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BIOCHEMICAL AND INFLAMMATORY MARKERS OF CARDIAC REMODELING IN EXPERIMENTAL METABOLIC OBESITY

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Abstract: Objective: to investigate the biochemical and inflammatory mechanisms underlying myocardial remodeling in a rat model of diet-induced metabolic obesity. Methods: twenty male albino rats were divided into control and high-fat–high-carbohydrate diet (HFD) groups and observed for 12 weeks. Serum lipid profile, oxidative stress markers (MDA, SOD, catalase), and inflammatory mediators (IL-6, TNF-α, CRP) were assessed. Histological analysis of myocardial samples (H&E) included morphometry of cardiomyocyte area, left ventricular wall thickness, and interstitial fibrosis. Statistical and correlation analyses were performed. Results: the HFD group showed marked dyslipidemia — total cholesterol (+42.3%), triglycerides (+58.6%), LDL (+61.9%), and decreased HDL (−27.4%) ($p < 0.01$). MDA levels increased by +67.8%, while SOD and catalase decreased by 34–30% ($p < 0.01$). IL-6, TNF-α, and CRP levels were elevated 2.4–2.5-fold versus controls ($p < 0.001$). Morphometric data revealed cardiomyocyte hypertrophy and 2.6-fold greater interstitial fibrosis. Correlation analysis confirmed strong positive associations between MDA and fibrosis ($r = 0.63$; $p < 0.01$) and between IL-6 and fibrosis ($r = 0.58$; $p < 0.01$). Conclusion: chronic HFD exposure induces biochemical and inflammatory disbalance that drives oxidative stress, fibrosis, and cardiac remodeling in metabolic obesity. The observed changes may serve as early indicators of metabolic cardiomyopathy and potential therapeutic targets for antioxidant and anti-inflammatory intervention.

Keywords: metabolic obesity; oxidative stress; inflammation; myocardial remodeling; malondialdehyde (MDA); interleukin-6 (IL-6); tumor necrosis factor-α (TNF-α); lipid metabolism; cardiac fibrosis; experimental model.

Introduction

Metabolic obesity represents one of the most pressing biomedical challenges of the 21st century, closely linked to the global rise in cardiovascular morbidity and mortality. According to the World Health Organization (WHO, 2024), more than 1.3 billion adults are classified as obese, and the prevalence of metabolic syndrome continues to increase worldwide. Obesity is no longer considered a simple imbalance between caloric intake and expenditure but a complex systemic disease characterized by chronic low-grade inflammation, oxidative stress, and profound metabolic dysregulation that directly affect cardiac structure and function [1,5-8,12,13].

Experimental and clinical data suggest that prolonged consumption of high-fat and high-carbohydrate diets (HFD) leads to the development of metabolic obesity, accompanied by insulin resistance, dyslipidemia, and systemic inflammation. These metabolic alterations contribute to cardiac remodeling, even in the absence of hypertension or coronary artery disease [2-7,9-13]. The resulting condition, often termed metabolic cardiomyopathy, is characterized by

cardiomyocyte hypertrophy, interstitial fibrosis, mitochondrial dysfunction, and impaired diastolic relaxation [3,5,9,11-15].

One of the key mechanisms underlying metabolic cardiomyopathy is the imbalance between lipid accumulation and energy utilization within cardiomyocytes. Excess circulating free fatty acids (FFAs) lead to lipotoxicity, mitochondrial overload, and overproduction of reactive oxygen species (ROS), initiating oxidative stress and subsequent cellular injury [8,13,14]. The oxidative environment disrupts redox homeostasis by depleting endogenous antioxidant defenses such as superoxide dismutase (SOD) and catalase, thereby promoting lipid peroxidation and membrane damage, reflected by increased malondialdehyde (MDA) concentrations [1-5,10-12,14].

Simultaneously, adipose tissue expansion in obesity results in macrophage infiltration and the secretion of pro-inflammatory cytokines, notably tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) [8]. These mediators activate nuclear transcription factors such as NF-κB and STAT3 in the myocardium, leading to fibroblast proliferation, collagen deposition, and progressive interstitial fibrosis [2-6,10]. The synergistic action of oxidative stress and inflammation forms a vicious cycle that accelerates cardiac remodeling and impairs myocardial compliance [11].

