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High sucrose diet attenuates oxidative stress, inflammation and liver injury in thioacetamide-induced liver cirrhosis

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ABSTRACT

Aims: Liver cirrhosis is the main chronic liver disease and is considered a catabolic disease. Cirrhotic patients have a low energy intake and high energy expenditure at rest, leading to metabolic disorders. Malnutrition is associated with complications of cirrhosis and have been shown that a nutritional intervention with increase of energy intake improves the survival of cirrhotic patients. Therefore, our aim was to evaluate the effect of a high sucrose diet in the liver of animals with cirrhosis induced by thioacetamide and investigate the mechanism involved. **MainMethods**: Male *Wistars* rats were divided into three groups: Control; Thioacetamide; and Thioacetamide+high sucrose diet. The thioacetamide was administrated (100mg kg^{-1}) intraperitoneally and the sucrosewas offered in drinking water (300g L^{-1}). **Key findings**: The administration of thioacetamide was associated with fibrosis and inflammatory infiltrate in the liver and increased levels of transaminases enzymes. The high sucrose diet promoted a reduction of theses parameters in cirrhotic rats. The malnutrition observedin cirrhotic rats was attenuated by the high sucrose diet shown by theimprovements inweight loss, subcutaneous fat, and caloric intake.The high sucrose diet also attenuated the oxidative stress present in the liver of animals with thioacetamide-induced cirrhosis.**Significance**:

The high sucrose diet had anti-inflammatory and anti-oxidant effects in the liver of animals with thioacetamide-induced cirrhosis. In addition, the high sucrose diet also improved malnutrition and catabolism present in cirrhosis. Thus, a high sucrose diet may be a therapeutic option for cirrhotic patients in a catabolic state.

Keywords: liver cirrhosis; high sucrose diet; thioacetamide, oxidative stress, catabolism

INTRODUCTION

Liver cirrhosis is the major chronic liver disease, with a high degree of morbidity and mortality, causing 1.03 million deaths per year worldwide[1]. Liver cirrhosis is a catabolic disease characterized by muscle weakness, anorexia, and weight loss. It has been shown that cirrhotic patients have a low energy intake and higher energy expenditure at rest[2]. An insufficient energy intake of less than 30 kcal / kg is associated with a worse prognosis in cases of liver cirrhosis[3].

The liver supplies glucose to the body from glycogen during periods of fasting, so that cells that consume glucose, like neurons and hemaceas are supplied. When there is an increase in blood glucose, the liver increases glycogen storage (glycogenesis) and reduces the breakdown of this glycogen and the production of glucose from non-glycid compounds[4]. However, in cirrhosis the metabolism and storage of glycogen is reduced, leading to impaired glucose supply to other tissues for energy production. Thus, in an attempt to fill this lack, oxidation of fatty acids, gluconeogenesis and proteolysis occurs, resulting in a hepatic catabolic state and consequently a compromised nutritional state[5].

Because in a catabolic situation such as cirrhosis, there is a reduction in hepatic glucose synthesis from glycogen, the use of proteins becomes essential for the supply of energy, generating protein-caloric malnutrition[5].The supply of glucose can be an alternative to avoid energy depletionand attenuate malnutrition.

The result of deregulation in hepatic metabolism is protein-energy malnutrition, present in 20% in cases of compensated cirrhosis and 60% in decompensated cirrhosis[6]. Protein-energy malnutrition causes serious complications such as encephalopathies, ascites, gastrointestinal bleeding, anorexia, and sarcopenia, increasing the mortality of these patients[6].

Liver injury induced by thioacetamide (TAA) is a model recognized for producing liver injury, regenerative nodules, and fibrosis similar to those of human liver

fibrosis[7,8]. Oxidative stress is involved in the process of fibrogenesis. TAA stimulates the formation of free radicals, which can decrease glutathione (GSH) and other antioxidant defense mechanisms in hepatocytes causing lipid peroxidation. This oxidative stress condition leads to cell necrosis[8,9,10].

Nutritional status is an important predictor of morbidity and mortality in cirrhosis, and it has important implications in the selection candidates for liver transplant, as poorer nutritional status correlates with higher postoperative complications[11].Randomized studies have already shown that a nutritional intervention aimed at ensuring sufficient energy intake significantly improves the survival of cirrhotic patients[3]. Although there is clinical evidence of the benefit of an energy diet in cirrhotic patients, little is known about the mechanisms involved and how a carbohydrate-rich diet can relieve liver damage and improve the glucose offer to cells that depend on the energy supplied by the liver. Thus, the aim of this study was to test the hypothesis that a high sucrose diet attenuate the liver injury and the catabolism condition of rats with cirrhosis induced by thioacetamide.

