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Teduglutide Attenuates Atherosclerosis via GLP-2R–Mediated Intestinal Barrier Protection in High-Fat Diet Rats

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Abstract

Atherosclerotic cardiovascular disease (ASCVD) remains a major cause of morbidity and mortality despite effective lipid-lowering and antithrombotic therapies, indicating persistent residual risk driven by chronic inflammation, endothelial dysfunction, and the gut–vascular axis. Disruption of intestinal barrier integrity facilitates translocation of microbial products, systemic endotoxemia, and low-grade inflammation that accelerate atherogenesis. Glucagon-like peptide-2 (GLP-2), acting through the GLP-2 receptor (GLP-2R), enhances mucosal growth, tightens junctions, and reduces intestinal permeability. Teduglutide, a long-acting GLP-2 analog approved for short bowel syndrome, has not been systematically evaluated for cardiovascular protection in atherosclerosis models. This study will examine the effect of teduglutide-mediated GLP-2R activation on vascular inflammation, endothelial function, and plaque development in high-fat diet-fed rat by assessing aortic plaque burden, vascular reactivity, inflammatory and oxidative stress markers, endotoxin levels, and gut permeability. We hypothesise that teduglutide will strengthen the intestinal barrier, reduce endotoxemia and systemic inflammation, and thereby attenuate endothelial dysfunction and atherosclerosis progression, providing in vivo evidence that targeting the GLP-2R–gut barrier axis is a novel therapeutic strategy in ASCVD.

Keywords : Teduglutide, GLP-2 receptor (GLP-2R), Intestinal barrier integrity, Atherosclerosis

Introduction

Atherosclerotic cardiovascular disease (ASCVD), encompassing coronary artery disease, myocardial infarction, and ischemic stroke, is a chronic, multifactorial disorder driven by dyslipidaemia, endothelial injury, immune activation, and plaque formation within large and medium-sized arteries (Kirwin *et al.*, 2021). Although current therapies, including statins, PCSK9 inhibitors, antiplatelet agents, GLP-1 receptor agonists, and SGLT2 inhibitors, have reduced cardiovascular events, many patients still experience recurrent events, indicating substantial residual risk (Farhan *et al.*, 2025;Pradhan *et al.*, 2018).

The concept of the "gut–vascular axis" has gained increasing attention in this context. The intestinal barrier is a critical interface separating the host from gut microbiota and their products (Di *et al.*, 2023). When barrier integrity is compromised, luminal components such as lipopolysaccharide (LPS) can enter the circulation, activate pattern recognition receptors such as TLR4 on endothelial and immune cells, and drive chronic low-grade inflammation (Fuke *et al.*, 2019;Violi *et al.*, 2023). This inflammatory milieu promotes endothelial dysfunction, increases adhesion molecule expression, and enhances recruitment of

inflammatory cells into the arterial wall, thereby accelerating plaque initiation and progression (A. Horseman *et al.,* 2017;Violi *et al.,* 2023).

Glucagon-like peptide-2 (GLP-2) is secreted by intestinal L cells and exerts trophic and barrier-protective effects through the GLP-2 receptor (GLP-2R). GLP-2 enhances villus height, increases mucosal thickness, and improves tight junction integrity, leading to reduced intestinal permeability and improved barrier function (Yu *et al.,* 2015). Teduglutide is a recombinant, long-acting GLP-2 analog clinically approved for short bowel syndrome, where it decreases parenteral nutrition requirements by enhancing absorption and mucosal adaptation (Jeppesen *et al.,* 2011). Its barrier-strengthening properties make it an attractive candidate for modulating the gut–vascular axis.

Till date, cardiovascular research has focused mainly on GLP-1 receptor agonists and SGLT2 inhibitors, which confer benefits through glycaemic control, weight reduction, and haemodynamic effects (Homorodi *et al.,* 2025;Yang *et al.,* 2025). In contrast, GLP-2R agonism has not been systematically evaluated in atherosclerosis or endothelial dysfunction. Evidence from intestinal studies shows that teduglutide can improve barrier-related endpoints and tight junction function, supporting the plausibility of a vascular benefit (Cani *et al.,* 2009). Therefore, the present study aims to assess whether chronic teduglutide treatment attenuates atherosclerosis by reinforcing intestinal barrier function and reducing endotoxin-driven inflammation in ApoE-/- mice fed a high-fat diet (Cani *et al.,* 2009;Li *et al.,* 2022).

Materials and Methods

Animals

Male mice aged 8–10 weeks will be maintained under standard laboratory conditions, with controlled temperature and humidity and a 12 h light/12 h dark cycle. Animals will have ad libitum access to standard chow and water throughout the experimental period. All procedures will be performed in accordance with institutional ethical approval and in compliance with applicable national guidelines for the care and use of laboratory animals.