Rodent models of diet-induced obesity have proven particularly valuable for investigating the biochemical and morphological pathways of cardiac injury. After 10–12 weeks of HFD exposure, rats typically exhibit increased body weight, hyperlipidemia, elevated MDA levels, and decreased antioxidant enzyme activities, accompanied by histological signs of myocardial hypertrophy and fibrosis [9-11,14,15]. Furthermore, the correlation between lipid metabolism abnormalities and the degree of fibrosis supports the concept of metabolic–inflammatory remodeling, where biochemical and morphological alterations progress in parallel [1].

Emerging studies highlight the predictive value of circulating inflammatory markers for early cardiac changes in obesity. Elevated IL-6 and TNF-α levels correlate with increased collagen type I/III synthesis and reduced left ventricular compliance [12]. Similarly, CRP has been recognized as a sensitive systemic biomarker of low-grade inflammation that precedes overt structural remodeling of the myocardium [4].

Despite accumulating evidence linking metabolic disorders, inflammation, and oxidative stress to cardiac pathology, integrated experimental assessments combining biochemical and morphological parameters remain scarce. Understanding these interactions is essential for identifying early markers of metabolic cardiomyopathy and developing targeted interventions aimed at preventing irreversible myocardial fibrosis.

Therefore, the present study aimed to evaluate biochemical and inflammatory markers of oxidative stress and lipid metabolism in a rat model of diet-induced metabolic obesity and to determine their correlation with morphometric indicators of cardiac remodeling. This approach allows for a comprehensive characterization of the biochemical and morphological continuum underlying obesity-related cardiac injury.

Materials and Methods

Experimental design. The study was conducted at the Laboratory of Experimental Surgery and Pathomorphology, Republican Specialized Scientific–Practical Medical Center of Surgery named after Academician V. Vakhidov (Tashkent, Uzbekistan). All experimental procedures complied with the principles of the European Convention for the Protection of Vertebrate Animals (ETS No. 123) and the study protocol was approved by the institutional ethics committee.

Twenty male albino rats (6–8 weeks old, body weight 180–220 g) were used in the experiment. The animals were housed under standard vivarium conditions (temperature 22 ± 2 °C, humidity

55 ± 5 %, 12-hour light/dark cycle) with ad libitum access to food and water. Following a 7-day acclimatization period, the animals were randomly assigned into two groups (n = 10 each):

1. Control group – standard laboratory diet.
2. Metabolic obesity group (HFD) – high-fat, high-carbohydrate diet for 12 weeks.

The diet in the experimental group contained 45–60% fat and 20–30% carbohydrates of total caloric content, providing an energy-dense composition comparable to human metabolic syndrome–inducing diets. The feeding duration of 12 weeks was selected as optimal for inducing stable obesity and related cardiac alterations, as reported in previous studies (Kruszewska et al., Int J Mol Sci, 2022; Yang et al., Ann Transl Med, 2022).

Assessment of Body and Organ Weights. Body weight was recorded weekly throughout the experiment. At the end of week 12, animals were euthanized under light ether anesthesia. The heart, liver, and kidneys were excised and weighed. The cardiac mass index (CMI) was calculated as:

$$CMI=\text{Heart weight}/\text{Body weight}\times 100\%$$

This parameter served as an indicator of cardiac hypertrophy in metabolic obesity.

Biochemical analysis. Blood samples were collected by cardiac puncture immediately after euthanasia. Serum was separated by centrifugation at 3000 rpm for 10 minutes and stored at −20 °C until analysis.

Lipid profile. The serum lipid spectrum was determined using certified diagnostic kits (Cypress Diagnostics, Belgium) on a Cyan Smart automated analyzer. The following parameters were measured:

- Total cholesterol (TC),
- Triglycerides (TG),
- High-density lipoproteins (HDL-C),
- Low-density lipoproteins (LDL-C).

