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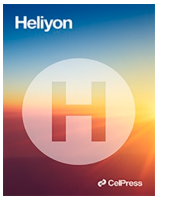

Research article

Reduction of oxidative stress response and protection of liver and renal cell functions by reduced glutathione in lower limb arterial ischemia–reperfusion in New Zealand white rabbits with high triglyceride levels

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ABSTRACT

Objective: Acute liver and kidney injury is the most common complication after aortic surgery, which seriously affects the survival and safety of perioperative patients. The presence of chronic preoperative liver and renal insufficiency, presence of preoperative blood inflammation indicators, duration of intraoperative extracorporeal circulation, and volume of red blood cell transfusion are the main influencing factors for acute postoperative liver and kidney injuries. In recent years, with the research progress on oxidative stress, a growing body of evidence has demonstrated that oxidative stress may cause tissue damage after ischemia–reperfusion (IR). However, the impact of the oxidative stress of distal tissues caused by IR on liver and renal cells after arterial surgeries has not yet been elucidated.

Methods: New Zealand white rabbits were used for the experiments and were divided into three groups. Among them, two groups were fed high-fat feed to establish a white rabbit model of hypertriglyceridemia, whereas the control group was provided with ordinary feed. In the experiment, white rabbits were subjected to occlusion of the infrarenal aorta abdominalis to simulate IR of the lower limbs. The effects of high triglyceride levels after the arterial IR of the lower limbs were investigated using the contents of reactive oxygen species (ROS) and malondialdehyde (MDA), a fat metabolite, in ischemic muscle tissues and blood tissues. One of the groups receiving high-fat feed received intervention with reduced glutathione (GSH) before IR of the lower limbs. Pathological studies were performed to identify the expression levels of inflammatory factors and inflammatory cells in liver and renal cells as well as cell apoptosis. The effects of GSH administration before IR on reducing the oxidative stress in adipose tissues and alleviating liver and kidney damage after stress response were investigated.

Results: After IR, the increases in ROS and MDA in ischemic muscle tissues and blood tissues were higher in white rabbits with high triglyceride levels than in those that only received ordinary feed or received intervention with GSH. In addition, for white rabbits with high triglyceride levels, the TNF-α expression levels in the liver increased after IR. Moreover, a considerable increase in the expression of TNF-α, IL-6, macrophages, and T lymphocytes were observed in renal cells. A large number of inflammatory cells and the formation of immune complexes were also noted in the glomeruli; in addition, cell apoptosis was promoted.

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Conclusion: This study showed that high triglyceride levels enhanced the oxidative stress response and increased ROS production in New Zealand white rabbits after arterial IR of the lower limbs. High ROS levels activated the expression of inflammatory factors and inflammatory cells in the liver and kidney, which affected cell functions and promoted apoptosis. At high triglyceride levels, GSH downregulated ROS production in oxidative stress after IR, thereby protecting liver and kidney functions.

1. Introduction

Hyperlipidaemia and obesity are major contributing factors to the occurrence of aortic dissection and other aortic diseases [1,2]. Open surgery is the main method to treat these diseases, including Sun's procedure for aortic dissection and arterial bypass surgery for the treatment of atherosclerosis obliterans [3,4]. In the event of surgical vascular trauma or skeletal muscle injuries that require long surgeries of vascular reconstruction, the distal tissues would be subject to ischemia–reperfusion (IR), and the skeletal muscle injuries induced by such a process are inevitable [5]. In addition, acute damage to the liver and kidney functions after aortic surgery is generally believed to be related to insufficient tissue perfusion after prolonged hypothermia [6,7].

Obesity not only increases the risk of aortic dissection and aortic aneurysm but also elevates the risk of perioperative death [8]. Although aortic disease affects more men than women, more women die during the perioperative period than men [9]. Although the BMI of men is higher than that of women, the body fat percentage of women is higher than that of men [10]. Factors such as female gender, dyslipidaemia, smoking, diabetes mellitus, and hypertension have been associated with the postoperative increases in interleukin—1β(IL-1β), tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), C-reactive protein, malondialdehyde (MDA), and white blood cell levels after aortic dissection surgery, rendering them risk factors for postoperative mortality after surgery for type A aortic dissection [11].

Aortic surgery may cause IR to distal tissues, during which hypoxia can trigger the production of a large amount of reactive oxygen species (ROS) in underperfused tissues, resulting in oxidative damage to the ischemic tissues [12]. The causes and prevention of liver and kidney damage after aortic surgeries remain unclear. Intervening to modulate glutathione (GSH) levels prior to the onset of oxidative stress can mitigate or avert tissue harm by enhancing cellular antioxidant defense mechanisms. Nevertheless, the precise applications and their corresponding outcomes may differ among distinct pathological contexts and individual variations, necessitating further investigation and validation [13,14]. In this study, a high triglyceride model was established through high-fat feed for New Zealand white rabbits, and a vascular clamp was used to block the abdominal aorta to simulate IR of the lower limbs to investigate the effect of administration of glutathione (GSH) before arterial ischemia on the damage of liver and renal cells caused by adipose oxidative stress after IR.

2. Materials and methods

2.1. Animals

Laboratory animals: Thirty New Zealand white rabbits were used in this study, which were purchased from Jiangsu Zhenlin Biotechnology Co., Ltd. The rabbits weighed 600–950 g and were clean-grade male rabbits aged 30–45 days. The certificate number was 202237519.

This thestudy was performed according to the National Standard of the People's Republic of China GB/T35892-2018 for Ethical Review of Experimental Animal Welfare, taking into account animal experimentation, clinical research, and biodiversity rights. This research protocol has been approved by the Experimental Animal Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China (Anhui Provincial Hospital). Ethical approval number: 2023-N (A) −54.