METHODOLOGY

Animals and experimental protocol

All animal procedures were performed following the regulations of the National Council on Animal Experimental Control (CONCEA, Brazil). The experimental protocol was approved by the Ethics Committee on the Use of Animals (CEUA, under protocol n° 23108.053273/2019-60) of the Federal University of MatoGrosso. Rats were housed at constant room temperature and light cycle (12:12-h light-dark cycle). The animals used were male *Wistar* rats weighing about 300 g, divided randomly into three groups: Control (C), TAA-treated rats (TAA), and rats treated with TAA and a high sucrose diet (TAA+HSD). The administered dose of TAA was 100 mg kg^{-1} intraperitoneally, twice weekly for 8 weeks[7]. Control rats received vehicle (saline) in the same volume and same administration protocol. The C and TAA groups werefed ad *libitum* with a standard chow diet (3.77 kcal g^{-1}) – NUVILAB CR-1 (NuvitalVR, Colombo, Paraná, Brazil) and water.The TAA+HSD group besides receiving the same diet ad *libitum*, had sucrose added to the drinking water (300 g L^{-1}; 1.2 kcal mL^{-1}).

Caloric consumption was calculated by adding daily feed intake (g) x 3.77 kcal and daily water consumption with sucrose x 1.2 kcal[12].

After 8 weeks of the experimental period, the animals were euthanized under anesthesia with a mixture of ketamine (113 mg kg^{-1} body weight; b.w.) and xylazine (7.4 mg kg^{-1} b.w.) at a dose of 0.15 mL $100g^{-1}$ b.w., intraperitoneally).The rats were weighed at the beginning and end of the experimental period. After euthanasia, the liver and epididymal, mesenteric, and retroperitoneal fat padswere weighed.The animals' weight gain was calculated by subtracting the initialbody weight from the final body weight.

Oral glucose tolerance test

Three day prior to euthanasia, an oral glucose tolerance test was performed. After subjecting the animals to a 15-h period of fasting, blood samples were collected from the caudal vein. This time point corresponded to the basal glycemic level (T0). Then, glucose solution (0.5 g mL^{-1}) was administered to the rats via gavage at a dose of 2.5 gkg^{-1} b.w. at time 0 min (T0′). Blood samples were collected at the following times: 15, 30, 60, 90 and 120 min after glucose was administered.

Blood glucose was determined on a glucose meter (Glucosimeter SENS II®, Injex, Ourinhos-SP, Brazil).

Histological analysis

Tissue samples from the liver werefixed in 10% buffered formaldehyde, and dehydrated in various concentrations of ethanol, then immersed in resin, sectioned in 3 µm cross sections, and stained with hematoxylin and eosin (HE). The liver tissue morphology wasobserved under light microscope. HE-stained liver sections were evaluated for fibrosis (FS), inflammation and steatosis(IS) scores, both classified on a scale of 0–3[13,14]. A mean liver injury score was calculated as follows: (FS + IS) / 2.

Biochemical and oxidative stress analyses

Blood samples were collected in Falcon tubes, centrifuged (3000 rpm; 10 min; Eppendorf®Centrifuge 5804-R, Hamburg, Germany) and the serum was used for

biochemical analysis. The levels of C-reactive protein (CRP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were analyzed using commercial kits (Labtest – Lagoa Santa, MG; Biotécnica Advanced - Varginha, MG).

In order to assess the effect of a high sucrose diet on the oxidative stress produced in liver cirrhosis, the levels of biochemical parameters (enzymatic and non-enzymatic antioxidants, biomarkers of lipid and protein damage) were determined in the liver tissue. Lipid peroxidation levels were evaluated according to Buege and Aust (1975)[15] by determining the levels of substances reactive to thiobarbituric acid (TBARS). TBARS concentration was expressed in nmol MDA mg protein^{-1} following the calibration curve for MDA. The protein carbonyl was determined according to Colombo et al (2016)[16] by a modified dinitrophenylhydrazine assay (DNPH). The total carbonyl content was expressed as nmol carbonyl mg protein^{-1}. Superoxide dismutase (SOD) activity was assessed by inhibition of adrenaline oxidation according to Misra and Fridovich (1972)[17] and expressed as UI SOD mg protein^{-1}.Glutathione-S-transferase (GST) activity was determined according to Habig et al. (1974)[18], the enzymatic activity was measured based on the formation of GS-DNB adduct, and the result was expressed in µmol GS-DNB min^{-1} mg protein^{-1}.Catalase (CAT) activity was determined according to Nelson and Kiesow (1972)[19]. The principle is based on decomposition of H_2O_2 that is expressed in µmol H_2O_2 min^{-1} mg protein^{-1}. Reduced glutathione (GSH) was measured using the colorimetric method consisting of a reaction of sulfhydryl groups developed by Sedlak and Lindsay (1968)[20]. The result was expressed in µmol GSH mg protein^{-1} and compared to a standard GSH curve. Ascorbic acid (ASA, vitamin C) levels were determined according to Roe (1954)[21] by colorimetric method. The result was expressed in µmol ASA g^{-1} of tissue and compared to a standard curve of ascorbic acid.Protein content (except ASA) was estimated according to Bradford (1976)[22] using bovine serum albumin as a standard.Samples were read in spectrophotometer.