The atherogenic index was calculated as (TC − HDL-C) / HDL-C.

Oxidative stress markers. Indices of oxidative stress were determined spectrophotometrically:

- Malondialdehyde (MDA) – marker of lipid peroxidation, measured by thiobarbituric acid–reactive substances assay (TBARS).
- Superoxide dismutase (SOD) and catalase (CAT) activities – evaluated according to the standard methods of Misra & Fridovich (1972) and Aebi (1984), respectively. Enzyme activity was expressed as units per mg of protein, determined by the Lowry method.

Inflammatory markers. Serum levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) were quantified using ELISA kits (Elabscience, USA) according to manufacturer instructions. Absorbance was measured at 450 nm using a BioTek Epoch 2 microplate reader.

Histological and morphometric correlation. Left ventricular (LV) myocardial samples from each rat were fixed in 10% neutral-buffered formalin, paraffin-embedded, and sectioned at 4 µm thickness. Hematoxylin and eosin (H&E) staining was performed to evaluate general histoarchitecture. Morphometric measurements of cardiomyocyte cross-sectional area, LV wall thickness, and fibrosis percentage were obtained using ImageJ 1.53u software (NIH, USA) in 10 non-overlapping high-power fields (×400).

Morphological data were correlated with biochemical parameters (MDA, IL-6, TC) to determine the relationship between oxidative/inflammatory stress and structural myocardial remodeling.

Statistical analysis. Data were expressed as mean ± standard deviation (M ± SD). The normality of distribution was tested using the Shapiro–Wilk test. Between-group comparisons were performed using the Student's t-test for normally distributed variables or the Mann–Whitney U-test otherwise.

Pearson's correlation analysis was applied to assess relationships between biochemical markers (MDA, IL-6, TNF-α, TC) and morphometric parameters (cardiomyocyte area, fibrosis area, LV wall thickness). Statistical significance was considered at $p < 0.05$. All analyses were performed using Statistica 10.0 (StatSoft, USA).

Results

Body weight and cardiac index. After 12 weeks of high-fat, high-carbohydrate feeding, rats in the metabolic obesity group showed a significant increase in body weight compared with controls (462.8 ± 21.4 g vs. 330.6 ± 17.2 g; $p < 0.001$). The cardiac mass index (CMI) was also elevated (0.46 ± 0.03% vs. 0.38 ± 0.02%; $p < 0.01$), indicating moderate myocardial hypertrophy associated with obesity-induced metabolic stress. (Figure 1 illustrates the changes in body weight and CMI between the groups.)

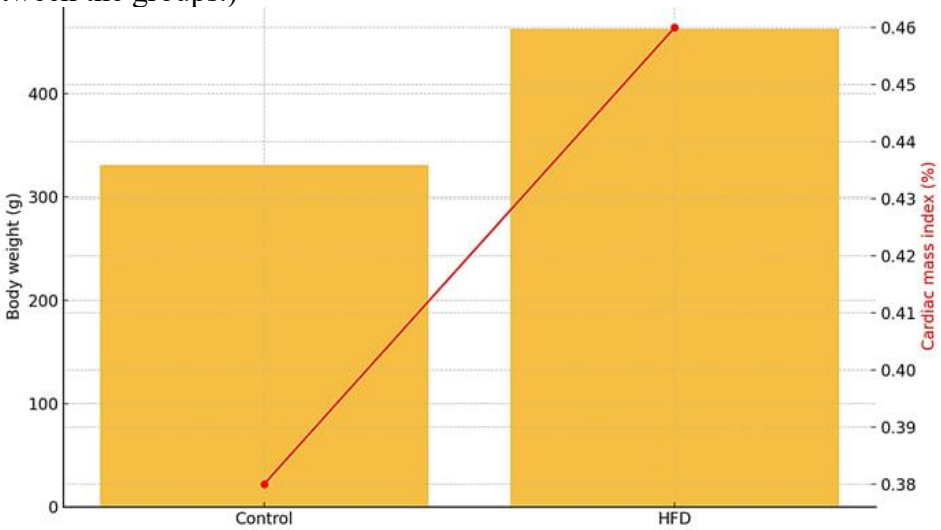

Figure 1. Body weight and cardiac mass index in control and high-fat diet (HFD) groups (mean ± SD).