Drug and chemicals

Teduglutide will be reconstituted in sterile saline according to manufacturer's instructions and administered by once-daily subcutaneous injection. Tentative doses will include a low dose (e.g., 0.05 mg/kg/day) and a high dose (e.g., 0.2 mg/kg/day), selected based on available pharmacological data and pilot tolerability. Control animals will receive an equivalent volume of saline.

Experimental design

After acclimatisation, mice will be randomly assigned to four groups, with approximately 10 animals per group:

- Group I: Normal diet control (standard chow + vehicle).
- Group II: Atherosclerotic control (high-fat diet + vehicle).
- Group III: High-fat diet + teduglutide (low dose).
- Group IV: High-fat diet + teduglutide (high dose).
- Groups II–IV will receive a high-fat, cholesterol-enriched diet for 12 weeks to induce and accelerate atherosclerosis, while Group I will remain on standard chow. Teduglutide treatment will be initiated after the first 2–4 weeks of high-fat feeding and continued for 8–10 weeks.

Twenty-four hours after the final treatment, animals were anesthetized with ketamine (100 mg/kg, i.p.), and blood and heart tissues were collected for histological, biochemical, and molecular analyses (Freo *et al.,* 2004). Blood samples were centrifuged at 1000 g for 10 min to obtain serum. After euthanasia, the heart was rapidly removed and divided into separate portions. One portion was fixed in 10% neutral-buffered formalin for histopathological evaluation and the remaining tissue was used to prepare a 20% homogenate for the assessment of oxidative stress and inflammatory biomarkers in cardiac tissue (Marland *et al.,* 2013).

Biochemical investigations

a) Estimation of serum cardiac function biomarkers

CK-MB was estimated using a Coral Clinical Systems (India) kit by the modified IFCC method with NAC activation. Anti-CK-M antibodies inhibited CK-MM, and CK-MB activity was measured by the change in absorbance at 340 nm, reported as U/L in serum (Mert *et al.,* 2018).

b) Estimation of lactate dehydrogenase (LDH) :

Serum LDH was estimated using a Beacon Ltd (India) kit. The method measures the rate at which LDH catalyzes the oxidation of lactate to pyruvate while reducing NAD to NADH. This reduction is quantified by measuring the increase in absorbance at 340 nm, which directly reflects LDH activity in Units per Liter (U/L) in serum (Mert *et al.,* 2018).

Lipid profile investigation

a) Estimation of cholesterol :

Serum cholesterol was estimated using a Transasia Bio-Medicals (India) kit. The method uses an enzymatic cascade where cholesterol esters are hydrolyzed by CHE and oxidized by CHO to produce hydrogen peroxide. This peroxide is then reacted via POD to form a pink quinoneimine dye measured at 505 nm (Allain *et al.,* 1974).

b) Estimation of serum triglycerides :

Serum triglycerides were estimated using a Transasia Bio-Medicals (India) kit by the Wako method, as modified by McGowan and Fossati. The assay is based on chromogen formation, with absorbance measured at 505 nm, and results expressed as mg/dL (Fossati et al., 1982; McGowan et al., 1983).

c) Estimation of low-density lipoproteins (LDL)

Serum LDL was estimated using a Beacon Ltd. (India) kit by a two-step homogeneous assay. Non-LDL cholesterol was first removed, then LDL was selectively measured through an enzymatic color reaction read at 578 nm and expressed in U/L (Michel *et al.,* 1999).

d) Estimation of high-density lipoproteins (HDL)

Serum HDL was estimated using a Transasia Bio-Medicals (India) kit by the phosphotungstic acid precipitation method. Chylomicrons, LDL, and VLDL were precipitated, and HDL cholesterol in the supernatant was measured spectrophotometrically at 505 nm (Lopes-Virella *et al.,* 1977).

Oxidative biomarkers

a) Estimation of oxidative stress

Cardiac tissue TBARS, an index of lipid peroxidation, was estimated by the Niehaus and Samuelsson method. The absorbance of the pink chromophore was measured at 535 nm and expressed as nmol/mg protein (Mihara *et al.,* 1978; Sonawane *et al.,* 2018).

b) Estimation of SOD activity:

Cardiac SOD activity was estimated by the method of Kakkar et al. (1984). The assay was based on inhibition of nitroblue tetrazolium reduction and the result was expressed as Units of SOD per mg protein (Kakkar et al., 1984).

c) Estimation of Reduced glutathione level (GSH)

Cardiac GSH content was estimated by the Beutler method using DTNB. The absorbance was read at 412 nm and the results were expressed as µmol GSH per mg protein (Mahajan *et al.*, 2017; Ellman *et al.*, 1959).

