AUCTORES
Globalize your Research

International Journal of Clinical Case Reports and Reviews
Rafael Sarikov *

Open Access

Research Article

Role of Homocysteine in Endothelial Dysfunction During Experimental Atherosclerosis and Its Pharmacological Modulation

Baykulov Azim Kenjayevich*

Department of Pharmaceutical and Toxicological Chemistry, Samarkand State Medical University, Uzbekistan, Samarkand

***Corresponding Author:** Baykulov Azim Kenjayevich, Department of Pharmaceutical and Toxicological Chemistry, Samarkand.

Received Date: May 04, 2026 | **Accepted Date:** May 12, 2026 | **Published Date:** May 28, 2026

Citation: Baykulov A. Kenjayevich, (2026), Role of Homocysteine in Endothelial Dysfunction During Experimental Atherosclerosis and Its Pharmacological Modulation, *International Journal of Clinical Case Reports and Reviews*, 36(1); **DOI:10.31579/2690-4861/1100**

Abstract:

Endothelial dysfunction is a fundamental mechanism underlying the development of atherosclerosis and its complications. Among modifiable risk factors, hyperhomocysteinemia has emerged as a significant contributor to vascular injury. This study aimed to evaluate serum homocysteine levels in experimental atherosclerosis and to analyze their relationship with lipid metabolism and endothelial dysfunction. Hypercholesterolemia was induced in rabbits, followed by pharmacological correction using gemfibrozil, chitosan derivatives, and heparin. A progressive increase in homocysteine levels was observed during the development of atherosclerosis, accompanied by dyslipidemia and oxidative stress. Pharmacological interventions reduced homocysteine concentrations, with chitosan derivatives demonstrating the highest efficacy. The findings confirm the critical role of homocysteine in atherogenesis and highlight the therapeutic potential of chitosan-based compounds.

Key words: homocysteine; endothelial dysfunction; atherosclerosis; hyperlipoproteinemia; chitosan; oxidative stress

Introduction

Endothelial dysfunction represents a central pathological process involved in a wide spectrum of diseases, including inflammatory and autoimmune disorders, as well as vascular injury. It plays a decisive role in the initiation and progression of atherosclerosis, where impairment of endothelial homeostasis leads to structural and functional vascular alterations [1,4]. Homocysteine has recently been recognized as a significant modifiable risk factor in cardiovascular diseases. Elevated plasma levels of homocysteine are as-sociated with endothelial injury, enhanced platelet aggregation, and disturbances in coagulation, thereby accelerating atherogenesis and increasing cardiovascular mortality [2,5,10]. The pathogenic mechanisms of homocysteine are multifactorial. It exerts cy-totoxic effects on endothelial cells, induces oxidative stress through the genera-tion of reactive oxygen species, and activates inflammatory signaling pathways, including nuclear factor κB (NF-κB) [2,6,7,11]. Additionally, homocysteine re-duces nitric oxide bioavailability by promoting the formation of peroxynitrite, which impairs vasodilation and contributes to vascular inflammation. Hyperhomocysteinemia also disrupts lipid metabolism, facilitating the ac-cumulation of atherogenic lipoproteins and reducing vascular elasticity. Clinical studies have demonstrated a strong association between elevated homocysteine levels and increased risk of atherosclerosis in coronary, cerebral, and peripheral arteries [3,8,9]. Despite the availability of lipid-lowering therapies, their long-term use is of-ten limited by adverse effects and incomplete efficacy. Therefore, the search for novel therapeutic strategies targeting both lipid abnormalities and homocysteine metabolism remains highly relevant.

Aim: to determine serum homocysteine levels in experimental atherosclerosis and evaluate their relationship with endothelial dysfunction and lipid metabolism disorders.

Materials and Methods

The study was performed on 28 Chinchilla rabbits (2.5–3.0 kg) maintained under standardized laboratory conditions.

Experimental hypercholesterolemia was induced using the Anichkov method through daily oral administration of cholesterol (0.2 g/kg) dissolved in sunflower oil for three months [12].

After two months, animals were randomized into six groups:

Intact control

Hypercholesterolemia control

Hypercholesterolemia + gemfibrozil (100 mg/kg)

Hypercholesterolemia + chitosan derivative (25 µg/kg)

Hypercholesterolemia + chitosan derivative (50 µg/kg)

Hypercholesterolemia + heparin (15 U/kg)

Pharmacological correction was conducted for one month.

Serum homocysteine levels were measured using ELISA. Statistical analysis was performed using Student's t-test, with significance set at $p < 0.05$.