Lipid metabolism alterations. Serum lipid analysis revealed marked dyslipidemia in the HFD group compared with controls (Table 1).

- Total cholesterol (TC) increased by +42.3% ($p < 0.001$);
- Triglycerides (TG) — by +58.6% ($p < 0.001$);
- LDL-C rose by +61.9% ($p < 0.001$);
- HDL-C decreased by −27.4% ($p < 0.01$).

Consequently, the atherogenic index was 2.3-fold higher in the obesity group.

These changes confirm the development of atherogenic dyslipidemia, typical of metabolic syndrome.

Oxidative stress markers. Biochemical assays demonstrated a significant intensification of oxidative stress in rats fed the high-fat diet (Table 1). The MDA level, reflecting lipid peroxidation, increased by +67.8% compared with controls ($p < 0.001$). Conversely, the activity of antioxidant enzymes SOD and catalase decreased by −34.6% and −29.8%, respectively ($p < 0.01$). This imbalance between pro-oxidant and antioxidant mechanisms indicates a pronounced oxidative burden on myocardial tissue.

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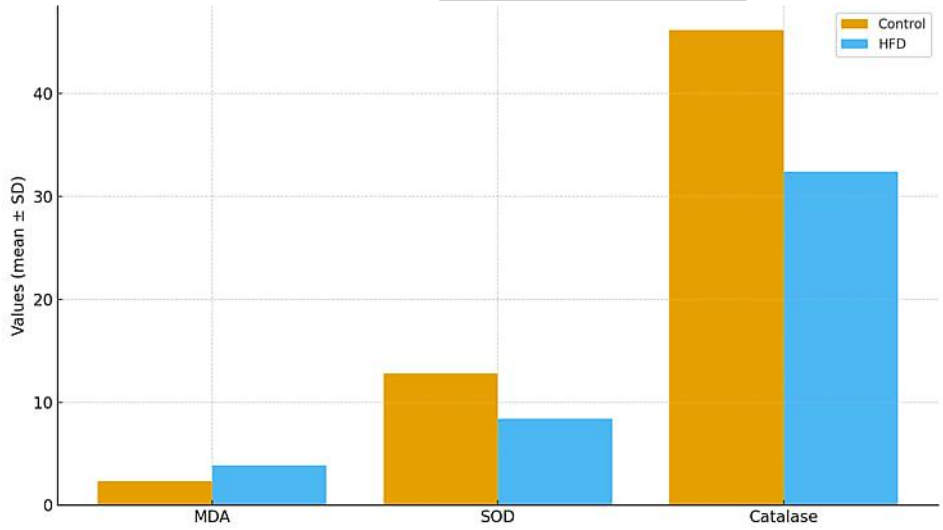

Figure 2. Serum levels of malondialdehyde (MDA), superoxide dismutase (SOD), and catalase (CAT) in control and HFD groups (mean ± SD).

Inflammatory response. Systemic inflammation accompanied metabolic obesity. Serum concentrations of IL-6 and TNF-α were approximately 2.5-fold higher than in controls ($p < 0.001$), and CRP increased by +72% ($p < 0.001$). These findings confirm the presence of chronic low-grade inflammation, characteristic of the metabolic phenotype of obesity.

