of fenofibrate treatment. Additionally, this indicates greater utilization or oxidation compared to uptake or

lipogenesis. These results indicate a potential mechanism for how fenofibrate improves clinical outcomes post-burn.

There are several limitations to this study. The first is that, while many of the experiments showed clear signals, due to the small number of animals used, the results did not reach statistical significance in all of our data. Secondly, we studied up to 48 hours post-burn which is considered an acute burn condition. We chose to study up to 48 hours since fenofibrate reaches peak concentration in the liver 8 hours after administration [43] and since we mainly assessed gene expressions in this study. Although we were able to observe differences within this time frame, in the future, it may be interesting to study long-term fenofibrate effects on post-burn rats. In summary, we have shown that burn-induced liver dysfunction and ER stress is not ameliorated by fenofibrate. On the other hand, at 48 hours post-burn, liver triglyceride content is significantly decreased with the drug, most likely due to the upregulation of fatty acid metabolic genes downstream of PPAR .

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REFERENCES

1. Herndon DN, Tompkins RG. Support of the metabolic response to burn injury. *Lancet*. 2004; 363:1895. [PubMed: 15183630]
2. Jeschke MG, Chinkes DL, Finnerty CC, et al. Pathophysiologic response to severe burn injury. *Ann Surg*. 2008; 248:387. [PubMed: 18791359]
3. Jeschke MG, Gauglitz GG, Kulp GA, et al. Long-term persistence of the pathophysiologic response to severe burn injury. *PLoS One*. 2011; 6:e21245. [PubMed: 21789167]
4. Jeschke MG, Low JF, Spies M, et al. Cell proliferation, apoptosis, NF-kappaB expression, enzyme, protein, and weight changes in livers of burned rats. *Am J Physiol Gastrointest Liver Physiol*. 2001; 280:G1314. [PubMed: 11352826]
5. Jeschke MG, Micak RP, Finnerty CC, et al. Changes in liver function and size after a severe thermal injury. *Shock*. 2007; 28:172. [PubMed: 17529902]
6. Gauglitz GG, Halder S, Boehning DF, et al. Post-burn hepatic insulin resistance is associated with endoplasmic reticulum (ER) stress. *Shock*. 2010; 33:299. [PubMed: 22011639]
7. Jeschke MG, Gauglitz GG, Song J, et al. Calcium and ER stress mediate hepatic apoptosis after burn injury. *J Cell Mol Med*. 2009; 13:1857. [PubMed: 20141609]
8. Jeschke MG, Kraft R, Song J, et al. Insulin protects against hepatic damage postburn. *Mol Med*. 2011; 17:516. [PubMed: 21267509]
9. Wolfe RR. Metabolic response to burn injury: nutritional implications. *Semin Nephrol*. 1993; 13:382. [PubMed: 8351453]
10. Wolfe RR, Durkot MJ, Allsop JR, et al. Glucose metabolism in severely burned patients. *Metabolism*. 1979; 28:1031. [PubMed: 491960]
11. Wolfe RR, Herndon DN, Jahoor F, et al. Effect of severe burn injury on substrate cycling by glucose and fatty acids. *N Engl J Med*. 1987; 317:403. [PubMed: 3614284]
12. Wolfe RR, Herndon DN, Peters EJ, et al. Regulation of lipolysis in severely burned children. *Ann Surg*. 1987; 206:214. [PubMed: 3606248]
13. Wolfe RR, Jahoor F, Hartl WH. Protein and amino acid metabolism after injury. *Diabetes Metab Rev*. 1989; 5:149. [PubMed: 2647433]
14. Cree MG, Zwetsloot JJ, Herndon DN, et al. Insulin sensitivity and mitochondrial function are improved in children with burn injury during a randomized controlled trial of fenofibrate. *Ann Surg*. 2007; 245:214. [PubMed: 17245174]

