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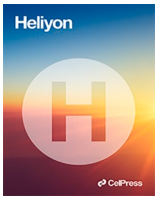

A short-term high-sugar diet is an aggravating factor in experimental allergic contact dermatitis

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ABSTRACT

Allergic contact dermatitis (ACD) is an inflammatory skin reaction whose incidence has increased and has been associated with a dietary pattern rich in saturated fats and refined sugars. Considering the increased incidence of ACD and the lack of research about the influence of a short-term high-sugar diet on dermatitis, our aim is to improve understanding of the influence of a high-sugar diet on ACD. We introduced a diet rich in sugar fifteen days before inducing contact dermatitis with oxazolone, in mice, and maintained it until the end of the experiment, which lasted three weeks in total. The dermatitis model increased cholesterol and triglycerides in the liver, and the combination of diet and dermatitis increased weight and worsened liver cholesterol measurements. Furthermore, the high-sugar diet increased the production of IL-6, IFN-γ and TNF-α in the skin, which may be involved in the increase in epithelial skin thickness observed in experimental ACD.

1. Introduction

Allergic contact dermatitis (ACD) is a frequent skin problem that negatively interferes with people's quality of life and generates high socioeconomic costs [1]. Its incidence has increased mainly in industrialized countries [2,3]. ACD is a type IV delayed hypersensitivity reaction to exogenous antigens from the activation of T cells specific to the allergen [4–6]. It is considered one of the most common dermatological diseases, representing the main occupational cause of skin diseases [1]. It consists of an inflammatory change in the skin that is characterized by pruritus, erythema, vesicles, and peeling of the skin [4]. Histologically, ACD is characterized by dermal inflammatory infiltrates with a predominance of lymphocytes and other mononuclear cells [7]. Contact hypersensitivity (CHS) is a term used for humans, whereas ACD is commonly used for rodents.

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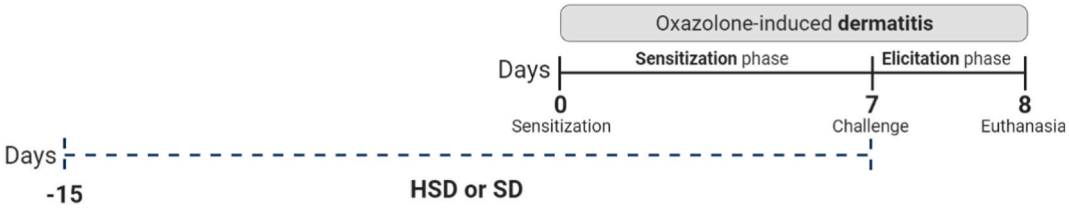

Fig. 1. Schematic mouse model of contact dermatitis and condensed milk intake.

ACD induced by topical application of haptens, as oxazolone (OXA), it is a commonly used model to study dermal inflammatory responses [8]. First contact of skin with a hapten, are low molecular wight chemical substances, occurs in the sensitization phase, hapten bind to an endogenous protein in the skin forming hapten-protein complexes which are immunogeneic [8]. The hapten-protein complex leads to the migration of activated Langerhans cells and dermal dendritic cells (DCs) via lymphatic vessels to draining lymph nodes (dLNs), where the hapten-protein complex is presented to naïve T cells [8]. The newly activated T cells proliferate and migrate out of the lymph node and into circulation. In the elicitation phase, re-exposure of the skin to the hapten activates the specific T cells in the dermis and triggers a strong local inflammatory response [9].

Feeding habits have an impact on the immune system, and depending on these habits, they can lead to an imbalance in the immune system, potentially triggering the development of diseases [7,10]. The increased intake of refined sugar and saturated fats favors the increased incidence of immunological alterations, including allergies [11]. Western countries have high rates of allergic processes [12], and the typical diet of these countries is rich in sugars and fats [13]. Animals fed a long-term high-fat diet have increased adiposity associated with chronic low intensity systemic inflammation [14]. Obese patients show immunological changes evidenced by the fact that they have a higher incidence of secondary infections and surgical wounds, reduced wound healing, and increased time required for antibiotic therapy [15].

In this study, we focus specifically on a high-sugar diet because sugar consumption has increased and has been associated with various health problems. Sugars were intensively incorporated into the diet by being inserted into industrialized foods to improve their flavor [16]. Excessive consumption of sugars can contribute to the development of type 2 diabetes, cardiovascular disease, obesity, insulin resistance, and inflammation [17,18]. Interestingly, the amount of sugar in the diet determines the amount of this component in blood and skin [19]. In the skin, much of the sugar binds to elastin and collagen in the dermis, producing glycation end products or "AGEs" (advanced glycation end-products) [19], thus promoting the cross-linking of collagen and decreasing tissue elasticity [20].

There is evidence showing the relationship between high-sugar consumption and the development of atopic diseases in children, as well as studies showing the association between high-fat diets and allergic diseases [11,21,22]. Although there are many studies investigating the effect of a high-fat diet on obesity and atopic dermatitis, there are few reports about skin alterations, especially on ACD in humans and mice fed diets rich in refined carbohydrates (15). In addition, studies with both a high-carbohydrate diet and a high-fat diet typically do not address the effect of a short-term high-sugar diet [17], such as during festivities when many sweets are consumed in a short period. There is also a lack of data in the literature reporting whether a short-term high-sugar diet causes significant metabolic changes that could affect the skin. Considering all evidence that sugar may affect the skin and the lack of studies linking ACD exacerbation and excess sugar consumption in the short term, we investigate the effects of a short-term high-sugar diet on ACD induced in mice.