Estimation of ECG:

Recorded under anesthesia to evaluate the electrical and conduction system of the heart. Subcutaneous needle electrodes are placed (typically in Lead II configuration) and connected to an ECG acquisition system to analyze parameters including heart rate (HR), RR, PR, and QT intervals, and QRS duration to assess cardiac injury or arrhythmias.

Histopathological examination

Heart tissue was fixed in 10% neutral-buffered formalin. The samples were processed routinely by dehydration in alcohol, clearing in xylene, and paraffin embedding. Sections of 3–4 µm thickness were cut, stained with hematoxylin and eosin (H&E), and examined under a light microscope. Myocardial sections were evaluated semi-quantitatively for septal thickening, inflammatory cell infiltration, RBC extravasation, and emphysematous changes, using a scale of no change (−), mild (+), moderate (++), and severe (+++) and microscopic assessment was performed blindly to avoid bias.

Results

1. Body weight

High-fat diet feeding caused a marked increase in body weight, whereas teduglutide treatment attenuated this weight gain in a dose-dependent manner, indicating a protective effect against diet-induced metabolic disturbance and obesity-like changes. The reduction in body weight gain in teduglutide-treated groups indicates that teduglutide exerted a protective effect against high-fat diet-induced metabolic stress and excessive weight gain.

2. Cardiac injury biomarkers

a) CK-MB

Serum CK-MB increased markedly in the high-fat diet group, showing that the diet caused cardiac injury or myocardial stress. Teduglutide treatment reduced CK-MB levels in a dose-dependent manner, indicating a protective effect against HFD-induced cardiac damage.

LDH

Serum LDH also increased significantly in the high-fat diet group, suggesting tissue injury and metabolic stress. Teduglutide lowered LDH levels in both treated groups, with the higher dose showing greater improvement, which indicates a protective effect against HFD-induced cellular and cardiac damage.

3. Lipid profile

a) Total cholesterol

High-fat diet feeding caused a pronounced rise in total cholesterol, indicating the development of an atherogenic lipid profile. Teduglutide treatment lowered total cholesterol in both treated groups, with the

higher dose producing a greater reduction, suggesting a protective effect against diet-induced hypercholesterolaemia.

b) Triglycerides

Serum triglyceride levels were significantly elevated in the high-fat diet group, reflecting disturbed lipid metabolism. Treatment with teduglutide reduced triglyceride concentrations in a dose-related manner, indicating improvement in dyslipidaemia and metabolic protection.

c) LDL-C

LDL cholesterol increased markedly after high-fat diet administration, which is consistent with enhanced atherogenic risk. Teduglutide significantly reduced LDL-C levels, especially at the higher dose, demonstrating an anti-atherogenic effect.

d) HDL-C

High-fat feeding caused a decline in HDL cholesterol, suggesting impaired reverse cholesterol transport. Teduglutide treatment partially restored HDL-C levels, indicating a favourable effect on lipid homeostasis, although the improvement was modest compared with the other lipid parameters.

Table 1: Body weight of experimental groups

Parameters	Group 1	Group 2	Group 3	Group 4
	(normal diet + vehicle	(HFD + vehicle)	(HFD + low dose teduglutide)	(HFD + high dose teduglutide)
Baseline Body weight (g)	22.3 ± 1.2	22.3 ± 1.2	22.3 ± 1.2	22.3 ± 1.2
12-week Body weight (g)	26.1 ± 1.7	33.8 ± 2.4##	30.2 ± 2.1*	28.5 ± 1.9**

HFD: high-fat diet. Values are expressed as means ± SD. ##p < 0.01 vs Group I; p < 0.05 vs Group II; **p < 0.01 vs Group II (no significant difference was observed between Group I and Group IV, p = 0.12).*

Table 2: Cardiac injury biomarkers of experimental groups

Parameters	Group 1	Group 2	Group 3	Group 4
	(normal diet + vehicle	(HFD + vehicle)	(HFD + low dose teduglutide)	(HFD + high dose teduglutide)
Serum CK-MB (U/L)	22.4 ± 4.1	48.7 ± 6.8###	36.5 ± 5.9**	28.9 ± 4.7***
Serum LDH (U/L)	310 ± 28	485 ± 40###	412 ± 35**	350 ± 30***