Feeding method and group assignment: NONGFU SPRING drinking mineral water was used as drinking water for the rabbits. The feed that was used was Shandong Beibeiwo whole rabbit breed complete rabbit food (ingredients: crude protein 10–13 %, crude fibre 10–25 %, crude ash 6–20 %, moisture $<$14 %, total phosphorus 0.4 %, calcium 0.5–1.4 %, methionine + cystine $\geq$0.35 %, sodium chloride 0.3–1.2 %). Independently prepared high-fat feed: egg yolk powder and lard.

All white rabbits were individually housed and divided into three groups, namely the control group (C group), high-fat feed without intervention group (H group), and the intervention group receiving high-fat feed and preoperative intervention with GSH (H + G group), with 10 rabbits per group. Among them, the C group was only provided with basic feed, whereas 15 % egg yolk powder and 5 % lard were added on top of the basic feed for the H and H + G groups. After 8 weeks of feeding, three rabbits from each group were randomly selected for the experiments.

3. Methods

3.1. IR model

After the 9th week of feeding, the white rabbits received arterial IR surgery in the lower limbs. The surgical method was as follows: The rabbits underwent a 12 h preoperative fasting and were anesthetised using 3 % isoflurane. Thereafter, they were placed in a supine

position, and the abdominal hair was shaved. A 3 cm longitudinal incision was made in the middle 1/3 of the lower abdomen. A cotton swab was used to free the intestinal tissues and for the blunt dissection of the posterior peritoneum to fully expose the abdominal aorta and the inferior vena cava. Thereafter, a cotton swab was used for the blunt dissection of the abdominal aorta below the renal arteries and the free artery was marked with a plastic strip (Fig. 1A). Low molecular weight heparin (LMWH, 500 μ) was injected through the marginal ear vein. After 5 min, a vascular clamp was used to block the abdominal aorta for 3.5 h (Fig. 1B). After blocking, the vascular clamp was released, and the operator used their hands to examine the pulse of the blocked artery and the distal artery. The incision was sutured layer by layer, and the rabbit skin was disinfected with iodine before the rabbits were returned to the cage. The rabbits may be resuscitated after a 5 min observation. The intervention group receiving GSH (H + G group) was intravenously injected with 81 mg of GSH + 2 mL of normal saline via the ear vein 1.5 h preoperatively before the IR experiment was performed.

Reduced glutathione for injection (0.9 g/phial, Atuomolan) manufactured by Chongqing YaoPharma Co., Ltd. was used. Preparation ratio of GSH solution: GSH was dissolved in 10 mL of saline. The solution (0.9 mL) was diluted with 2 mL of saline to prepare 81 mg of GSH solution.

Heparin sodium for injection (Chenxin) (2 mL: 12500 U) from Sinopharm Rongsheng Pharmaceutical Co., Ltd. was used as the LMWH sodium for this study. Preparation ratio of LMWH sodium: A 1 mL syringe was used to draw 1 mL of heparin sodium for injection, of which 0.08 mL was retained. Thereafter, the syringe containing 0.08 mL of the solution was used to draw saline to 1 mL to prepare 500 μ of LMWH sodium solution.

3.2. Methods for experimental material collection

The first step was to collect the preoperative materials of the experimental white rabbits. Two blood samples were collected via the marginal ear vein (biochemical tubes were used for biochemical and enzyme-linked immunosorbent assay (ELISA) assays, whereas the anticoagulation tubes were used for blood ROS detection). A 3 × 3 mm tissue sample from the gastrocnemius muscle of the left calf was collected to determine ROS levels in muscle tissues.

In the second step, IR surgery was performed 1 week after the completion of the first step. Blood samples and muscle tissue samples of the left calf were collected 0 h post-IR as in the first step.

In the third step, 3 % isoflurane was used for inhalational anaesthesia 4 h post-IR. Each rabbit was placed in a supine position and a 5 cm longitudinal incision was made on the left abdomen. The left kidney was exposed after blunt dissection, and the renal portal artery and vein as well as the ureter were blocked with a vascular clamp. After ligating them on the proximal end, the kidney was removed. The incision was sutured layer by layer, and the skin was disinfected. The lower edge of the left lobe of the liver became visible after making a 1 cm transverse incision below the xiphisternal joint. After harvesting the material, the incision was sutured layer by layer and the skin was disinfected. After the right calf was disinfected, the gastrocnemius muscle was exposed layer by layer and a 3 × 3 mm tissue sample was taken to determine the ROS levels in muscle cells and tissues.

3.3. Immunohistochemistry

Immunoenzyme techniques were adopted to perform the immunohistochemistry tests on the liver and kidney tissues of white rabbits 4 h post-IR. Antigen selection: monoclonal antibody TNF-α antibodie Sc-52746 from Santa Cruz Biotechnology was used. The expression sites included membrane and secreted proteins, and the dilution ratio was 1:150. The IL-6 antibodie Sc-28343 from Santa Cruz Biotechnology was used. The expression site was composed of secretory proteins, and the dilution ratio was 1:150. The F4/80 antibodie 70076S from Cell Signaling Technology was used. The expression site was the membrane, and the dilution ratio was 1:300. CD3 antibodie MAB-0740 from Maxim Biotechnologies was used. The expression site was the membrane, and the dilution ratio was 1:150 for antigen staining.