2. Materials and methods

2.1. Animals

All experiments involving laboratory animals were evaluated and approved by the Institutional Animal Care and Use Committee of the Federal University of São Paulo under protocol 5901280619. All methods were performed in accordance with relevant national and international regulations and guidelines including the ARRIVE guideline and Brazilian National Law number 11.794 (Arouca Law), Decree 6.899, and normative resolutions from the Conselho Nacional de Controle de Experimentação Animal (CONCEA), the federal agency that regulates all research activities involving animal use in Brazil. BALB/c female mice (5–6 weeks old) were housed in groups of five per cage in a light- and temperature-controlled room (12 h light/dark cycles and 21 $\pm$ 2 °C) and were given free access to a standard chow diet (Nuvilab CR1, Quimtia, Paraná, Brazil). The animals were euthanized by an overdose of anesthetic (300 mg/kg of ketamine and 30 mg/kg of xylazine) and later the rupture of the rib cage was performed as a second method of euthanasia.

2.2. OXA-induced contact hypersensitivity model

The OXA-induced contact hypersensitivity model in mice reproduces a clinical condition similar to that observed in ACD in humans. The induction of ACD was performed according to the method described by Aebischer et al. (2014), with some adaptations (Fig. 1). Briefly, the animals had their backs shaved using an electric shaver (Wahl Clipper, EUA) 24 h before sensitization. For sensitization, the OXA groups were sensitized by the application of a solution of oxazolone (4-ethoxymethylene-2-phenyl-2-oxazoline-5-one, Sigma–Aldrich, St. Louis, MO, USA) 2 % in acetone and olive oil (4:1) (50 μL on the back) 15 days after starting the sugar diet.

On Day 22, the animals were challenged by topical application of a solution of oxazolone 1 % in acetone and olive oil (4:1) (20 μl in each of the ears and 50 μl on the back). The control groups treated with OXA received topical application of the vehicle to the ears and back in the same proportions (4:1).

2.3. High-sugar diet

The mice were fed a standard Nuvilab CR-1 diet (SD) composed of 76 % carbohydrates, 9 % fat, and 15 % proteins (3.1 kcal/g). In addition to the standard diet, animals received a separate bowl of condensed milk (ITALAC - 3.25 kcal/g), which is composed of 68 % carbohydrates, 23 % fat, and 9 % protein, with an added mix of vitamins and minerals [11]. The condensed milk diet was started fifteen days before the sensitization episode and maintained until the day of euthanasia. The mice were observed daily. The animals and feed were weighed three times a week. The 15-day diet time was considered short-term based on the terminology of the scientific literature [23–25].

2.4. Experimental groups

The animals were randomly assigned to four experimental groups. Group 1 (control group with a standard diet (C-SD): mice sensitized and challenged with the vehicle (without ACD) and fed a standard diet (n = 5); Group 2 (OXA group with a standard diet (OXA-SD): mice sensitized and challenged with OXA and fed a standard diet (n = 6); Group 3 –(sugar-rich diet control group (C - HSD): animals sensitized and challenged with the vehicle (without ACD) and fed a standard feed and condensed milk (ITALAC - 3.25 kcal/g) ad libitum via drinker (n = 5); and Group 4 (OXA group with sugar-rich diet (OXA - HSD): animals sensitized and challenged with OXA and fed a standard feed and condensed milk (ITALAC - 3.25 kcal/g) ad libitum in drinking fountains (n = 6).

2.5. Metabolic parameters

Biochemical measurements of triglycerides, cholesterol, HDL-cholesterol, glucose, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were performed using colorimetric assay kits (Labtest Diagnostica, MG, Brazil) according to the manufacturer's instructions. The calculation of LDL cholesterol was performed using the Friedewald equation [LDL] = (CT - HDL) - (TG/5) [26]. For liver lipid extraction, the protocol used is an adaptation of Folch [27]. We removed 30 mg of tissue that was homogenized in 1 mL of methanol:chloroform (2:1) solution and left shaking overnight at 4 °C. Then, we added 0.5 mL of 0.6 % NaCl and centrifuged it at 2000×*g* for 20min. We separated the lower phase and evaporated it in a speed vac. Finally, we resuspended the organic phase in 200 μL of isopropanol and measured the cholesterol and triglycerides with a colorimetric assay kit (Labtest Diagnostica, MG, Brazil).

The oral glucose tolerance test (OGTT) is very accurate for verifying glucose intolerance [28]. The animals were fasted for 6 h. The weight of the animals was measured and recorded. The tip of the mouse's tail was cut using sterile surgical scissors, and blood drops were collected directly on the glucose meter test strip, measuring the baseline glucose level. Then, a 25 % glucose solution (8 μL for each g) was administered by gavage. At 15, 30, 45, 60, and 75 min after glucose gavage, new blood samples were collected to record glucose levels at these specific times. Glucose levels were measured using the Accu-Chek Active® digital blood glucose meter (Roche Diagnostics GmbH, Mannheim, Germany). A glucose concentration curve was plotted by time, and the area was calculated for each animal [11].