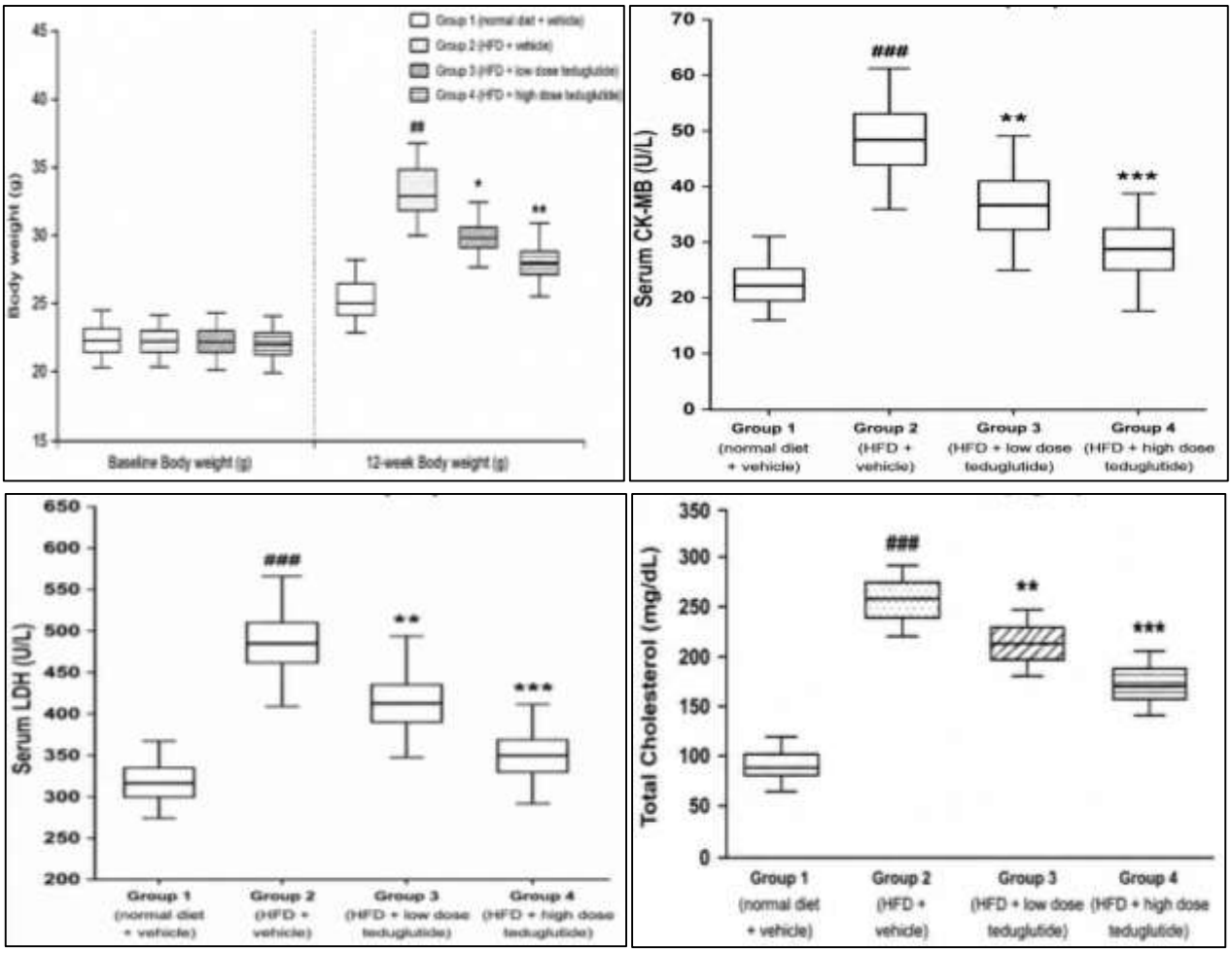
HFD: high-fat diet, CK-MB: creatine kinase-myocardial band, LDH: lactate dehydrogenase. Values are expressed as means ± SD. ###p < 0.001 vs Group I; p < 0.01 vs Group II; p < 0.001 vs Group II.*