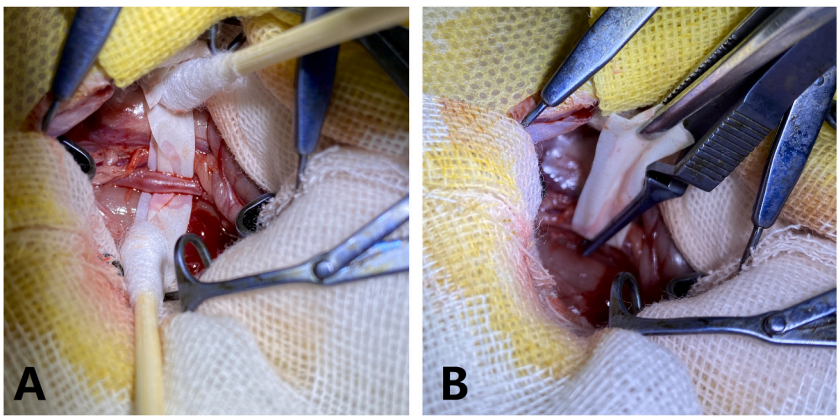

Fig. 1. A. A sterile cotton swab was used for the blunt dissection of the abdominal aorta, which was marked with a plastic strip; B. A vascular clamp was used to block the abdominal aorta.

3.4. Histology

The TUNEL assay was performed to determine the apoptosis of liver and renal cells [15] using the C1088 TUNEL Cell Apoptosis Detection Kit from Beyotime Biotech. Inc. The B022 Masson's trichrome staining solution from Ebiogo was used for Masson's trichrome staining of renal tissues.

3.5. Detection of serum markers

The kits JYM0055Rb, JYM0045Rb, JYM0047Rb, and JYM0058Rb from Wuhan JYM Biotechnology Co., Ltd. were used to perform ELISA to determine rabbit oxidized low-density lipoprotein (ox-LDL), rabbit total cholesterol (TC), rabbit triglyceride, and rabbit myoglobin levels [16]. Serum MDA levels were measured using the A003-1 MDA assay kit (thiobarbituric acid, TBA method) from Nanjing Jiancheng Bioengineering Institute [17].

3.6. ROS detection

The dichloro-dihydro-fluorescein diacetate (DCFH-DA) fluorescent probe was used [18]. ROS in oxidative stress was determined by flow cytometry using a commercial ROS detection kit (cat. No. S0033S) from Beyotime, and the data were analysed using FlowJo V10.

Extensive and meticulous testing procedures were applied to each sample, encompassing the triplicate assessment of serum markers and reactive oxygen species (ROS) to guarantee precision and reproducibility. The computation of mean optical density (MOD) values for each sample was derived from the immunohistochemical (IHC) evaluation of TNF-α, IL-6, F4/80, and CD3 expressions. This computation was executed by calculating the average optical density (AOD) across three randomly selected regions within each sample. The resulting dataset is presented as mean ± standard deviation (SD) with a sample size of n = 9 for each group.

3.7. Statistical analysis

Statistical analysis of the data and production of charts were performed using GraphPad Prism 9.3. Two-way analysis of variance (ANOVA) with Holm–Sidak correction was applied. A p-value <0.05 was considered statistically significant.

4. Results

The blood lipid levels of white rabbits were measured 1 week preoperatively. Fig. 2A shows that the triglyceride levels of white rabbits receiving ordinary feed added with egg yolk powder and lard were higher than those of white rabbits receiving ordinary feed. Most triglycerides are obtained from diet. After long-term consumption of large amounts of fats, especially food containing animal fat, the triglyceride levels in the body may increase significantly [19]. There were no statistical differences in ox-LDL and TC levels between the two feeding methods, as shown in Fig. 2B and C.

ROS are oxygen-containing reactive molecules. Low-level ROS are involved in normal physiological activities such as immune response, muscle contraction, and exercise. In pathological scenarios, the antioxidant system collapses, which may lead to the release of a large amount of ROS, causing oxidative stress and tissue damage [20].

Fig. 3A indicate no significant differences in the preoperative ROS levels in the skeletal muscles of the lower limbs between the three groups of white rabbits. At 0 h after IR, the ROS level in the muscle tissues of the H group was significantly higher than that of the C and H + G groups, with no significant difference between the H + G group receiving intervention with GSH and the C group. Four hours after IR, the ROS levels in the muscle cells of all three groups started rising. The ROS level in the muscle cells of the lower limbs of the H + G group receiving preoperative treatment with GSH was significantly higher than that of the C group. However, the ROS levels

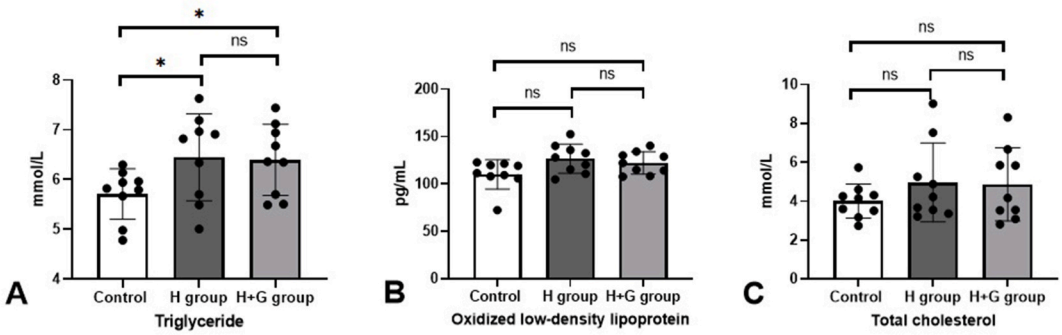

Fig. 2. Blood lipid levels in white rabbits before ischemia-reperfusion (IR): A. Triglyceride levels in three groups of white rabbits before IR; B. Oxidized low-density lipoprotein levels of three groups of white rabbits before IR; C. Total cholesterol (TC) levels in three groups of white rabbits before IR. Data shown represent means ± SD; n = 9 independent samples per group; *$p < 0.05$, ns: no significance.

in both groups were significantly lower than in the H group.