2.6. Skin surface pH and transepidermal water loss

Skin pH and transepidermal water loss (TEWL) were measured using a Tewameter® MPA580 (Courage + Khazaka, Germany). The measurements were performed 24 h after elicitation. For the pH analyses, five individual pH values were obtained, while for the TEWL analyses, 30 serial measurements were performed in a total time of 30 s expressed in g/hm^2. The data were recorded as the mean ± standard error of the mean. The thickness of both ears was measured using an external digital micrometer (ZAAS). The measurements were performed in the central region of the ears, and the values were expressed in mm [29–31].

2.7. Histology

At the end of the experiment, the ears were excised and washed to remove the blood, fixed by immersion in 4 % paraformaldehyde and embedded in paraffin. Subsequently, they were cut into 5 μm sections. Tissue sections (5-μm thickness) were stained with hematoxylin-eosin for evaluation of the skin structure and cellular infiltrate. Epidermal and dermal hyperplasia was assessed based on epidermal and dermal thickness, respectively. Epidermal and dermal thickness was measured at five different locations on each image at a magnification of 40× using Zen Core software (ZEISS, Jena, Thuringia, Germany) by an analyst blinded to the identity of the samples. The amount of cell infiltration was measured using Image-Pro Plus software, using a quadrant with an area of 134,550 μm^2.

2.8. Cytokine assessment

For the evaluation of cytokines in tissues, 100 mg of skin taken from the back of each mouse was homogenized on ice in RIPA lysis buffer using a tissue homogenizer (Politron®). Samples were centrifuged, and the supernatant was analyzed using a sandwich enzyme-linked immunosorbent assay (ELISA) or CBA Mouse Cytokine Kit (BD Biosciences). We used antibodies and standards for IL-6, IL-4, and

Table 1
Body weight, food intake, cholesterol and serum metabolites levels in mice fed either the standard diet or high-sugar diet (HSD). *Caloric ingestion considered the food ingestion calories for C- SD and OXA-SD group and food ingestion plus condensed milk intake calories for C-HSC and OXA HSD groups. The results are shown as the mean ± SEM of 6–11 animals for group. The values were analyzed using the one-way ANOVA and Tukey's post-test. (a) $p < 0.05$ versus C-SD, (b) $p < 0.05$ versus C-HSD, (c) $p < 0.05$ versus OXA-SD.

	C-SD n = 5	C-HSD n = 6	OXA-SD n = 5	OXA-HSD n = 6
Initial body weight (g)	18,1 ± 0,30	19,0 ± 0,63	17,3 ± 0,42	18,8 ± 0,48
Body weight gain (g)	2,20 ± 0,19	3,48 ± 0,15[a]	2,53 ± 0,17[b]	3,30 ± 0,30[a]
Food ingestion (g/day)	3,57 ± 0,45	0,96 ± 0,23[a]	3,91 ± 0,44[b]	0,94 ± 0,21[a,c]
Condensed milk intake (g/day)	–	2,64 ± 0,37	–	2,67 ± 0,40
Caloric ingestion (kcal/day)*	11,0 ± 1,37	11,5 ± 1,67	12,1 ± 1,36	11,5 ± 1,54
Visceral adipose tissue (g)	0,36 ± 0,05	0,60 ± 0,10	0,28 ± 0,02[b]	0,58 ± 0,06[c]
Fasted serum glucose (mg/dL)	119 ± 2,11	142 ± 2,61[a]	104 ± 3,77[b]	129 ± 8,77[c]
Total cholesterol (mg/dL)	82,4 ± 4,17	121 ± 7,41[a]	90,8 ± 3,95[b]	136 ± 8,22[a,c]
LDL-cholesterol (mg/dL)	70,7 ± 4,49	111 ± 7,05[a]	83,0 ± 4,23[b]	122 ± 7,84[a,c]
HDL-cholesterol (mg/dL)	1,55 ± 0,12	1,88 ± 0,20	1,40 ± 1,0	1,75 ± 0,08
Triacylglycerol (mg/dL)	50,7 ± 4,12	40,9 ± 4,26	32,3 ± 2,00	61,0 ± 8,22[c]
Liver weight (g)	0,96 ± 0,04	0,98 ± 0,06	0,93 ± 0,03	1,26 ± 0,03[a,b,c]
AST (U/L)	35,7 ± 7,91	40,9 ± 5,92	43,4 ± 2,6	40,91 ± 4,6
ALT (U/L)	11,4 ± 2,7	15,4 ± 1,62	16,1 ± 0,98	15,81 ± 0,79
Liver cholesterol (mg/mg)	2,14 ± 0,22	2,8 ± 0,11	4,15 ± 0,30[a,b]	5,13 ± 0,21[a,b,c]
Liver triglycerides (mg/mg)	23,5 ± 1,06	24,24 ± 1,14	32,28 ± 1,6[a,b]	36,6 ± 1,7[a,b]