Glycogen was determined following the method of Bidinotto et al. (1997)[23]. The result was expressed in µmol glucose g^{-1} tissue. Glucose and lactate were measured according to Duboie et al. (1956)[24,] result was expressed inmmol g^{-1} tissue and Harrower and Brown (1972)[25], result was expressed in µmol g^{-1} tissue respectively. Protein and amino acids content were determined through the method described by Bradford (1976)[22], was expressed in mmol g^{-1} tissue and Spies (1957)[26],was expressed in mg g^{-1} tissue, respectively. Samples were read in spectrophotometer.

STATISTICAL ANALYSIS

Data arepresented as mean ± SD, and "n" represents the number of animals used in the experiments.The homogeneity of variances among groups was tested using the Bartlett's test.Data were analyzed by one-way ANOVA followed by Tukey's*post-hoc* test for multiple comparisons, or by Kruskal-Wallis test (non-parametric) as appropriate, followed by Dunn's *post-hoc* analysis. Differences were considered significant at P values <0.05.

RESULTS

High sugar diet improved the catabolism present in liver cirrhosis

General characteristics are shown in Table 1 and 2. As expected, calorie intake, weight gain and adipose deposits (except mesenteric fat) were lower in groups under the thioacetamide administration. In addition, TAA increased liver weight and serum ALT and AST. High sucrose diet was able to significantly prevent the decrease in weight gain and liver weightwhileincreased calorie intake and the epididymal, retroperitoneal and mesenteric adipose tissue deposits (Table 1). The sucrose use also decreased serum ALT levels. No difference were found in CRP measurement.

Table 1.Morphological and Biochemical parameters of control animals and thioacetamide treated or not with a high sucrose diet.

	Groups		
Parameters	**C**	**TAA**	**TAA+HSD**
IBW (g)	291.5 ± 25.72	324.6 ± 20.98*	327.8 ± 21.46*
FBW (g)	430.9 ± 38.37	363.5 ± 44.67*	411.1 ± 25.76#
Weight gain (g)	139.4 ± 32.23	47.43 ± 22.13*	83.38 ± 18.3*#
Liver FBW^{-1} (g)	2.67 ± 0.26	3.83 ± 0.44*	3.32 ± 0.35*#
Epididymal fat (g)	9.84 ± 0.99	5.38 ± 1.36*	7.66 ± 1.31*#
Retroperitoneal fat (g)	14.1 ±1.93	7.92 ± 2.13*	13.8 ± 0.89#
Mesenteric fat (g)	5.91 ± 0.59	4.75 ± 0.69	7.57 ± 1.63*#
ALT ($U\ L^{-1}$)	76.14 ± 15.65	148.3 ± 22.35*	110± 24.63*#
AST ($U\ L^{-1}$)	280.2 ± 35.29	519.3 ± 62.84*	527.3 ± 73.11*
CRP ($mg\ dL^{-1}$)	2.48 ± 0.61	3.41 ± 0.86	2.73 ± 0.30

Data presented as mean ± standard deviation. C, control (n=8); TAA, Thioacetamide (n=8); TAA+HSD, Thioacetamide + high sucrose diet (n=8); IBW, initial body weight; FBW, final body weight; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein.* indicate significant

differences in relation to the C and # indicate significant differences in relation to the TAA according to ANOVA followed by Tukey's post-hoc test analysis (P<0.05).

Table 2. Feed intake of control and thioacetamide animals treated or not with a high sucrose diet.

	Groups		
Parameters	**C**	**TAA**	**TAA+HSD**
Chow (g)	27.05 ± 0.52	21.62 ± 0.69*	13.53 ± 0.46*#
Water (mL)	43.22 ± 1.27	38.09 ± 2.68*	36.8 ± 0.19*
Calorie (kcal) day^{-1}	102 ± 1.97	81.49 ± 2.62*	95.17 ± 1.96*#

Data presented asmean ± standard deviation. C, control (n=8); TAA, Thioacetamide (n=8); TAA+HSD, Thioacetamide + high sucrose diet (n=8). * indicate significant differences in relation to the C and # indicate significant differences in relation to the TAA according to ANOVA followed by Tukey's*post-hoc* test or by Kruskal-Wallis test followed by Dunn's post-hoc analysis (P<0.05)**.**

High Sucrose diet attenuates thioacetamide-induced liver injury

TAA treatment induced liver injury characterized by inflammation and fibrosis (Figure 1). A significant reduction in fibrosis and inflammatory infiltrate was observedin cirrhotic animals treated with high sucrose diet (Figure 1 g and h). In addition,HSD was associated with regression of cirrhosis, with incomplete septal fibrosis and signs of parenchymal remodeling. There was no difference between groups in steatosis (Figure 1 i).