Fig. 3B show that the ROS level in the blood of white rabbits receiving high-fat diets preoperatively was significantly higher than that of white rabbits receiving conventional diets, which was related to the increase in blood lipids as a result of high-fat diets [21]. ROS levels increased in all three groups 0 h after IR. There was no significant difference in the blood ROS levels between the H + G group treated with GSH and the C group. The blood ROS levels of the H group were significantly higher than those of the C and H + G groups. Similarly, 4 h after IR, no significant difference was detected in blood ROS levels between the H + G group receiving intervention with GSH and the C group. Moreover, the blood ROS levels of the H group were significantly higher than those of the C and H + G groups.

Fig. 4A shows the myoglobin measurements of muscle tissue damage after IR. There was no difference in preoperative myoglobin levels among the three groups of white rabbits. The myoglobin level of the H group was higher than those of the C and H + G groups at 0 and 4 h post-IR.

In cardiovascular diseases, aldehydes are released in biological fluids (blood, saliva, gingival crevicular and cerebral fluids, and urine) when cells are damaged by lipid peroxidation. Therefore, MDA levels in serum or plasma have been used as indirect diagnostic indicators of oxidative stress in diseases such as myocardial infarction, reperfusion hypoxia, and atherosclerosis [22–24]. MDA, the by-product of lipid peroxidation, is an effective biomarker of adipose oxidative stress [25]. Fig. 4B shows that the level of blood lipid oxidation was expressed by the blood adipose oxidation product MDA. The blood MDA levels of white rabbits receiving high-fat feed before IR were higher than those of white rabbits receiving ordinary feed. At 0 and 4 h post-IR, the MDA levels in the H group were significantly higher than those in the C and H + G groups. The MDA levels in the H + G group of white rabbits receiving intervention with GSH were significantly higher than in the C group 0 and 4 h post-IR.

4.1. Pathological examination

ROS are closely related to the immune system and inflammatory response. The release of large amounts of ROS inevitably damages the liver and deep kidneys [26]. In the immunohistochemistry assays, TNF-α, IL-6, F4/80, and CD3 antigens were used to mark the expression of inflammatory factors TNF-α, IL-6, inflammatory cells, macrophages, and T lymphocytes in liver and renal cells.

Fig. 5 shows the expression of TNF-α, IL-6, F4/80, and CD3 in liver cells of white rabbits 4 h after IR of the lower limbs.

Fig. 5A shows that TNF-α expression levels were higher in the liver cell membrane and cytoplasm of the H group that did not receive intervention with GSH than in the liver cells of white rabbits fed with ordinary feed or received intervention with GSH. Fig. 5B shows that IL-6 was expressed in the cytoplasm of liver cells of the two groups of white rabbits that received a high-fat diet after IR, whereas that in the liver cells of the white rabbits that received a normal diet was very low. Fig. 5C and D shows that the expression levels of F4/

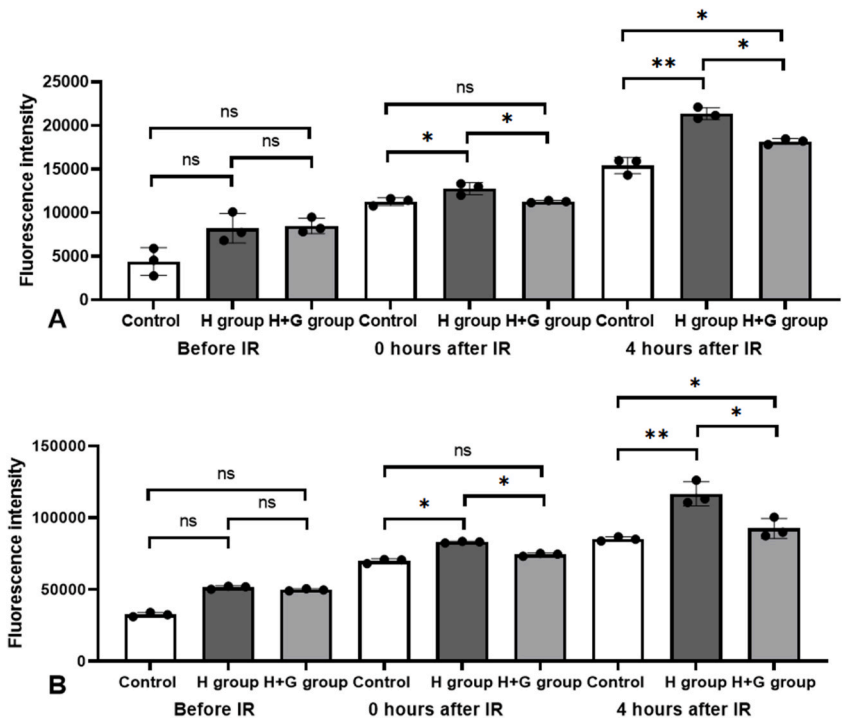

Fig. 3. Changes in the reactive oxygen species (ROS) in the skeletal muscles and blood of the lower limbs after ischemia-reperfusion (IR) of the abdominal aorta in white rabbits: A. ROS content in the skeletal muscle tissues of the lower limbs before and after IR; B. ROS content in blood before and after IR. Data shown represent means ± SD; n = 3 independent samples per group; $*p < 0.05$, $**p < 0.01$, ns: no significance.