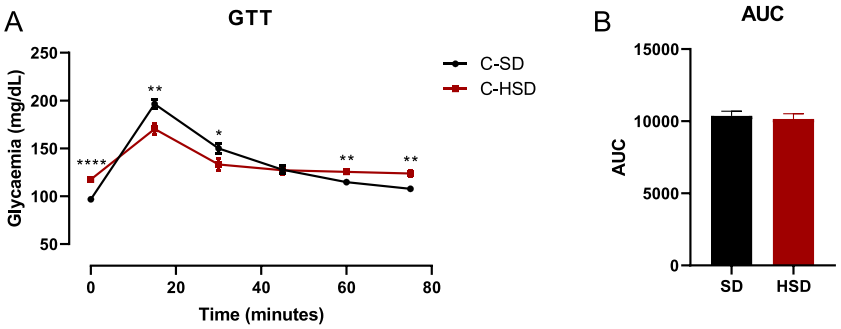

Fig. 2. Glucose tolerance panel of mice fed a standard diet (CD) or a high-sugar diet (HSD). A: Variations in blood glucose levels during the glucose tolerance test (GTT) in mice fed the diets for 15 days, measured 1 day before the first sensitization for allergic contact dermatitis induction; B: AUC, area under the curve for blood glucose - values obtained from the glucose tolerance test (GTT). The results are expressed as the mean ± SEM of 11 animals per group. Significant differences among groups were analyzed by Student's *t*-test.

IL-33 from R&D Systems and 96-well microplates (Immunoplate Maxisorb; Nunc), according to the manufacturer's instructions. IL-17, IL-10, TNF-α and IFN-γ were analyzed using BD cytometric bead array (CBA) Mouse Cytokine Kit (BD Biosciences) in skin-homogenized tissue, following the manufacturer's instructions. The data were acquired using a BD FACS Accuri flow cytometry system (BD Biosciences) and analyzed using BD FCAP Array v. 3.0 software (BD Biosciences). A standard curve was generated using a 5-parameter logistic (5-PL) equation.

2.9. Statistical analyses

The data are expressed as the mean ± standard error of the mean (SEM). Statistically significant differences were determined using one-factor variance analysis (ANOVA), followed by Tukey's test for multiple comparisons. Differences with $p < 0.05$ were considered statistically significant.

3. Results

3.1. Effects of a high-sugar diet on body weight and metabolic parameters

First, the effects of the HSD on metabolic parameters before the induction of allergic contact dermatitis, body weight, glucose tolerance test, adiposity, liver, and serum biochemistry parameters were evaluated. Animals fed an HSD showed a higher gain in body weight than animals fed a SD. These data were confirmed when comparing the final weight gain to the initial weight of each group (Table 1), and there was no significant difference in the initial weights between the different groups. The SD animals consumed more feed than the HSD animals (Table 1). Most of the caloric intake of the HSD group came from the consumption of condensed milk rather than from feed intake. Regarding total calorie intake, there were no significant differences in the amount of food consumed by the

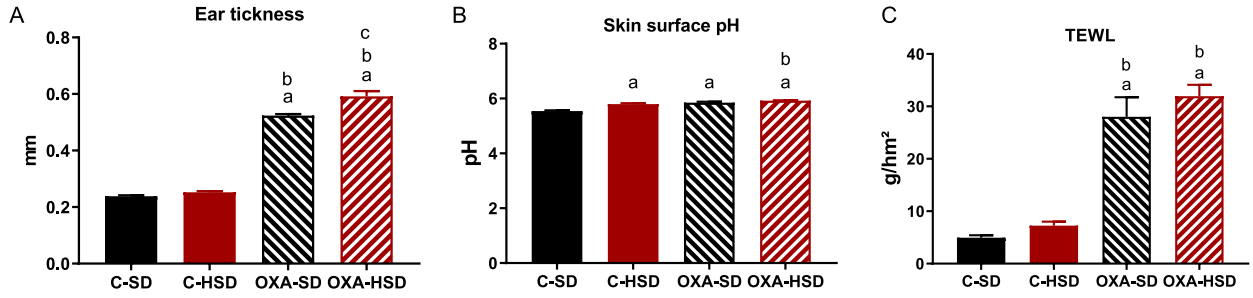

Fig. 3. Ear thickness obtained from the mean measurements of the right and left ears (A); skin surface pH (B) and transepidermal water loss (TEWL) (C) of mice fed a standard diet (C-SD) or a high-sugar diet (C-HSD) and mice with allergic contact dermatitis fed a standard diet (OXA-SD) or a high-sugar diet (OXA-HSD). The results are expressed as the mean ± SEM of 6 animals per group. Statistical significance was determined using ANOVA (with Tukey's post-test). (a) $p < 0.05$ versus C-SD, (b) $p < 0.05$ versus C-HSD, (c) $p < 0.05$ versus OXA-SD.