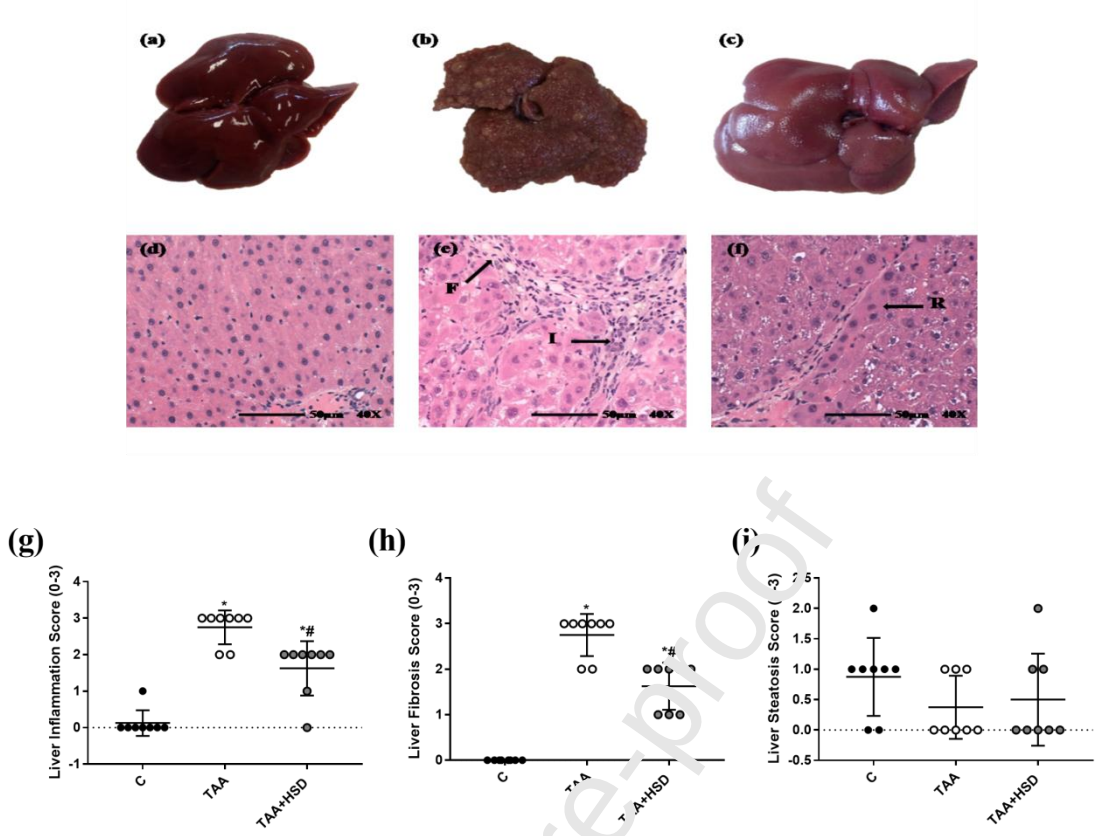

Figure 1. .Representative macroscopic and histological images of livers. C, control (a and d); TAA, Thioacetamide (b and e); TAA+HSD (c and f). Histological analysis of liver sections. inflammation score (g); fibrosis score (h) and steatosis score (i). C, control (n=8); TAA, Thioacetamide (n=8); TAA+HSD, Thioacetamide + high sucrose diet (n=8) * indicate significant differences in relation to the C and # indicate significant differences in relation to the TAA according to ANOVA followed by Tukey's*post-hoc* test ($P<0.05$).

The oral glucose tolerance testwas performed and area under the curve were similar among the groups (Figure 2). Figure 3 shows the biochemical parameters involved in the liver metabolism. In the liver there was a significant decrease in glucose concentrations in TAA group when compared with C group (Figure 3 a), but glycogen levels was not altered. However, glucose, glycogen, and lactate levels significantly increased in the liver of high sucrose diet group (Figure 3 a,b,c).There was no difference between groups on the amino acids and protein levels in the liver.