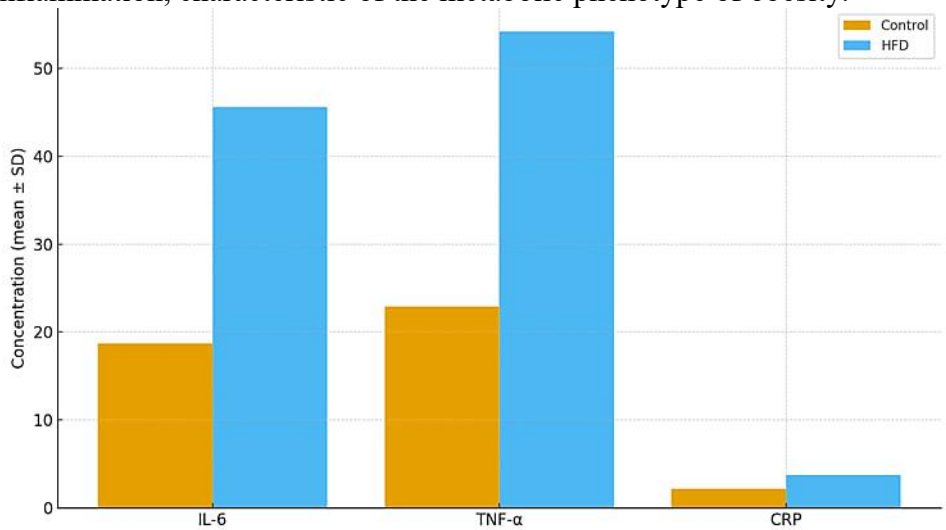

Figure 3. Inflammatory markers (IL-6, TNF-α, and CRP) in control and HFD rats (mean ± SD).

Correlation analysis. Pearson's correlation analysis revealed several significant associations between biochemical markers and morphometric indices of cardiac remodeling:

- Body weight ↔ cardiomyocyte area: $r = 0.79$; $p < 0.001$
- MDA ↔ fibrosis area: $r = 0.63$; $p < 0.01$
- IL-6 ↔ fibrosis area: $r = 0.58$; $p < 0.01$
- HDL-C ↔ LV wall thickness: $r = -0.47$; $p < 0.05$

These correlations demonstrate the close interplay between oxidative stress, inflammatory activation, and the structural remodeling of the myocardium in metabolic obesity.
(Figure 4 presents representative scatter plots of key correlations.)

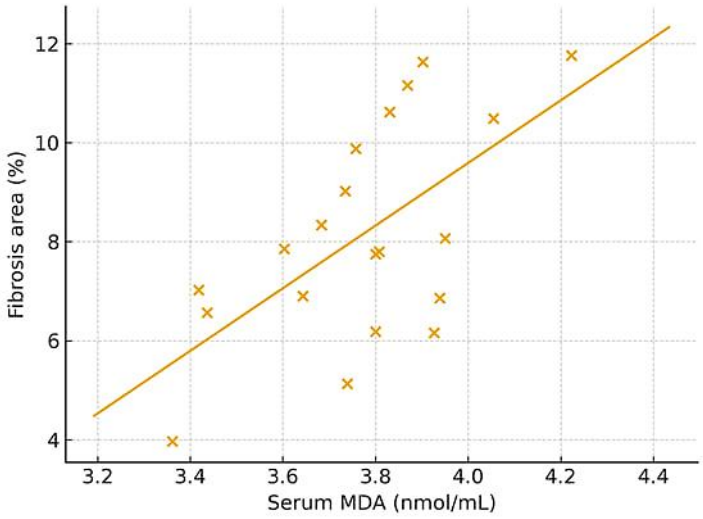

Figure 4. Correlation between serum MDA levels and myocardial fibrosis area (r = 0.63; p < 0.01) in HFD-fed rats.

Table 1.

Biochemical and inflammatory parameters in control and HFD rats (mean ± SD)

Parameter	Control	HFD	Change (%)	p value
Body weight, g	330.6 ± 17.2	462.8 ± 21.4	+39.9	< 0.001
Cardiac mass index, %	0.38 ± 0.02	0.46 ± 0.03	+21.1	< 0.01
Total cholesterol, mmol/L	3.15 ± 0.18	4.48 ± 0.22	+42.3	< 0.001
Triglycerides, mmol/L	0.98 ± 0.10	1.55 ± 0.14	+58.6	< 0.001
LDL-C, mmol/L	0.72 ± 0.08	1.17 ± 0.09	+61.9	< 0.001
HDL-C, mmol/L	1.14 ± 0.11	0.83 ± 0.09	−27.4	< 0.01
MDA, nmol/mL	2.31 ± 0.19	3.88 ± 0.24	+67.8	< 0.001
SOD, U/mg protein	12.8 ± 1.1	8.4 ± 0.9	−34.6	< 0.01
Catalase, U/mg protein	46.2 ± 3.7	32.4 ± 2.9	−29.8	< 0.01
IL-6, pg/mL	18.7 ± 2.3	45.6 ± 4.1	×2.4	< 0.001
TNF-α, pg/mL	22.9 ± 2.8	54.2 ± 4.9	×2.4	< 0.001
CRP, mg/L	2.18 ± 0.21	3.75 ± 0.28	+72.0	< 0.001