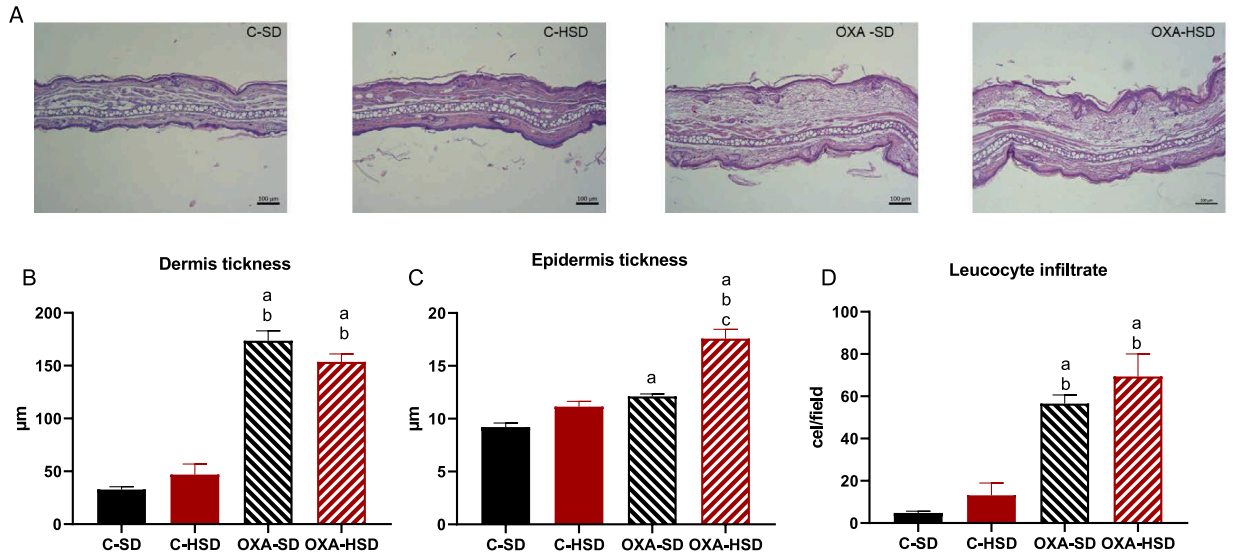

Fig. 4. Photomicrograph of H&E-stained ear tissue sections using a 10× objective. (A); Epidermal thickness (B); Dermis thickness (C) and total leukocyte infiltrate in ear tissues (D) of mice fed a standard diet (C-SD) or a high-sugar diet (C-HSD) and mice with allergic contact dermatitis fed a standard diet (OXA-SD) or a high-sugar diet (OXA-HSD). The results are expressed as the mean ± SEM of 6 animals per group. Statistical significance was determined using ANOVA (with Tukey's post-test). (a) $p < 0.05$ versus C-SD, (b) $p < 0.05$ versus C-HSD, (c) $p < 0.05$ versus OXA-SD.

different groups (Table 1). The HSD favored an increase in gonadal, subcutaneous, and retroperitoneal adipose tissues. Consequently, the visceral adipose tissue, which is the result of the sum of these adipose tissues, was significantly higher in the groups fed the HSD diet when compared to the groups fed a standard diet (Table 1). The total cholesterol and LDL levels were higher in Groups C-HSD and OXA-HSD, showing that a higher sugar intake led to an increase in these levels (Table 1). Animals fed an HSD had higher fasting glucose rates than animals fed a SD (Table 1). In the glucose tolerance test, it was verified that at 15 min, the animals fed an HSD had a lower glycemic index than the animals fed a SD (Table 1). There was no significant difference in HDL between the groups (Table 1). For triacylglycerol rates, there was a significant increase only in the OXA-HSD group (Table 1). Regarding liver weight, the OXA-HSD group showed a significant increase when compared to the other groups (Table 1). It was necessary to combine the two interventions (diet and dermatitis) for weight change to occur. By evaluating the activity of ALT and AST enzymes, we observed that there were no significant differences between the groups. Regarding the cholesterol rates in the liver, we observed that the OXA-SD and OXA-HSD groups had higher rates than the control groups (Table 1), and among the groups with dermatitis, the group fed a high-sugar diet had higher values than the normal diet group (Table 1). Animals with dermatitis had higher rates of hepatic triglycerides than the control groups (Table 1). The glycemic index of SD animals returned to normal standards, while the parameters for animals on HSD remained higher (Fig. 2A). In the analysis of the area under the curve (Fig. 2B), no significant differences were observed, therefore indicating no glucose intolerance in the HSD group. It is important to remember that the diet duration in this study was short and that if it were longer, glucose intolerance could manifest.