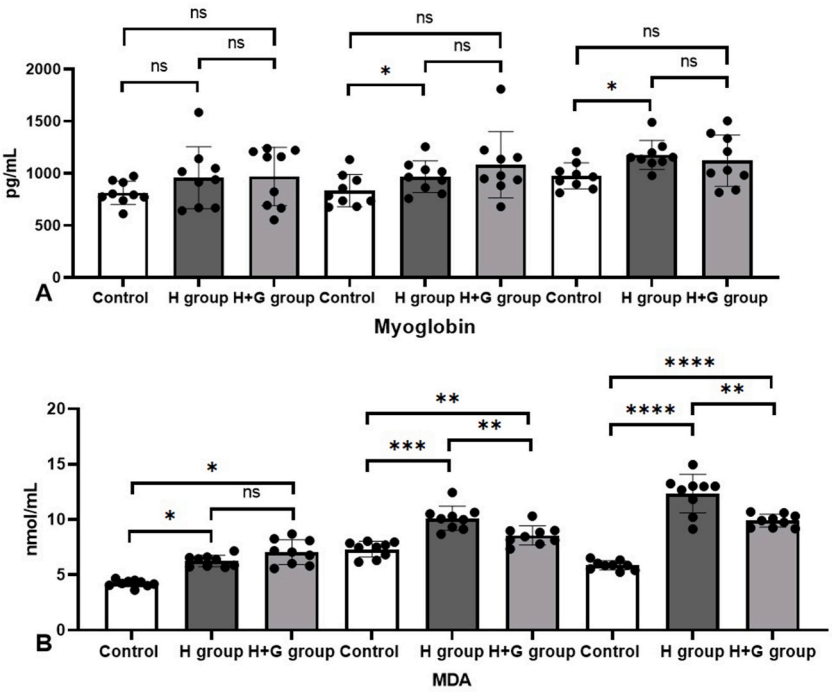

Fig. 4. Changes in myoglobin and the fat oxidation product malondialdehyde (MDA) in blood during ischemia-reperfusion (IR) of the abdominal aorta in white rabbits: A. Myoglobin content in the blood of the three groups of white rabbits before and after IR; B. MDA content in the blood before and after IR. Data shown represent means ± SD; n = 9 independent samples per group; $*p < 0.05$, $**p < 0.01$, $***p < 0.005$, $****p < 0.001$, ns: no significance.

80 and CD3 in the liver cells of the three groups of white rabbits 4 h after IR of the lower limbs were very low.

Fig. 6 demonstrates the expression of TNF-α, IL-6, F4/80, and CD3 in the renal cells of white rabbits 4 h after IR of the lower limbs. Fig. 6 shows that the expression levels of TNF-α, IL-6, F4/80, and CD3 in renal corpuscle cells and kidney tubular cells increased 4 h after IR in the lower limbs of white rabbits in the H group, whereas those in the cell membrane and cytoplasm of kidney corpuscle and kidney tubular cells in both the H + G group that received preoperative intervention with GSH and the control group were low.

Fig. 7 shows the pathology examination of Masson's trichrome staining, and the results indicated the thickening of the basement membrane of the renal capsule, also known as the Bowman's capsule, in the H group. Thrombus formation by several red-stained complexes was observed in the capillary lumen of the glomerulus, and significant thickening was observed for the basement membrane of the glomerulus.

Fig. 8 demonstrates the TUNEL assay for detecting apoptosis, and the results show that after IR of the lower limb arteries, there were more necrotic cells in the liver (Fig. 8A) and kidney (Fig. 8B) of the white rabbits in the H group that received high-fat feed than in those of white rabbits that received preoperative intervention with GSH in the H + G group and those of the control group.

5. Discussion

IR in distal tissues may cause ischemia–reperfusion injury (IRI) to distal tissues. Ischemia may lead to hypoxia and the production of large amounts of ROS, which consume endogenous antioxidants and result in the collapse of the antioxidant system, thus eliciting cellular oxidative stress [23]. Dysfunction of the Na–K–ATPase pump during tissue ischemia may lead to an overload of sodium and calcium in the cytoplasm. Such accumulation of calcium would lead to the activation of multiple cytoplasmic proteases, which are responsible for degrading proteins and activating apoptotic processes in the mitochondria [27]. Moreover, during this process, anaerobic glycolysis and mitochondrial dysfunction are enhanced under anaerobic conditions, which may lead to a decrease in intracellular pH levels and excessive ROS production after reperfusion due to increased oxygen supply [28].

Oxidative stress is more likely to occur after IR of the tissue to produce more ROS [29]. In IRI, ATP undergoes an enzymatic process that results in its conversion to hypoxanthine. The xanthine oxidase system may produce ROS by oxidizing hypoxanthine to xanthine and xanthine to uric acid. Under hypoxic conditions, due to low ATP levels, xanthine dehydrogenase would replace xanthine oxidoreductase and induce ROS formation during the conversion of hypoxanthine into uric acid, thereby ultimately enhancing the oxidative environment [30]. In addition, increased white adipose tissue may promote oxidative stress, leading to the accumulation of peroxides and the oxidative stress product MDA [31].

Oxidative stress in white adipose tissue: Following the restoration of blood flow, cells release different mediators (such as phospholipase A2, TNF-α, IL1β, and IFN-γ) that enhance the action of NADPH oxidase [32]. Several cells have the ability to attract nearby