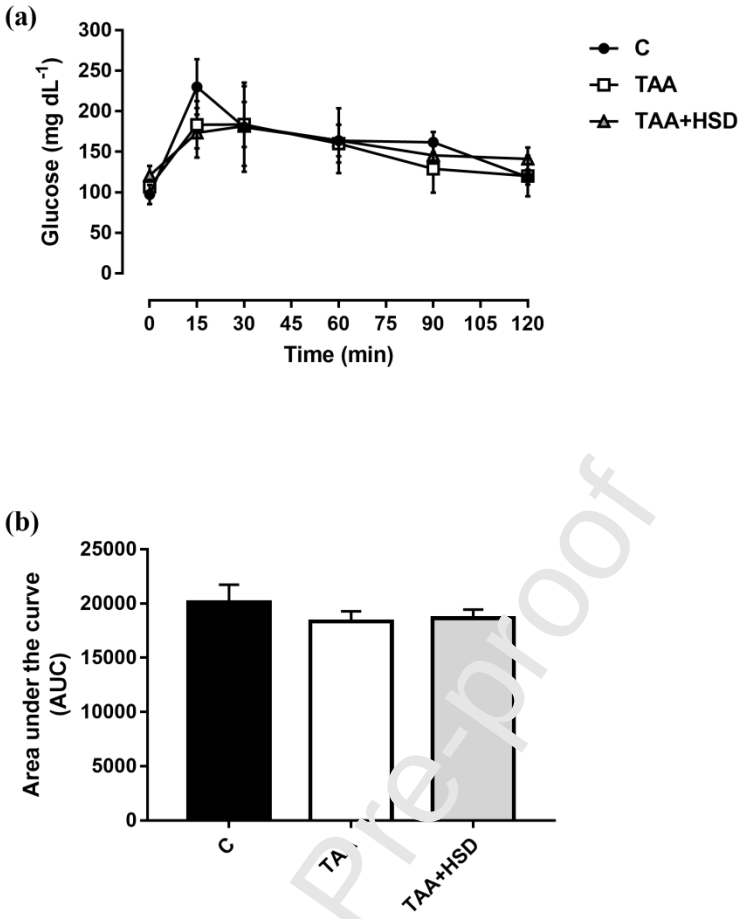

Figure 2. Oral glucose tolerance test. Glycemic curves (a); area under the curves (b).Data presented as mean ± standard deviation. C, control (n=8), TAA, Thioacetamide (n=8); TAA+HSD, Thioacetamide + high sucrose diet (n=8).

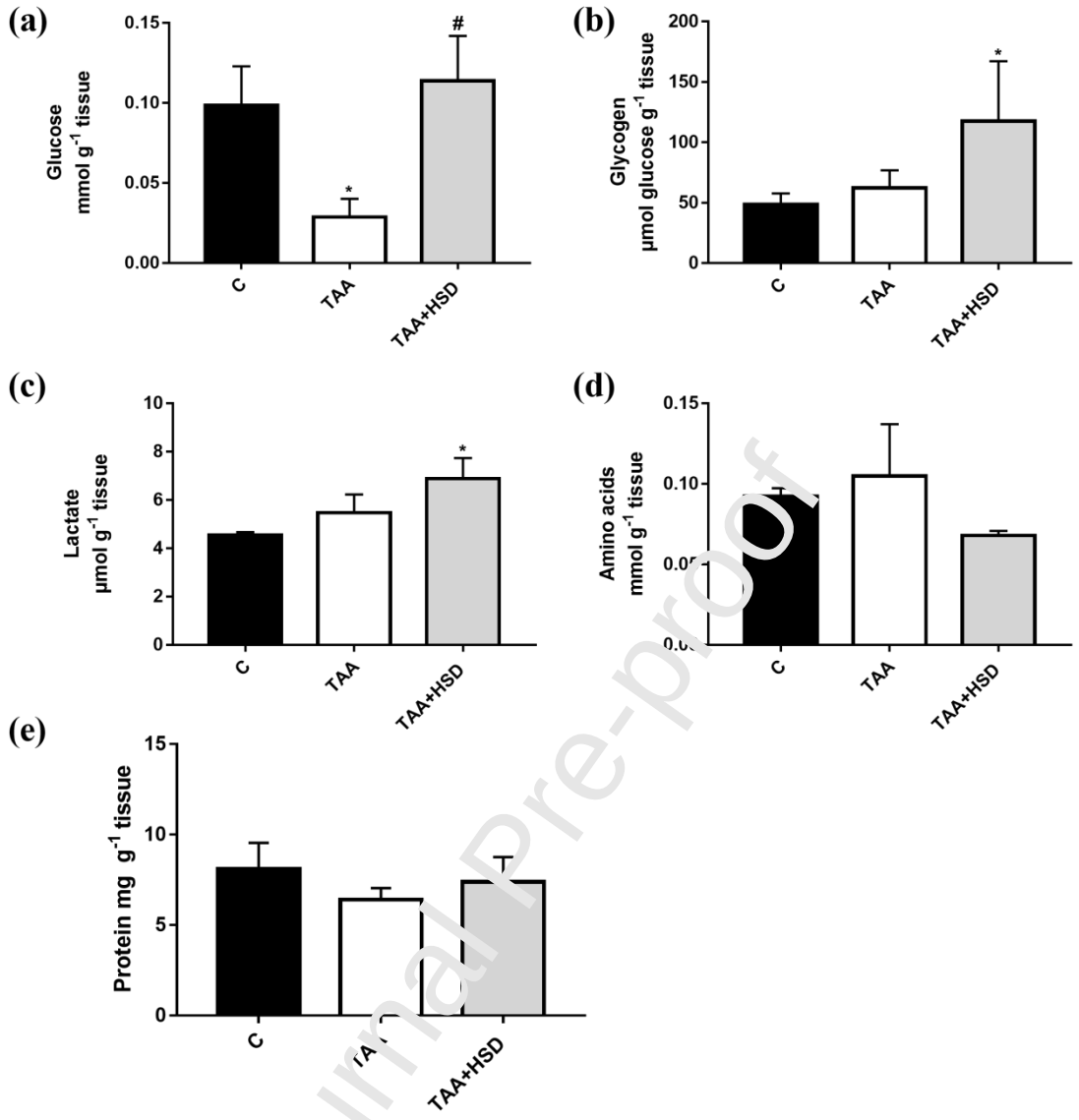

Figure 3. Metabolic biochemical parameters of liver tissue. Glucose (a); Glycogen (b); Lactate (c); Amino acids (d); Protein (e).Data presented as mean ± standard deviation. C, control (n=8); TAA, Thioacetamide (n=8); TAA+HSD, Thioacetamide + high sucrose diet (n=8).* indicate significant differences in relation to the C and # indicate significant differences in relation to the TAA according to ANOVA followed by Tukey's*post-hoc* test or by Kruskal-Wallis test followed by Dunn's post-hoc analysis ($P<0.05$).