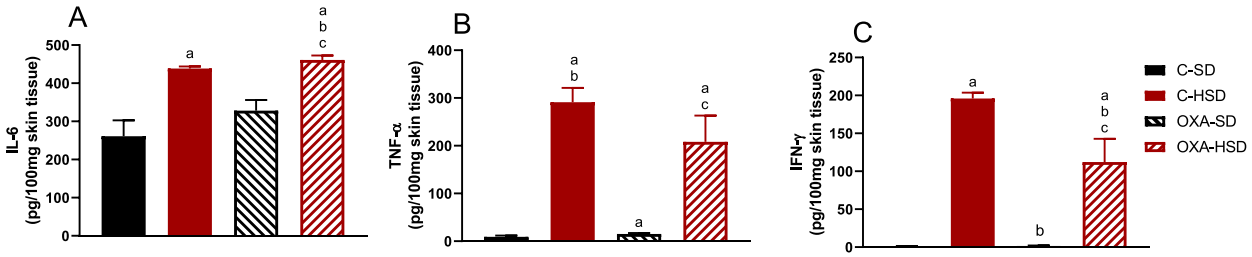

Fig. 5. Levels (ρg/ml) of interleukins IL-6 (A), TNF-α (B), and IFN-γ (C) in the skin homogenate of mice fed a standard diet (C-SD) or a high-sugar diet (C-HSD) and mice with allergic contact dermatitis fed a standard diet (OXA-SD) or a high-sugar diet (OXA-HSD). The results are expressed as the mean ± SEM of 6 animals per group. Statistical significance was determined using ANOVA (with Tukey's post-test). (a) $p < 0.05$ versus C-SD, (b) $p < 0.05$ versus C-HSD, (c) $p < 0.05$ versu OXA-SD. The results are shown as the mean ± S.E.M. The values were analyzed using one-way ANOVA and Tukey's posttest. (a) $p < 0.05$ versus C-SD, (b) $p < 0.05$ versus C-HSD, (c) $p < 0.05$ versus OXA-SD.

3.2. A high-sugar diet affects skin parameters in ACD mice

Every single intervention in the animals increased the pH of the skin, dermatitis induction protocol, and diet (Fig. 3B) Groups OXA-SD and OXA-HSD had higher water loss through the skin compared to their respective control groups (Fig. 3C). Experimental dermatitis promoted greater damage to the skin barrier structure since water loss is proportional to epithelial barrier dysfunctions. The diet did not provide greater water loss in animals with experimental dermatitis (Fig. 3C). Animals with dermatitis had thicker ears than control animals (Fig. 3A). The OXA-HSD group had thicker ears than the OXA-SD group (Fig. 3A), indicating that the diet favored increased edema in these tissues. Through the histological findings, it was observed that there was an increase in the thickness of the epidermis in the animals with dermatitis (Fig. 4 A). Animals fed a high-sugar diet had greater epidermis thickness than animals fed a standard diet (Fig. 4C). Regarding the thickness of the dermis, there was a significant increase in the OXA-SD and OXA-HSD groups compared to the control groups (Fig. 4B), but there was no difference between the OXA-SD and OXA-HSD groups (Fig. 4B). There was a significant increase in inflammatory cell infiltrate in the OXA groups compared to the respective control groups (Fig. 4D), but there was no relevant difference between the OXA-SD and OXA-HSD groups (Fig. 4D). When evaluating the quantification of mast cells, no differences were seen between the groups, and the data are not shown.

3.2.1. IFN-γ, IL-6, and TNF-α are increased in the skin of mice fed a high-sugar diet

Animals fed a high-sugar diet had greater IFN-γ, IL-6, and TNF-α production observed in the skin homogenate (Fig. 5A–C). The combination of high-sugar and induced ACD maintained IL-6 and TNF-α levels high but IFN-γ was reduced compared to animals fed a SD (Fig. 5). We also evaluated IL-4, IL-33, IL-10 and IL-17. We did not find differences in IL-4 and IL-33 between the groups. IL-10 and IL-17 values were below the detection limit.

4. Discussion

There is a high incidence of skin diseases worldwide, and ACD is one of the most common dermatological diseases, representing the main occupational cause of skin problems [4,31]. Many studies have addressed the relationship between high-fat diets and chronic diseases, but few studies have associated the consumption of a high-sugar diet with diseases, especially skin disease [32]. Taking into consideration that food promotes metabolic and immunological changes, we planned to evaluate the impact of a short-term high-sugar diet on mice with ACD. To achieve this goal, ACD was induced in mice with the used of oxazolone, thus reproducing the processes that occur in human ACD. To characterize a diet rich in sugar, we offered the mice a standard chow supplemented with a portion of condensed milk. The main macronutrient presents in the sweetened condensed milk used, which is usually commercially available at the supermarket, is carbohydrate (~53 % sucrose and ~15 % lactose) [33]. Our results show that this diet resulted in metabolic alterations as well as alterations in skin parameters. First, we analyzed weight and metabolic changes and observed that the groups fed an HSD showed an increase in serum glucose levels compared to the groups fed a SD. Regarding body weight, animals fed an HSD showed greater weight gain than animals fed a standard diet. Corroborating our findings, the intake of an HSD for two months increased serum glucose levels in mice. Next, we evaluated fat deposits and total cholesterol. Our data show that an HSD favored an increase in gonadal, subcutaneous, and retroperitoneal adipose tissue, as well as an increase in total cholesterol levels. As with our results, others showed that a sucrose-rich diet resulted in increased total cholesterol as well as visceral adiposity, with increased epididymal, retroperitoneal, and mesenteric adipose tissue [14]. We observed that the HSD alone did not affect triglyceride levels. However, triglycerides were altered in the HSD-OXA group compared to the other groups, and skin inflammation and a high-sugar diet can alter it. Mice fed an HSD showed greater weight gain than mice fed a standard diet.