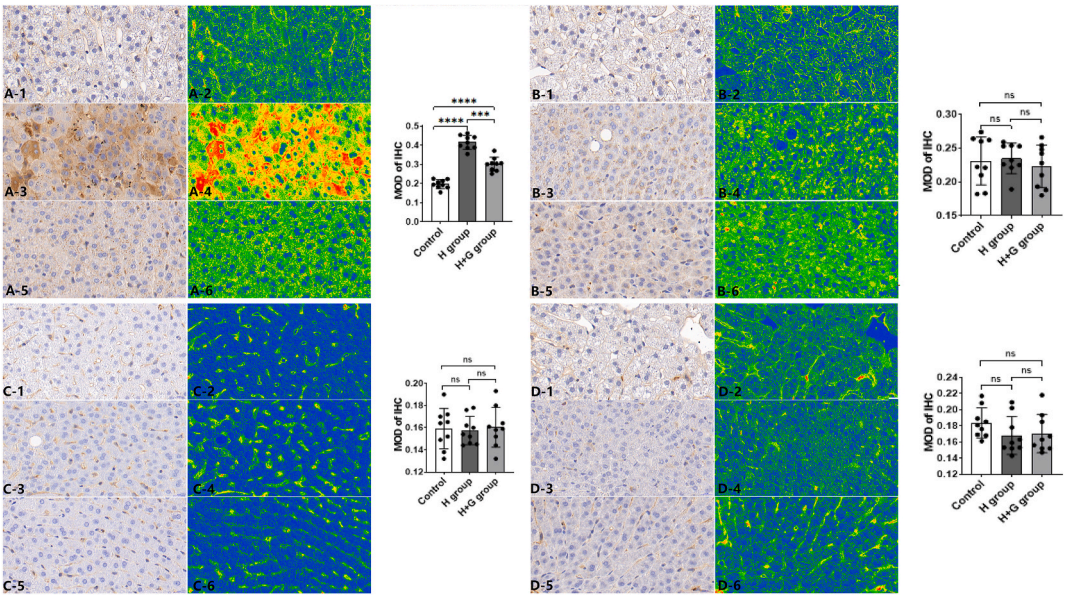

Fig. 5. Quantification of Mean Optical Density (MOD) for Immunohistochemical (IHC) Analysis of liver cells in Rabbits Following a 4 h Duration of Lower Limb Arterial Ischemia-Reperfusion (IR) (scale bar: 20 μm, brown—positive, immune complexes are produced with corresponding antigens; blue—cell nucleus; red—positive immunostaining complex after visual gradient image processing): A—Immunohistochemistry of inflammatory factor TNF-α in the liver tissue; B—Immunohistochemistry of inflammatory factor interleukin 6 (IL-6) in the liver tissue; C—Immunohistochemistry of macrophage marker F4/80 in the liver tissue; D—Immunohistochemistry of T cell marker CD3 in the liver tissue 1—Hepatocyte tissue of the control group; 2—Hepatocyte tissue of the control group after visual gradient image processing; 3—Hepatocyte tissue of the high-fat feed without intervention group (H group); 4—Hepatocyte tissue of the H group after visual gradient image processing; 5—Hepatocyte tissue of the intervention group receiving high-fat feed and preoperative intervention with reduced glutathione (H + G group); 6—Hepatocyte tissue of the H + G group after visual gradient image processing. Data shown represent means ± SD; n = 9 independent samples per group; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.005$, $^{****}p < 0.001$, ns: no significance.

neutrophils, thereby intensifying the inflammatory mediator response. Chemotactic cytokine activation by neutrophils leads to the production of more ROS, which explains the ROS regeneration later in the earliest recovery stage after the reperfusion phase [33].

IR has been associated with multi-organ failure in the heart, lungs, liver, gastrointestinal tract, nervous system, and kidneys, as well as an increase in ROS in the plasma post-IR [34,35]. A large amount of ROS is generated and reaches the target organs via blood circulation, where it breaks the antioxidant defence capacity, thereby eliciting oxidative distress in the target organ [36]. The consequence of oxidative distress is oxidative damage to intracellular organelles and biomolecules, and severe oxidative damage would ultimately lead to cell apoptosis and/or necrosis [37].

Oxidative stress and inflammatory response are pathological processes that promote each other [38,39]. Neutrophils are one of the sources of ROS, and ROS from endothelial cells and cardiomyocytes amplify the inflammatory response and affect nearby neutrophils, thereby inducing a chain reaction of ROS production [22]. Toll-like receptors are a major bridge in the interaction between oxidative stress and inflammatory responses as demonstrated by the IR models of multiple organs [40]. NF-κB activated by ROS regulates the expression of inflammatory genes, such as IL-1β, IL-6, and TNF-α [41,42]. Severe inflammation during myocardial ischemia–reperfusion injury is believed to be due to increased cytokines, namely IL-6, IL-1β, and TNF-α [43].

GSH is one of the crucial redox buffers in cells [44], playing a vital role in drug detoxification and elimination as well as in the protection of cells from damage by free radicals, peroxides, and toxins [45,46]. Supplementation of the antioxidant GSH before IR reduced oxidative stress response during IR of the lower limbs in white rabbits with high triglyceride levels. Moreover, the levels of the adipose metabolite MDA as well as ROS in ischemic tissues and blood were all significantly inhibited.

The expression levels of TNF-α in liver cells decreased after white rabbits with high triglyceride levels received preventive intervention with GSH before IR, indicating that the high levels of ROS were related to the activation of the TNF-α signalling pathway in liver cells. However, the intervention did not change the expression levels of IL-6, which is related to the adipose storage and metabolic function of the liver [47]. Under hypoxic conditions, high triacylglycerol levels would upregulate cellular IL-6 secretion and result in liver damage [48]. Non-alcoholic fatty liver disease (NAFLD) has been associated with cardiovascular disease (CVD) [49]. The main cause of death for patients with NAFLD is CVD, rather than cirrhosis, liver cancer, or liver failure [50]. Hypothermia, hypoxia, and ROS release caused by oxidative stress during open surgery for CVDs are the main factors that aggravate liver injury in patients. Perioperative hepatic impairment is an independent risk factor for major perioperative adverse events and death in cardiovascular surgery [51].