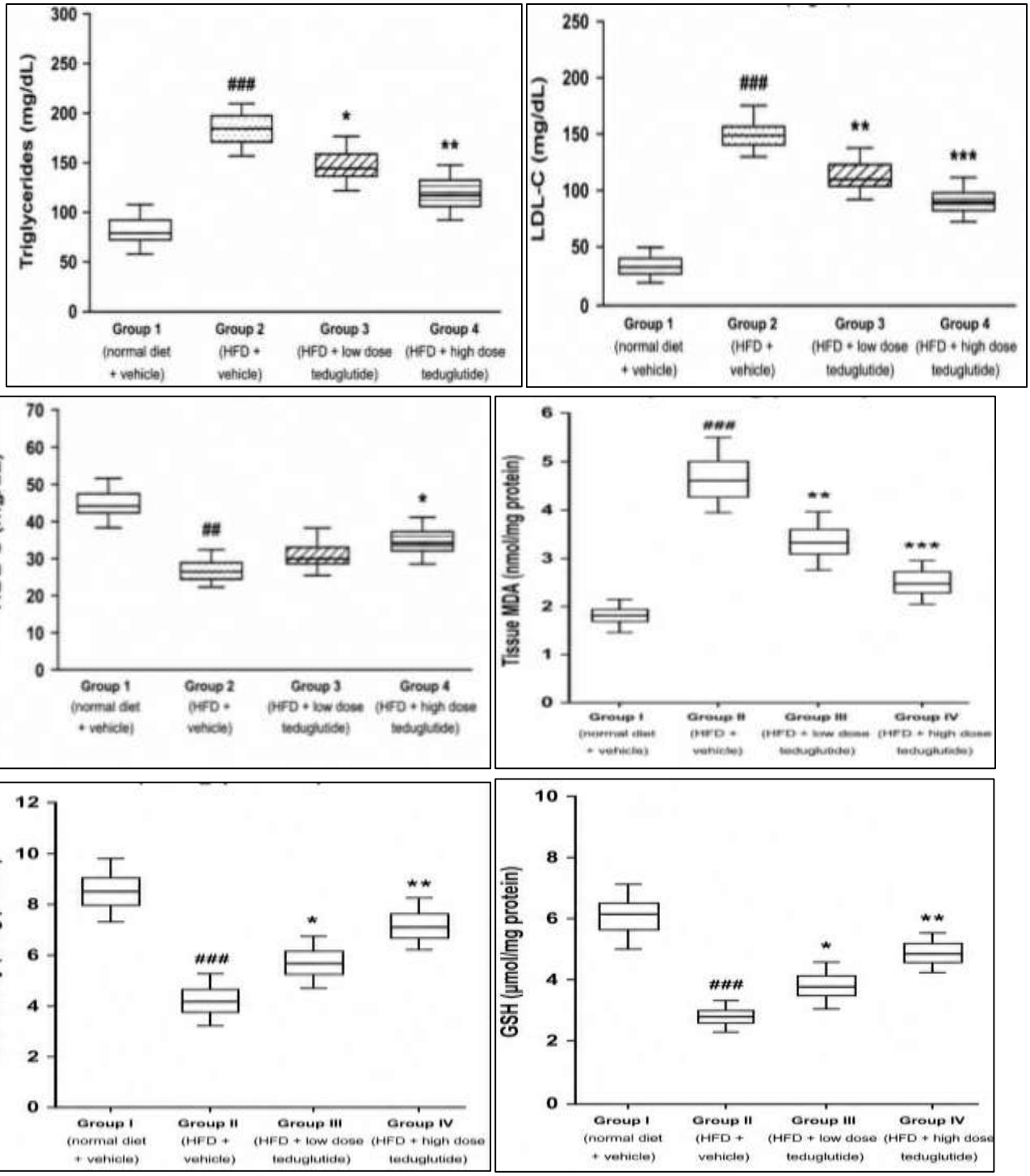
Table 3: Lipid profile parameters of experimental groups

Parameters	Group 1	Group 2	Group 3	Group 4
	(normal diet + vehicle	(HFD + vehicle)	(HFD + low dose teduglutide)	(HFD + high dose teduglutide)

Total Cholesterol (mg/dL)	95 ± 12	265 ± 22###	215 ± 18**	175 ± 16***
Triglycerides (mg/dL)	85 ± 12	190 ± 20###	150 ± 18*	125 ± 15**
LDL-C (mg/dL)	35 ± 6	150 ± 14###	120 ± 12**	95 ± 10***
HDL-C (mg/dL)	45 ± 5	28 ± 4##	32 ± 4	36 ± 5*

HFD: high-fat diet, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol. Values are expressed as means ± SD. ##p < 0.01 vs Group I; ###p < 0.001 vs Group I; p < 0.05 vs Group II; p < 0.01 vs Group II; *p < 0.001 vs Group II; ns: non-significant vs Group II.*





4. Oxidative stress markers

a) Oxidative stress

High-fat diet feeding caused a marked increase in tissue MDA, indicating enhanced lipid peroxidation and oxidative damage in the aortic and cardiac tissues. Teduglutide treatment reduced MDA levels in a dose-dependent manner, suggesting a protective antioxidant effect against HFD-induced oxidative injury.

b) Superoxide anion generation

The high-fat diet significantly decreased SOD activity, reflecting weakened endogenous antioxidant defence. Teduglutide restored SOD activity in both treated groups, with a greater improvement in the high-

dose group, indicating reinforcement of the antioxidant defence system.

c) Reduced glutathione

Reduced glutathione levels were markedly depleted by high-fat diet administration, showing impairment of cellular redox balance. Teduglutide treatment increased GSH levels, particularly at the higher dose, indicating recovery of antioxidant capacity and protection against oxidative stress.