In our study, we observed that a high-sugar diet associated with skin inflammation was related to increased liver weight. Animals fed a high-sugar diet for 18 weeks showed increased liver weight with an accumulation of hepatic lipids [34]. The serum activity of the enzymes ALT and AST is used to diagnose liver disorders [35]. In our study, no differences were observed between groups regarding ALT and AST activity. Corroborating these findings, after 18 weeks on a high-sugar diet, animals showed no changes in ALT and AST levels [14]. Through liver lipid levels, we observed that animals with dermatitis had higher levels of cholesterol and triglycerides than

control animals. Likewise, patients with atopic dermatitis are more likely to have fatty liver [36]. In addition, atopic dermatitis in mice is associated with increased cholesterol and triglycerides in the liver due to gene regulation, that is, upregulation of Cdkn1a (which promotes lipid accumulation) and downregulation of PPARα (peroxisome proliferator-activated receptor alpha), Acox1 (acyl-CoA oxidase 1) and Cpt2 (Carnitine O-palmitoyl transferase II), which promote fatty acid β-oxidation [37]. Inflammatory cytokines such as IL-6, IL-17, and TNF-α, produced by psoriatic skin injury, induce metabolic changes in the liver in the same way that subsequent liver inflammation promotes keratinocyte proliferation and skin inflammation [38], thus demonstrating a bilateral relationship between these organs. The mechanisms involved in the association between nonalcoholic fatty liver disease (NAFLD) and psoriasis, called hepato-dermal axis, are not fully understood [39]. Also, it is unclear whether psoriasis leads to NAFLD or the other way around [39, 40]. It is suggested that cytokines, like IL-6, produced by lymphocytes and keratinocytes in the skin circulates systemically to the liver inducing various metabolic changes. The literature also suggests that pro-inflammatory (such as IL-6 and C-reactive protein), pro-coagulant, pro-oxidant and pro-fibrogenic mediators of the inflamed liver influence skin disease, as psoriasis through increased proliferation of keratinocytes, increased inflammation, and molecules of vascular adhesion [39,41]. Experimentally, it has been also shown that induction of oxazolone-induced skin inflammation is more evident in NAFLD mice than in normal mice; oxazolone challenge significantly increases ear thickness, ear weight, nuclear factor-κβ activity, and histological features of skin inflammation in NAFLD mice as compared to normal mice [29]. After analyzing the metabolic changes that occurred in our experimental model, we evaluated the ACD.

The experimental dermatitis induced in this study showed similar alterations to those observed in the literature, such as an increase in the thickness of the epidermis, dermis, and leukocyte infiltrate when compared to control animals. Other studies with experimental dermatitis in mice showed increased edema and dermal inflammatory infiltrate 24 h after oxazolone challenge [42], and epidermal hyperplasia was observed 24 h after oxazolone challenge (124). First, we evaluated parameters related to the skin barrier, such as transepidermal water loss and pH. The disruption of the skin barrier results in increased transepidermal water loss [43]. Here, ACD induction promoted an increase in water loss from the skin. However, the ingestion of a high-sugar diet by animals with dermatitis did not influence this parameter. A study showed that mice fed a high-fat diet for 26 weeks had a 33 % greater transepidermal water loss than animals on a standard diet [44]. The pH plays an important role in maintaining the integrity of the stratum corneum, in addition to helping with skin homeostasis due to its antimicrobial action [45]. In this study, both dermatitis and diet, as well as the combination of the two interventions, promoted an increase in skin pH. There was no significant difference between the OXA-SD and OXA-HSD groups but there was a difference between the C-SD and OXA-HSD groups, leading us to consider that there was a greater influence of induced dermatitis than diet on the skin. Other studies show that inflammatory skin conditions increase skin pH [46,47]. Edema and leukocyte infiltrate are indicative of an inflammatory process [45]. Animals fed a high-sugar diet had greater epidermal thickness than animals fed a standard diet, but there was no significant difference in dermal thickness or inflammatory infiltrate. Interestingly, in a psoriasis model, a Western diet promoted greater ear thickness and epidermal hyperplasia than a high-fat diet [12]. Here, the high-sugar diet exacerbated the increase in ear thickness observed in animals with experimental dermatitis. Cytokines produced by epidermal cells can stimulate keratinocyte proliferation, promoting epidermal hyperplasia [48]. Several studies have demonstrated the production of IL-6 by epidermal keratinocytes and suggested a physiological role for IL-6 in the autocrine proliferation of epidermal keratinocytes [49–51]. We observed increased IL-6 in the skin of animals fed a high-sugar diet. Because an increased epidermal thickness was observed in animals with dermatitis, it was potentiated by a high-sugar diet, which may suggest that IL-6 and other cytokines could be involved in the skin alterations observed in this study. IL-6 deficient transgenic mice displayed significantly delayed cutaneous wound healing compared with wild-type control animals [51]. Interestingly, IL-6 induction and IL-6R function would appear to be distinctly dysregulated during diabetes and hyperglycemia, possibly contributing to delays in healing by affecting the epidermal response to this cytokine [52–54]. The data presented in this article are not enough to demonstrate the role of IL-6 in allergic contact dermatitis in the face of a high-sugar diet. Future studies using animals deficient for this cytokine would be interesting to unveil IL-6 role in our experimental model. The role of TNF in ACD has been extensively investigated. The most important function seems to be to promote migration of the antigen-presenting Langerhans cells to draining lymph nodes during the sensitization phase [55,56]. TNF also has an important role during the elicitation phase of ACD [57]. A high-sugar diet increases TNF-α and is not affected by ACD. Another cytokine that was increased in the skin due to a high-sugar diet was IFN-γ. The IFN-γ dependent chemokines are produced by keratinocytes, mainly during the clinically inflammatory phase of ACD [58]. Also, chemokine (C-X-C motif) receptor (CXCR) 3, the common receptor of the three IFN-γ dependent chemokines, is upregulated in chemical-induced allergic skin responses when compared with irritant skin responses [58]. Interestingly, the high-sugar diet increases the production of IFN-γ in the skin, but exposure to OXA-HSD mice shows a decrease in this cytokine compared to OXA-SD. As previously mentioned, high sugar consumption has been linked to increased production of pro-inflammatory cytokines, including IL-6, TNF-alpha, and IFN-gamma These cytokines can be produce by innate immune cells in the skin, such as keratinocytes, Langerhans, mast cells, fibroblasts or endothelial cells. However, it is not excluded that these cytokines may originate from sources other than the skin. These cytokines play critical roles in immune signaling and the regulation of inflammation. Elevated levels of these pro-inflammatory cytokines can contribute to chronic inflammation, disrupt the delicate immune system balance, and potentially lead to the development or worsening of inflammatory skin conditions. The relationship between a high-sugar diet and the cells of the skin's innate immunity is complex and multifaceted. Further research is needed to fully understand the mechanisms underlying the impact of high sugar intake on these immune cells and their role in skin health and disease". Nevertheless, our study has some limitations, cellularity and cytokines were not evaluated in the auricle lymph node. There is a general understanding that the second presentation of the antigen occurs in the skin and not in the draining lymph node since activated T cells (from the sensitization phase) migrated to the dermis and further epidermis [8]. However, studies evaluating the influence of a high-sugar diet on antigen presentation to T cells in lymph nodes that occurs in the sensitization phase would be interesting for this subject [9]. Another important aspect is that we sensitized the dorsum and, challenged the ear and dorsum