Excessive ROS production results in damage to the cellular components of the kidney, including DNA, proteins, and lipids, which may lead to cell death and kidney damage [52]. Excessive ROS production mainly affects the primary organs of IRI. The present study

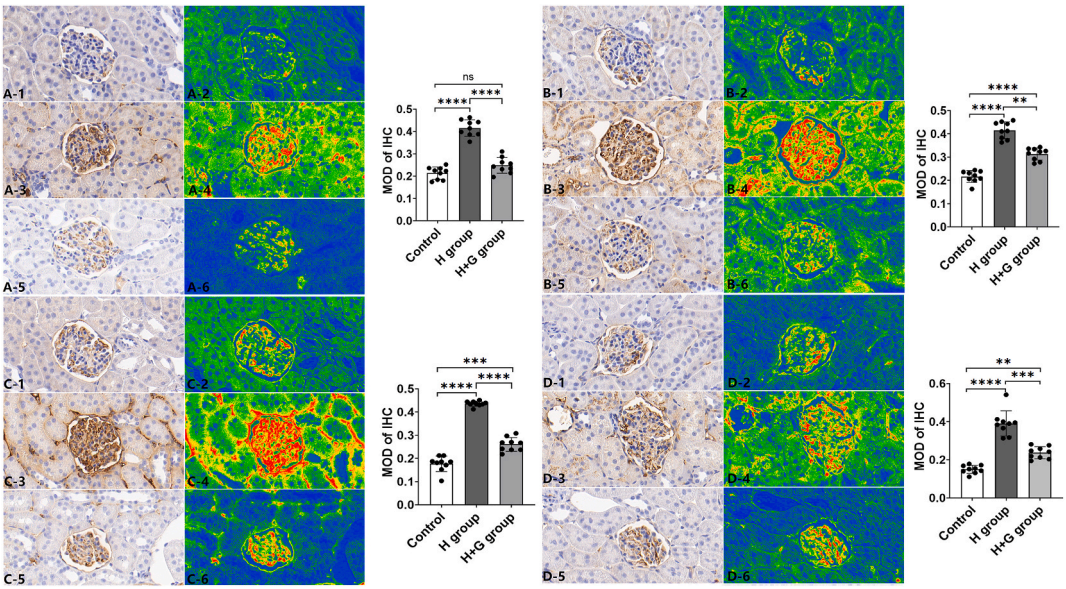

Fig. 6. Quantification of Mean Optical Density (MOD) for Immunohistochemical (IHC) Analysis of renal cells in Rabbits Following a 4 h duration of Lower Limb Arterial Ischemia-Reperfusion (IR) (scale bar: 20 μm, brown—positive, immune complexes are produced with corresponding antigens; blue—cell nucleus; red—positive immunostaining complex after visual gradient image processing): A—Immunohistochemistry of inflammatory factor TNF-α in the renal tissue; B—Immunohistochemistry of inflammatory factor interleukin 6 (IL-6) in the renal tissue; C—Immunohistochemistry of macrophage marker F4/80 in the renal tissue; D—Immunohistochemistry of T cell marker CD3 in the renal tissue 1—Renal tissue of the control group; 2—Renal tissue of the control group after visual gradient image processing; 3—Renal tissue of the high-fat feed without intervention group (H group); 4—Renal tissue of the H group after visual gradient image processing; 5—Renal tissue of the intervention group receiving high-fat feed and preoperative intervention with reduced glutathione (H + G group); 6—Renal tissue of the H + G group after visual gradient image processing. Data shown represent means ± SD; n = 9 independent samples per group; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.005$, $^{****}p < 0.001$, ns: no significance.

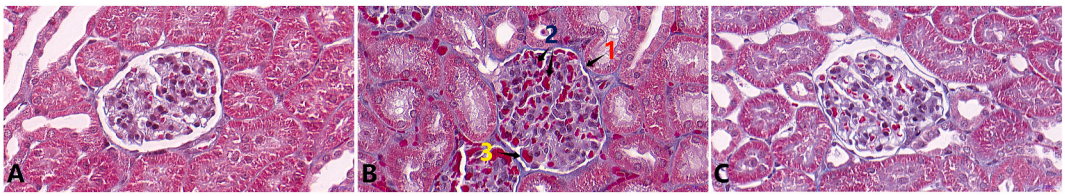

Fig. 7. Masson's trichrome staining of glomeruli (scale bar: 20 μm): A - control group; B -high-fat feed without intervention group (H group); A - intervention group receiving high-fat feed and preoperative intervention with reduced glutathione (H + G group); (1) Thickening of the basement membrane, namely the Bowman's capsule; (2) Several red-stained complexes formed a thrombus in the capillary lumen of the glomerulus; (3) Significant thickening of the basement membrane of the glomerulus.

demonstrated a substantial increase in ROS levels in the blood following IR of the lower limbs in white rabbits with high triglyceride levels. In addition, there were notable increases in the expression levels of TNF-α, IL-6, macrophages, and T lymphocytes in the renal capsule and renal tubular cells. Masson's trichrome staining showed the thickening of the basement membrane of the Bowman's capsule in the damaged renal capsules, thrombus formation in the capillary lumen by several red-stained complexes, and substantial thickening of the glomerular basement membrane. These findings demonstrate that ROS produced by non-primary organs can also damage renal cells. Acute kidney injury is the most common clinical complication after cardiovascular surgery [53–55]. In the present study, in addition to previously recognized risk factors, ROS released after long-term IR in distal tissues intraoperatively are one of the causes of postoperative acute kidney injury. The intervention of GSH before IR significantly downregulated ROS production in muscle tissues and blood after IR. Moreover, the expression levels of TNF-α, IL-6, macrophages, and T lymphocytes in the kidney capsule and renal tubular cells decreased, which alleviated the inflammatory response of the kidney to protect renal cells.