High sucrose diet improves hepatic redox status

The tests assessing the oxidative state of liver tissue demonstrated there was an increase in TBARS in TAA-treated rats versus C and decreased TAA+HSD groups (Figure 4 a). In addition, TAA group showed increased activity of the antioxidant defenses SOD, CAT, GST and levels GSH (Figure 4 c,d,e,f, respectively) and decreased the vitamin C (Figure 4 h) compared to control animals. The TAA+HSD group also exhibited increased activity of the antioxidant defenses SOD, CAT and levels GSH

compared to control animals.There was no difference in the levels of carbonylated proteins.

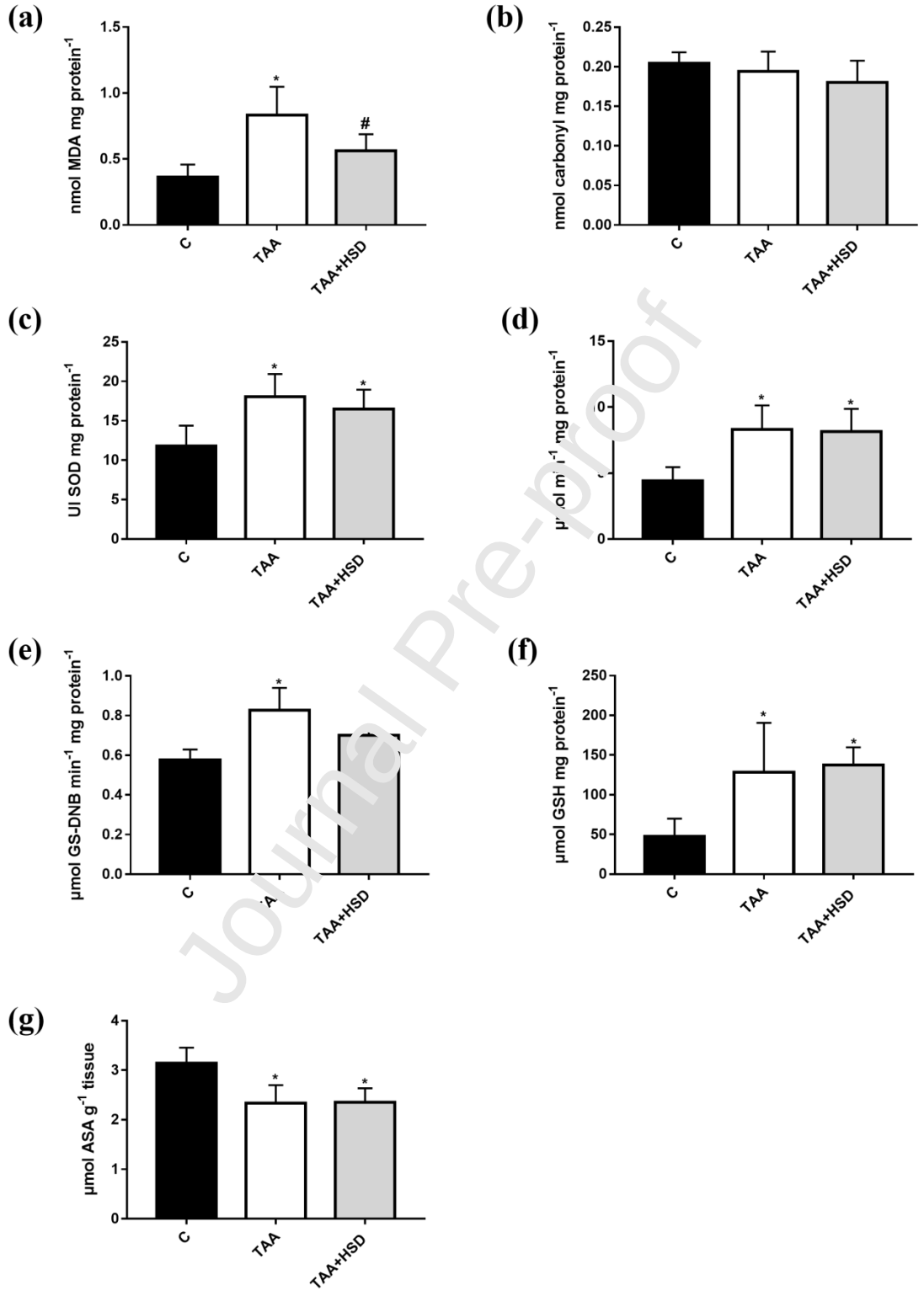

Figure 4. Oxidative state of liver tissue. Data presented as mean ± standard deviation. TBARS (a); Carbonylated proteins (b); Superoxide Dismutate (SOD) (c); Catalase (CAT) (d); Glutathione-S-transferase (GST) (e); reduced glutathione (GSH) (f); Vitamin C (g). Data presented as mean ± standard deviation. C, control (n=8); TAA, Thioacetamide (n=8); TAA+HSD, Thioacetamide + high sucrose diet

(n=8). * indicate significant differences in relation to the C and # indicate significant differences in relation to the TAA according to ANOVA followed by Tukey's*post-hoc* test (P<0.05).