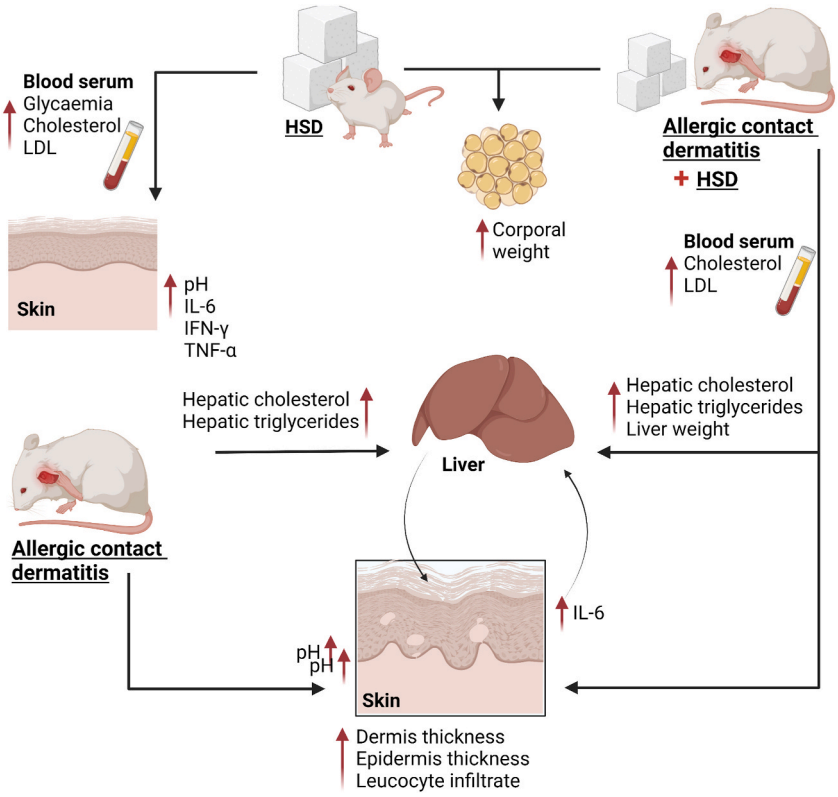

Fig. 6. Schematic effect of high-sugar diet in experimental allergic contact dermatitis.

with OXA. Thus, the back was exposed to the OXA twice within a 7-day interval. TEWL, pH, and cytokines were measured at the skin dorsum and these parameters may be influenced by two applications of OXA to the same area. Possibly due to this fact, the cytokines were not affected by OXA challenge.

5. Conclusions

In conclusion, we verified that a diet rich in sugar given to mice for three weeks was able to increase their total cholesterol, HDL and LDL. Interestingly, the dermatitis model increased cholesterol and triglycerides in the liver, and the combination of a high-sugar diet and dermatitis increased liver weight and exacerbated liver cholesterol measurements. A high-sugar diet increases skin IL-6, TNF-α and IFN-γ production, which could be involved in the exacerbated epithelial thickness observed in OXA-induced ACD mice. In turn, IL-6 produced by the skin may also induce liver alterations, which have been described to cause increased epithelial thickness (Fig. 6). Further studies elucidating the molecules that participate in this bidirectional relationship between skin and liver mechanisms would be relevant for treatment not only for ACD but also for other inflammatory skin disorders. Based on our results, nutrition professionals should pay attention to the diet of patients with skin inflammation to prevent the worsening of disease.

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CRediT authorship contribution statement

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Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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