According to the research results, hypertriglyceridemia caused by long-term intake of high-fat feed in New Zealand white rabbits. In the process of ischemia and reperfusion in arteries, high triglycerides will aggravate the oxidative stress response, further promote the secretion of inflammatory factors, and thus cause damage to the liver and kidney organs of the body. If GSH is given before the onset of ischemia-reperfusion for intervention, the degree of oxidative stress and the effects of inflammatory factors on the tissue can be effectively reduced. The confirmed roles of glutathione in tumor chemotherapy and radiotherapy encompass antioxidant activity, detoxification, facilitation of protein synthesis and repair, modulation of immune function, and redox signaling regulation. The

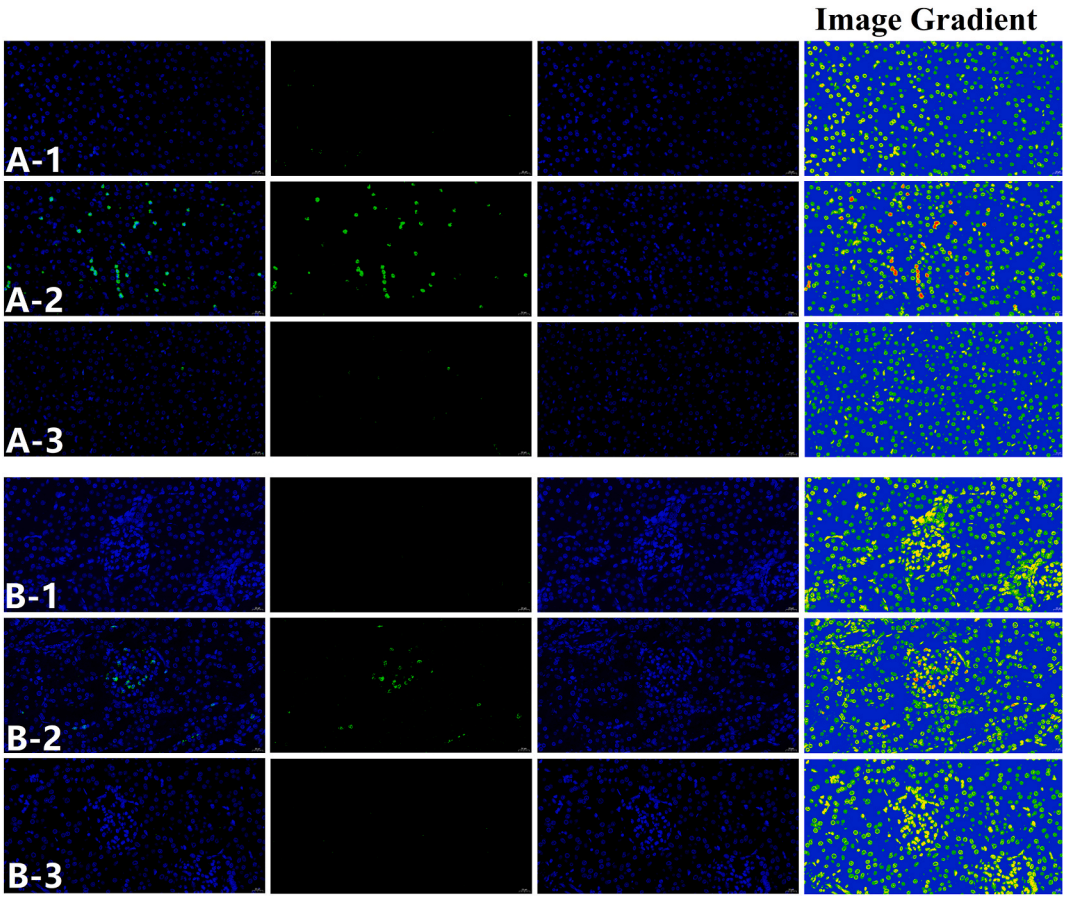

Fig. 8. TUNEL assay of liver and renal cells in white rabbits 4 h after ischemia-reperfusion (IR) of the lower limb arteries (scale bar: 20 μm, blue—positive cell nuclei; green—apoptotic cells; Image Gradient: green—positive cell nuclei; magenta—apoptotic cells): A—TUNEL assay of the liver tissue; B—TUNEL assay of the kidney tissue; 1—Control group; 2—high-fat feed without intervention group (H group); 3—intervention group receiving high-fat feed and preoperative intervention with reduced glutathione (H + G group).

exercise of these functions holds profound importance in enhancing treatment efficacy and mitigating patient discomfor[t] [56,57]. This research holds considerable importance in the clinical management of liver and kidney injuries resulting from arterial surgery. By administering GSH prior to surgery, the study demonstrates that it can effectively mitigate oxidative stress and inflammation, subsequently preserving the functionality of liver and kidney cells. This offers a solid experimental and theoretical foundation for clinical applications.

This study has several limitations. First, the preoperative immunohistochemistry pathology studies of the liver and kidneys of white rabbits were not used as controls. It was uncertain whether multiple surgeries within a short period affected the experimental results. Second, the study only preliminarily confirmed that a large amount of ROS released after IR in distal tissues elicited inflammatory reactions in liver and renal cells. However, the specific mechanism remains unclear. Lastly, it remains to be experimentally verified whether a large amount of ROS produced after IR would break the original oxidative balance and elicit secondary oxidative stress in the liver and kidneys.

In this study, high-fat feed was provided to white rabbits to elicit an increase in blood lipids, and the abdominal aorta was blocked to simulate arterial IR of the lower limbs. High triglyceride levels aggravate oxidative stress in the primary tissues and blood after IR. ROS generated in oxidative stress may damage the liver and renal cells in white rabbits. Inflammatory factors produced by oxidative stress caused more damage to the renal cells than liver cells. Preoperative intervention with GSH alleviated oxidative stress and reduced the production of ROS and inflammatory factors, thereby protecting liver and renal cells.

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Data availability

Data will be made available on request.

CRediT authorship contribution statement

Xiaochen Wang: Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Hailei Sun:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Funding acquisition, Formal analysis. **Guangcun Cheng:** Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology. **Jianjun Ge:** Visualization, Supervision, Software, Resources.

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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Appendix A. Supplementary data

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