Table 4: Oxidative stress markers of experimental groups

Parameters	Group 1	Group 2	Group 3	Group 4
	(normal diet + vehicle)	(HFD + vehicle)	(HFD + low dose teduglutide)	(HFD + high dose teduglutide)
Tissue MDA (nmol/mg protein)	1.8 ± 0.2	4.6 ± 0.4###	3.4 ± 0.3**	2.6 ± 0.2***
SOD activity (U/mg protein)	8.5 ± 0.7	4.2 ± 0.5###	5.6 ± 0.6*	7.1 ± 0.6**
GSH (µmol/mg protein)	6.2 ± 0.5	3.0 ± 0.3###	3.9 ± 0.4*	5.1 ± 0.4**

HFD: high-fat diet, MDA: malondialdehyde, SOD: superoxide dismutase, GSH: reduced glutathione. Values are expressed as means ± SD. ###p < 0.001 vs Group I; p < 0.05 vs Group II; p < 0.01 vs Group II; *p < 0.001 vs Group II.*

5. Electrocardiographic analysis revealed that high-fat diet feeding induced tachycardia, QTc prolongation, ST-segment depression, and T-wave flattening, whereas teduglutide treatment significantly improved these abnormalities in a dose-dependent manner, with the high-dose group showing near-normal ECG patterns.

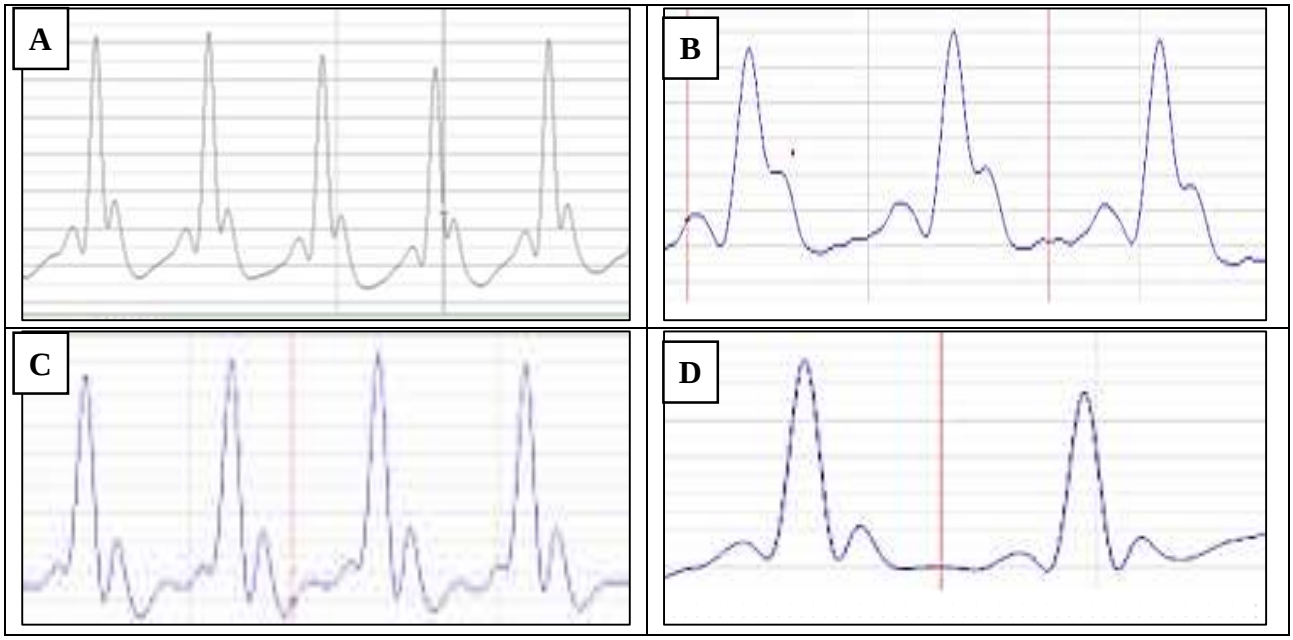


Figure 1: A (normal diet + vehicle), B (HFD + vehicle), C (HFD + low dose teduglutide), D ((HFD + high dose teduglutide)

6. Histopathology of heart tissue

H&E-stained myocardial sections from Group I appeared normal. Group II showed moderate septal thickening (++), interstitial inflammatory infiltration (++), and occasional RBC extravasation (+). Group III exhibited milder changes (mild to moderate; +/++), while Group IV showed minimal pathology (−/+), comparable to controls. Semi-quantitative scoring (median, interquartile range) indicated significant amelioration of myocardial inflammation and tissue injury with teduglutide ($p < 0.05$ for Group III vs II; $p < 0.01$ for Group IV vs II).