*Note: Values expressed as mean ± standard deviation; p values determined by Student's t-test versus control.

Discussion

The present study demonstrates that prolonged exposure to a high-fat and high-carbohydrate diet leads to complex biochemical and inflammatory alterations underlying cardiac remodeling in metabolic obesity. The marked elevation of serum triglycerides, total cholesterol, and LDL fractions, combined with decreased HDL, indicates the establishment of systemic dyslipidemia, which is known to trigger oxidative and inflammatory cascades in the myocardium.

A significant rise in malondialdehyde (MDA) levels, accompanied by reduced superoxide dismutase (SOD) and catalase activity, reflects the activation of lipid peroxidation and impaired antioxidant defense. Similar oxidative shifts have been reported in experimental models of diet-induced obesity, where mitochondrial overload by free fatty acids promotes excessive reactive oxygen species (ROS) generation, leading to cardiomyocyte damage and mitochondrial dysfunction [7-10,12-15].

Concurrently, the increased concentrations of IL-6, TNF-α, and C-reactive protein (CRP) observed in the HFD group indicate a persistent low-grade systemic inflammation. These cytokines are recognized mediators of cardiac fibrosis and hypertrophy through the activation of NF-κB and TGF-β1 signaling pathways, which stimulate fibroblast proliferation and extracellular matrix remodeling. Previous studies have shown that IL-6-dependent signaling contributes to myocardial stiffness and diastolic dysfunction in obese individuals [11-14].

Correlation analysis revealed a strong positive association between MDA levels and myocardial fibrosis area ($r = 0.63$; $p < 0.01$), suggesting a direct link between oxidative stress intensity and fibrogenic activity in the myocardium. This supports the concept that oxidative stress and chronic inflammation act synergistically in promoting metabolic cardiomyopathy, as described by Zou et al. (2018) and Yang et al. (2022).

Overall, the combination of lipid dysregulation, oxidative imbalance, and cytokine activation forms a pathogenic triad that drives both structural and functional cardiac remodeling in obesity. The observed biochemical alterations precede overt clinical manifestations, highlighting their potential value as early biomarkers of metabolic cardiomyopathy.

Conclusion

The present experimental study provides comprehensive evidence that long-term exposure to a high-fat and high-carbohydrate diet induces significant biochemical and inflammatory alterations closely associated with myocardial remodeling in metabolic obesity.

1. Systemic dyslipidemia — manifested by elevated total cholesterol, triglycerides, and LDL fractions — serves as a key metabolic trigger of myocardial stress.
2. Oxidative imbalance, reflected by a sharp increase in malondialdehyde levels and a decline in antioxidant enzymes (SOD and catalase), demonstrates enhanced lipid peroxidation and weakened cellular defense mechanisms.
3. Inflammatory activation, characterized by elevated IL-6, TNF-α, and CRP concentrations, supports the presence of chronic low-grade systemic inflammation driving fibroblast activation and extracellular matrix remodeling.
4. Strong positive correlations between MDA and myocardial fibrosis ($r = 0.63$; $p < 0.01$), and between IL-6 and fibrosis ($r = 0.58$; $p < 0.01$), confirm the integrative role of oxidative and inflammatory stress in the pathogenesis of metabolic cardiomyopathy.

Collectively, these findings indicate that biochemical and inflammatory markers can serve as early indicators of subclinical cardiac remodeling in obesity.

Targeted modulation of oxidative stress and cytokine signaling may thus represent a promising therapeutic strategy for preventing the transition from metabolic overload to structural and functional cardiac injury.

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