DISCUSSION

The major findings of this study are that a high sucrose diet showed a significant improvement in oxidative stress, inflammation, and fibrosis in the liver of rats with cirrhosis induced by thioacetamide. These results suggest that nutritional intervention by increasingtheenergy intake alleviates the catabolic effects of the disease and improves liver function in cirrhosis.

In the general population, the Academy of Nutrition and Dietetics (AND) defines malnutrition as meeting any two of the following parameters: insufficient energy intake, weight loss, loss of muscle mass or subcutaneous tissue, fluid accumulation, and/or decreased functional status as measured by hand grip strength. In patientswith cirrhosis, malnutrition is most commonly defined as a loss in skeletal muscle mass and/or strength, as well as decreased subcutaneous and visceral fat mass. Alterations in these structural components often occur in the setting of decreased protein and total energy consumption. Our results showed weight loss and decrease in total daily caloriesconsumption in TAA treated rats, suggesting a malnutrition condition in these animals. Malnutrition is estimated to affect 20% to 95% of cirrhotic patients, and its prevalence and severity correlates with the degree of liver disease. The mechanisms of malnutrition in cirrhosis and chronic liver disease are complex and multifactorial, and generally associated with inflammation, poor food intake due toanorexia, nauseaand vomiting, diarrhea, malabsorption, small intestine bacterial overgrowth, intestinal dysmotility and metabolic disturbances. The use of a high sucrose diet ameliorates the caloric intake, weight loss and fat deposit loss in TAA rats, showing that this nutritional intervention can attenuate the catabolic and malnutrition state in liver cirrhosis[11,27,28,29,30].

Liver histology has been considered the ‘‘gold standard’’ of diagnosis of liver diseases, as it is the most direct wayof visualizing the inflammatory and architectural status of the liver. Our results demonstrated an increase in inflammation and fibrosis in the liver of TAA animals, characterizing liver cirrhosis induced by thioacetamide. Hepatocyte injury, followed by inflammation and activation of the innate immune system, leads to liver fibrosis mediated by hepatic stellate cell activation and extracellular matrix (ECM) secretion and deposition.Hepatic inflammation is related

with malnutrition and low caloric intake in patients with liver cirrhosis, demonstrating the anorectic effect of the inflammatory state[6,30]. Malnutrition affects mainly the cellular immune response. The inflammatory response also activates factors like TGF-β1and increases fibrosis[31,32].In our study, we found that the high sucrose diet attenuated the inflammatory infiltrate and fibrosis in TAA+HSD group, which can be explainedby the increase in caloric intake and, consequently, improvement in the inflammatory state and fibrosis.

In the serum biochemistry analysis we observed an increase in transaminase levels (ALT and AST) in TAA group and reduced levels of ALT in TAA+HSD group compared to TAA animals, showing the effect of increasing sucrose intake on metabolism and liver function. This result suggests that high sucrose diet attenuates cells injury and liver lesions. ALT and AST are aminotransferase enzymes involved in the body's central metabolism. When damage occurs in certain cells, there is an overflow of aminotransferases from the tissue into the bloodstream, making the diagnosis possible by measuring the concentration of these enzymes in the blood. In liver cirrhosis, due to the injury that affects the hepatocytes, it is possible to identify an increase in transaminases[7,33].

The liver is a metabolic center of the body and acts in the regulation of the metabolism of glucose, proteins and lipids. One of the critical functions of the liver is the metabolism and storage of glycogen as a fuel source, to maintain glucose homeostasis in periods of fasting for cells that preferentially and / or exclusively consume glucose, such as neurons and red blood cells. When glucose levels rise, the liver increases glycogen storage and suppresses glycogenolysis, increasing glycogen stores to be used for fasting.In cirrhosis, glycogen storage capacity is decreased resulting in increased lipid oxidation, proteolysis, and gluconeogenesis, the liver thus becoming highly catabolic[34]. Previous work showed that cirrhotic patientsused 13% of energy derived from carbohydrates during a 12-hour overnight fast, while healthyindividuals used 39%[34]. For the control group, it was necessary, at least 36 hours for the proportion of calories produced from proteins and fat to be similar to that of the cirrhotic group in an overnight fast. This studydemonstrated that in cirrhosis the lack of glycogen leads to the use of other substrates such as proteins and lipids for energy in a short fasting period[34].

In our study, we observed a reduction in hepatic glucose levels in animals treated with TAA, but no change in glycogen levels. Failure of liver mechanisms such

as increased catabolism can lead to hypoglycemia[36,37]. Considering the normal levels of stored glycogen, our results suggested an alteration in glycogenolys is and consequently an inability to release this energy reserve. Gluconeogenesis is maintained, to supply the need for cells and tissues that obtain energy from glucose, which rapidly consumed. Animals submitted to a high sucrose diet had an increase in liver glucose levels as well as glycogen, reinforcing the idea that the increase in glucose supply increases the glycogen reserve stock to be used during the fasting period.