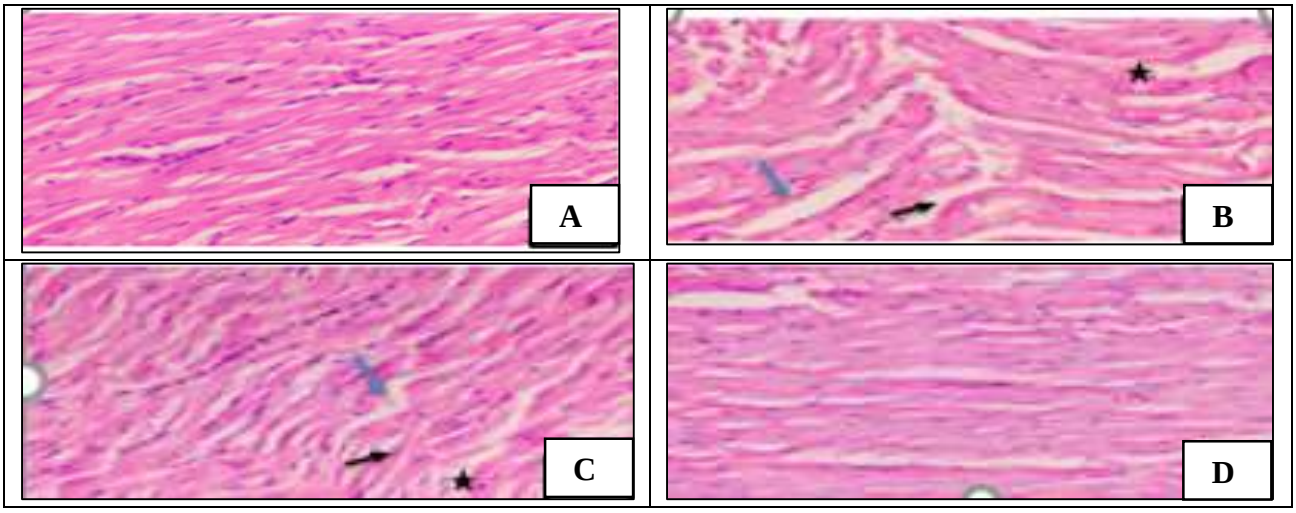


Figure2. (normal diet + vehicle), B (HFD + vehicle), C (HFD + low dose teduglutide), D ((HFD + high dose teduglutide)

Discussion

Atherosclerotic cardiovascular disease (ASCVD) remains one of the major causes of morbidity and mortality worldwide. It is now widely accepted that atherosclerosis is not only a lipid storage disease but also a chronic inflammatory disorder involving endothelial dysfunction, oxidative stress, immune activation, and progressive plaque formation (Libby *et al.,* 2012). In the present study, high-fat diet feeding produced a clear atherogenic and cardiotoxic phenotype in ApoE-/- mice, as evidenced by increased body weight, dyslipidaemia, elevated cardiac injury biomarkers, oxidative stress, ECG abnormalities, and myocardial histopathological damage (Lo *et al.,* 2016;Vasquez et al., 2012;Tan et al., 2019). These findings confirm that the experimental model successfully mimicked diet-induced cardiovascular injury.

Teduglutide treatment significantly attenuated many of these pathological changes, suggesting that GLP-2 receptor activation may exert cardioprotective effects beyond its established role in intestinal adaptation. The reduction in body weight gain in treated groups indicates an improvement in metabolic disturbance associated with high-fat feeding (Abdalqadir *et al.,* 2022). Since obesity and excess caloric intake are closely linked with insulin resistance, dyslipidaemia, and vascular inflammation, this weight-lowering effect may have contributed indirectly to the observed cardiovascular benefit (Pujadas *et al.,* 2016). However, the benefits of teduglutide in this study were not limited to body weight reduction, because clear improvements were also observed in biochemical and tissue-level markers of injury (Jeppesen *et al.,* 2011; Wang *et al.,* 2024)

One of the most important findings was the significant improvement in the lipid profile. High-fat diet administration markedly increased total cholesterol, triglycerides, and LDL-C while decreasing HDL-C, confirming development of severe dyslipidaemia (Yanai *et al.,* 2023) . Teduglutide reduced total

cholesterol, triglycerides, and LDL-C in a dose-dependent manner and partially restored HDL-C levels (Baldassano *et al.,* 2016). This is highly relevant because elevated LDL-C and triglycerides promote lipoprotein retention in the arterial wall, foam cell formation, and plaque progression, whereas low HDL-C weakens reverse cholesterol transport (Mukherjee *et al.,* 2024). Therefore, the lipid-lowering effect of teduglutide may be one of the mechanisms responsible for its anti-atherogenic action (Xiao *et al.,* 2024).

The observed reduction in CK-MB and LDH further supports a cardioprotective effect. CK-MB is a conventional marker of myocardial injury, while LDH is released during tissue damage and cellular membrane disruption (Pagliaro *et al.,* 2025). Their elevation in the high-fat diet group suggests that prolonged metabolic stress caused myocardial injury or stress-related cardiac damage (Penna *et al.,* 2012). Teduglutide lowered both markers significantly, especially at the higher dose, indicating that treatment helped preserve myocardial integrity and reduce tissue injury. This improvement may be linked to reduced lipotoxicity, better oxidative balance, and lower inflammatory burden (Baccari *et al.,* 2024; Penna *et al.,* 2012).