15. Elijah IE, Borsheim E, Maybauer DM, et al. Role of the PPAR-alpha agonist fenofibrate in severe pediatric burn. *Burns*. 2012; 38:481. [PubMed: 22226866]
16. Backes JM, Gibson CA, Ruisinger JF, et al. Fibrates: what have we learned in the past 40 years? *Pharmacotherapy*. 2007; 27:412. [PubMed: 17316152]
17. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet*. 2005; 366:1849. [PubMed: 16310551]
18. Forcheron F, Abdallah P, Basset A, et al. Nonalcoholic hepatic steatosis in Zucker diabetic rats: spontaneous evolution and effects of metformin and fenofibrate. *Obesity (Silver Spring)*. 2009; 17:1381. [PubMed: 19553925]
19. Harano Y, Yasui K, Toyama T, et al. Fenofibrate, a peroxisome proliferator-activated receptor alpha agonist, reduces hepatic steatosis and lipid peroxidation in fatty liver Shionogi mice with hereditary fatty liver. *Liver Int*. 2006; 26:613. [PubMed: 16762007]
20. Herndon DN, Wilmore DW, Mason AD Jr. Development and analysis of a small animal model simulating the human postburn hypermetabolic response. *J Surg Res*. 1978; 25:394. [PubMed: 713539]
21. Salmon DM, Flatt JP. Effect of dietary fat content on the incidence of obesity among ad libitum fed mice. *Int J Obes*. 1985; 9:443. [PubMed: 3830936]
22. Gauglitz GG, Halder S, Boehning DF, et al. Post-burn hepatic insulin resistance is associated with endoplasmic reticulum (ER) stress. *Shock*. 2010; 33:299. [PubMed: 22011639]
23. Jeschke MG, Boehning D. Endoplasmic reticulum stress and insulin resistance post-trauma: similarities to type 2 diabetes. *J Cell Mol Med*. 2012; 16:437. [PubMed: 21812914]
24. Song J, Finnerty CC, Herndon DN, et al. Severe burn-induced endoplasmic reticulum stress and hepatic damage in mice. *Mol Med*. 2009; 15:316. [PubMed: 19603103]
25. Gauglitz GG, Herndon DN, Jeschke MG. Insulin resistance postburn: underlying mechanisms and current therapeutic strategies. *J Burn Care Res*. 2008; 29:683. [PubMed: 18695610]
26. Jeschke MG. The hepatic response to thermal injury: is the liver important for postburn outcomes? *Mol Med*. 2009; 15:337. [PubMed: 19603107]
27. Blane GF. Comparative toxicity and safety profile of fenofibrate and other fibric acid derivatives. *Am J Med*. 1987; 83:26. [PubMed: 3318450]
28. Thulin P, Rafter I, Stockling K, et al. PPARalpha regulates the hepatotoxic biomarker alanine aminotransferase (ALT1) gene expression in human hepatocytes. *Toxicol Appl Pharmacol*. 2008; 231:1. [PubMed: 18455211]
29. Tolman KG. Defining patient risks from expanded preventive therapies. *Am J Cardiol*. 2000; 85:15E.
30. Harding HP, Zhang Y, Bertolotti A, et al. Perk is essential for translational regulation and cell survival during the unfolded protein response. *Mol Cell*. 2000; 5:897. [PubMed: 10882126]
31. Yoshida H, Matsui T, Yamamoto A, et al. XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor. *Cell*. 2001; 107:881. [PubMed: 11779464]
32. Yoshida H, Okada T, Haze K, et al. ATF6 activated by proteolysis binds in the presence of NF-Y (CBF) directly to the cis-acting element responsible for the mammalian unfolded protein response. *Mol Cell Biol*. 2000; 20:6755. [PubMed: 10958673]
33. Kanemoto S, Kondo S, Ogata M, et al. XBP1 activates the transcription of its target genes via an ACGT core sequence under ER stress. *Biochem Biophys Res Commun*. 2005; 331:1146. [PubMed: 15882996]
34. Lee AH, Iwakoshi NN, Glimcher LH. XBP-1 regulates a subset of endoplasmic reticulum resident chaperone genes in the unfolded protein response. *Mol Cell Biol*. 2003; 23:7448. [PubMed: 14559994]
35. Zhou Y, Lee J, Reno CM, et al. Regulation of glucose homeostasis through a XBP-1-FoxO1 interaction. *Nat Med*. 2011; 17:356. [PubMed: 21317886]
36. Zhou R, Yazdi AS, Menu P, et al. A role for mitochondria in NLRP3 inflammasome activation. *Nature*. 2010; 469:221. [PubMed: 21124315]

37. Rahman SM, Qadri I, Janssen RC, et al. Fenofibrate and PBA prevent fatty acid-induced loss of adiponectin receptor and pAMPK in human hepatoma cells and in hepatitis C virus-induced steatosis. *J Lipid Res.* 2009; 50:2193. [PubMed: 19502591]
38. Jeschke MG, Klein D, Herndon DN. Insulin treatment improves the systemic inflammatory reaction to severe trauma. *Ann Surg.* 2004; 239:553. [PubMed: 15024317]
39. Pereira C, Murphy K, Jeschke M, et al. Post burn muscle wasting and the effects of treatments. *Int J Biochem Cell Biol.* 2005; 37:1948. [PubMed: 16109499]
40. Jeschke MG, Mlcak RP, Finnerty CC, et al. Burn size determines the inflammatory and hypermetabolic response. *Crit Care.* 2007; 11:R90. [PubMed: 17716366]
41. Gauglitz GG, Herndon DN, Kulp GA, et al. Abnormal insulin sensitivity persists up to three years in pediatric patients post-burn. *J Clin Endocrinol Metab.* 2009; 94:1656. [PubMed: 19240154]
42. Mecott GA, Al-Mousawi AM, Gauglitz GG, et al. The role of hyperglycemia in burned patients: evidence-based studies. *Shock.* 2010; 33:5. [PubMed: 19503020]
43. Weil A, Caldwell J, Strolin-Benedetti M. The metabolism and disposition of fenofibrate in rat, guinea pig, and dog. *Drug Metab Dispos.* 1988; 16:302. [PubMed: 2898351]

Figure 1. Fenofibrate does not improve liver function post-burn. **A)** ALT and **B)** albumin levels were measured in rat livers and are presented relative to sham. * $p < 0.05$ sham vs. burn by one tail t-test.

Figure 2. Fenofibrate does not alleviate hepatic ER stress post-burn. ER stress markers were assessed at the mRNA level. Chop is a downstream target of PERK, while Bip, Dnajb9, and Pdia3 are activated by the spliced form of Xbp-1. Both **A**) 24 hours and **B**) 48 hours post-burn time points are shown. * $p < 0.05$ comparison to sham.

Figure 3. Fenofibrate increased fatty acid metabolism. Genes related to fatty acid metabolism were evaluated in rat livers 24 and 48 hours post-burn. * $p < 0.05$, ** $p < 0.01$ comparison to shams by one-way ANOVA.

Figure 4. Fenofibrate reduces hepatic triglyceride content in burn livers. Triglyceride content was measured in the rat livers. * $p < 0.05$ comparison to sham.

Figure 5. Fenofibrate increases glucose transport. Gene expression of glucose transporters, Glut1 and Glut4, were measured at 24 and 48 hours post-burn. * $p < 0.05$ comparison to sham. # $p < 0.05$ comparison to burn.