There was an increase in lactate levels in animals submitted to a high sucrose diet. Lactate has largely been considered a waste product of glycolysis[38]. The increase in lactate levels may be caused by to the anaerobic preference of the metabolism[36] to reduce the energy depletion timber from calorie which also may also occur in liver cirrhosis. Although there was no statistical difference in lactate levels between animals in the C and TAA groups, the high sucrose diet was efficient in increasing the concentration and availability of glucose in the liver, minimizing the catabolic effects found in liver cirrhosis.

Because we worked with a diet rich in sugar, it is important to measure the glucose concentration in the blood of these animals, to check the possibility that the diet is altering glucose levels. For that, we performed the oral glucose test in all groups, and we found that even the rats with cirrhosis had ingested sugar for 8 weeks, there was no change in the glucose values measured at different times after a glucose overload. This result demonstrates that the high glucosediet can be an interesting alternative for patients with cirrhosis in a catabolic state.

ROS are generated by various liver injuries such as alcohol abuse, hepatitis virus infection, and chronic cholestasis and contribute to hepatic fibrogenesis. ROS stimulate the production of collagen I in a HSCs/myofibroblasts, acting as intracellular signaling mediators for TGF-β1–induced fibrosis[40]. Because oxidative stress mediates hepatocyte death and hepatic stellate cell activation, regulation of ROS is a promising strategy for liver fibrosis therapy.

The inflammatory response is associated with ROS production. ROS can specifically activate signaling pathways in hepatic stellate cells, promoting fibrogenesis[40].In our results, oxidative stress in the liver of TAA rats was evidenced by increased MDA levels. MDA is a product from lipid peroxidation and can react with DNA and proteins, resulting in toxic products. The high sucrose diet was effective in reducing MDA levels, demonstrating an antioxidant effect. The metabolic alteration that

occurs in liver cirrhosis is characterized by an increase in fatty acid oxidation to supply the lack of energy due to lack of glucose, which may be causing damage to the cell's lipid membrane, increased MDA, and oxidative damage. The energy supply of glucose may be preventing this oxidation and consequently improving the oxidative state. However, no oxidative damage was observed in proteins, considering that the levels of carbonylated proteins were not altered[41,42,43].

Moreover, the presence of ROS can trigger signaling cascades that affect transcriptional regulation, notably through nuclear factor erythroid 2-related factor 2 (Nrf2). Some of these responses constitute homeostatic mechanisms against oxidative stress, by inducing the expression of antioxidant agents (i.e., catalase, glutathione S-transferase, glutathione peroxidase or heme oxygenase^{-1}), but these fail to compensate for excessive ROS accumulation under pathological conditions[44]. Although TAA ratsshowed an increase in some anti-oxidant enzymes, this compensatory mechanismwas not enough to decrease the oxidative stress present in the liver of these animals.On the other hand, cirrhotic animals treated with a high sucrose diet also presented increased activity of anti-oxidant enzymes which controlled oxidative stress in the liver of these rats. With these data, we confirmed that the high sucrose diet attenuated the oxidative stress in the liver of animals treated with TAA, by increasing the activity of various anti-oxidant enzymes, such as SOD, CAT and levels GSH, decreasing the inflammatory process.

It is important to note that in this work we evaluated the effect of ahigh sucrose diet in a model of chronic liver cirrhosis, with advanced liver injury and in the presence of a catabolic state. In other models of liver damage, such as non-alcoholic fatty liver disease, a diet rich in sucrose may not be a viable treatmentalternative, since in these conditions the aspect of obesitywould also need to be addressed.

CONCLUSION

The high sucrose diet is efficient in attenuatingliver cirrhosis, reducing oxidative stress, inflammation, and fibrosis in the liver. In addition, the diet also improves malnutrition and catabolism present in animals with cirrhosis induced by thioacetamide. Thus, a high sucrose diet may be an option for cirrhotic patients in catabolism situation.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Bianca Sulzbacher da Silva: Conceptualization, Writing - Original Draft;**Angélica Macedo Borgês Paulino**: Methodology;**Maiara Taffarel**: Methodology;**Ian Gabriel Borba**: Methodology;**Luciana Ortega Telles**: Methodology;**Victor Vitorino Lima**: Formal analysis;**Danilo Henrique Aguiar**: Investigation;**Marcos Correa Dias**: Investigation;**André Ferreira do Nascimento**: Conceptualization;**Valéria Dornelles GindriSinhorin**: Project administration;**Renata de Azevedo Melo Luvizotto**: Project administration;**Gisele Facholi Bomfim**: Writing - Review&Editing, Supervision, Project administration.

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HIGHLIGHTS

- Cirrhotic patients have low energy intake, leading to malnutrition and weight loss.
- In liver cirrhosis there is inflammation and high oxidative stress in the liver.
- A high sucrose diet improved the catabolism and liver function of cirrhotic rat.
- The high sucrose diet presented anti-oxidant effects in the liver of cirrhotic rat.
- A high sucrose diet may be an option for cirrhotic patients in a catabolic state.