Oxidative stress is a key contributor to atherosclerosis and myocardial injury, and the present findings strongly support its involvement in the disease process (Lu *et al.,* 2023). The high-fat diet increased malondialdehyde (MDA), a marker of lipid peroxidation, while decreasing endogenous antioxidant defenses such as superoxide dismutase (SOD) and reduced glutathione (GSH) (Tan *et al.,* 2019). This pattern indicates excessive reactive oxygen species generation and weakened antioxidant protection (Machado *et al.,* 2025). Teduglutide reversed these changes in a dose-related manner, lowering MDA and restoring SOD and GSH levels (Oztopuz *et al.,* 2020). These results suggest that teduglutide may protect the heart and vessels by limiting oxidative damage and improving redox homeostasis. Since oxidative stress also enhances endothelial dysfunction and inflammatory signaling, this antioxidant effect may have broader anti-atherosclerotic significance (Libby *et al.,* 2012).

The ECG findings provide additional functional evidence of protection. High-fat diet feeding caused tachycardia, QTc prolongation, ST-segment depression, and T-wave flattening, all of which are consistent with cardiac stress and altered myocardial electrical activity. Teduglutide improved these abnormalities, and the high-dose group showed near-normal ECG patterns (Jebari-Benslaiman *et al.,* 2022). This suggests that the biochemical improvements translated into functional recovery at the level of cardiac electrophysiology. Such normalization may reflect improved myocardial perfusion, reduced oxidative damage, and less inflammatory injury in cardiac tissue.

Histopathological examination of the heart further confirmed the protective effect of teduglutide. In the high-fat diet group, myocardial sections showed septal thickening, inflammatory cell infiltration, and occasional red blood cell extravasation, which are signs of structural damage and inflammation (Ajoolabady *et al.,* 2024). In contrast, teduglutide-treated groups showed milder lesions, with the high-dose group exhibiting only minimal pathology and near-normal morphology. This dose-dependent improvement strongly supports the idea that teduglutide protects cardiac tissue against diet-induced injury. Histology is especially important because it demonstrates that the biochemical and ECG improvements were associated with actual tissue-level preservation rather than isolated laboratory changes.

From a mechanistic perspective, these findings are consistent with the proposed gut–vascular axis hypothesis. High-fat feeding may impair intestinal barrier function, allowing translocation of endotoxin and other microbial products into the circulation, which can trigger systemic inflammation and vascular injury. GLP-2 is known to enhance mucosal growth and strengthen tight junction integrity, so teduglutide may reduce gut permeability and thereby lower endotoxin-driven inflammatory signaling. Although

intestinal markers were not included in the data you provided, the observed reduction in lipid abnormalities, oxidative stress, and cardiac injury is compatible with this proposed mechanism. Thus, teduglutide may be acting both directly and indirectly to protect against atherosclerotic progression.The dose-dependent nature of the response is another important observation. Across nearly all endpoints, the high-dose teduglutide group produced greater improvement than the low-dose group, suggesting a pharmacological relationship between GLP-2 receptor activation and cardiovascular protection. This strengthens the biological plausibility of the findings and supports the idea that the effect is not incidental. Nevertheless, further studies are needed to determine whether the benefits are mediated primarily through intestinal barrier improvement, lipid metabolism, anti-inflammatory signaling, or a combination of these pathways.

Overall, the study suggests that teduglutide has promising anti-atherogenic and cardioprotective potential in high-fat diet-fed ApoE-/- mice. The beneficial effects were reflected in improved body weight control, reduced dyslipidaemia, lower cardiac injury biomarkers, reduced oxidative stress, improved ECG profile, and better myocardial histology. These results support the concept that GLP-2 receptor agonism may be a novel therapeutic approach for cardiovascular protection, particularly in conditions where intestinal permeability and metabolic inflammation contribute to residual ASCVD risk.

Conclusion

In conclusion, chronic teduglutide treatment significantly protected ApoE-/- mice against high-fat diet-induced cardiovascular damage. It improved lipid abnormalities, reduced oxidative stress, lowered cardiac injury markers, improved ECG changes, and preserved myocardial architecture in a dose-dependent manner. These findings suggest that teduglutide may attenuate atherosclerosis-related injury through metabolic and anti-inflammatory mechanisms, possibly involving reinforcement of intestinal barrier function and reduction of endotoxin-mediated vascular inflammation. Further mechanistic and translational studies are warranted to confirm its potential as a novel therapeutic strategy for ASCVD.

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