Results and Discussion

The experimental findings demonstrated a progressive increase in serum homocysteine levels during the development of hypercholesterolemia. After 1, 2, and 3 months, homocysteine concentrations increased by 1.72, 2.33, and 2.89 times, respectively, indicating its active involvement in atherogenesis. A strong positive correlation was identified between homocysteine and LDL-cholesterol levels ($r=+0.89$), while an inverse relationship was observed with HDL-cholesterol ($r=-0.81$). These data confirm the close association between hyperhomocysteinemia and dyslipidemia [8,9]. Mechanistically, homocysteine promotes endothelial dysfunction by inducing oxidative stress and reducing nitric oxide availability. The formation of reactive oxygen species leads to activation of NF-κB and increased expression of inflammatory mediators, adhesion molecules, and matrix metalloproteinases, thereby accelerating vascular damage [6,7,11]. Pharmacological interventions resulted in a significant reduction in homocysteine levels compared to untreated hypercholesterolemic animals. Among the tested agents, chitosan derivatives exhibited the most pronounced effect, particularly at a dose of 50 µg/kg, followed by heparin. Gemfibrozil showed moderate efficacy. Despite the observed improvements, none of the treatments fully restored homocysteine levels to those of intact animals, suggesting that lipid-lowering therapy alone is insufficient to completely normalize metabolic disturbances associated with atherosclerosis [2,3]. Lipid profile analysis revealed that hypercholesterolemia caused a marked increase in total cholesterol, LDL, and triglycerides, along with a decrease in HDL levels. Treatment with chitosan derivatives and heparin significantly improved these parameters, indicating their combined hypolipidemic and antiatherogenic effects.

Group	n	Homocysteine (pg/mL)	% Change vs Intact	p-value
Intact control	3	3.00 ± 0.18	–	–
Hypercholesterolemia (control)	5	8.99 ± 0.23	+199.7%	<0.001
+ Gemfibrozil (100 mg/kg)	5	6.42 ± 0.21	+114.0%	<0.01
+ Chitosan derivative (25 µg/kg)	5	5.20 ± 0.17	+73.3%	<0.01
+ Chitosan derivative (50 µg/kg)	5	4.12 ± 0.15	+37.3%	<0.05
+ Heparin (15 U/kg)	5	4.38 ± 0.16	+46.0%	<0.05

Table 1: Serum Homocysteine Levels in Experimental Groups (M ± SEM, pg/mL).

Note: Values are expressed as mean ± standard error (M ± SEM). All treated groups show statistically significant differences compared to the hypercholesterolemia control.

Parameter	Correlation Coefficient (r)	Direction	Significance
LDL-cholesterol	+0.89	Strong positive	$p < 0.001$
HDL-cholesterol	−0.81	Strong negative	$p < 0.001$
Total cholesterol	+0.76	Moderate positive	$p < 0.01$
Triglycerides	+0.68	Moderate positive	$p < 0.05$

Table 2: Correlation Between Homocysteine and Lipid Profile Parameters.

Interpretation: Elevated homocysteine levels are strongly associated with increased atherogenic lipids (LDL) and decreased protective lipoproteins (HDL).

Group	Total Cholesterol	LDL-C	HDL-C	Triglycerides	Atherogenic Index
Intact control	2.35 ± 0.11	0.89 ± 0.07	1.12 ± 0.05	0.63 ± 0.04	0.80 ± 0.06
Atherosclerosis (control)	6.82 ± 0.28***	4.91 ± 0.24***	0.59 ± 0.04***	1.37 ± 0.08**	8.49 ± 0.42***
Gemfibrozil	4.03 ± 0.21**	2.67 ± 0.17**	0.84 ± 0.05*	0.95 ± 0.07*	3.18 ± 0.19**
Chitosan derivative (50 µg/kg)	3.62 ± 0.19**	2.34 ± 0.15**	0.96 ± 0.06*	0.87 ± 0.05*	2.63 ± 0.17**
Heparin	3.48 ± 0.18**	2.28 ± 0.14**	1.02 ± 0.07*	0.81 ± 0.06	2.41 ± 0.16**

Table 3: Lipid Profile in Experimental Atherosclerosis and After Treatment (M ± SEM, mmol/L).

Note: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs intact control.

Duration of Cholesterol Administration	Homocysteine Level (Fold Increase vs Baseline)
1 month	1.72×
2 months	2.33×
3 months	2.89×

Table 4: Dynamics of Serum Homocysteine During Atherosclerosis Development.

A progressive increase in homocysteine concentration confirms its involvement in the development and progression of atherosclerosis.

Treatment	Reduction in Homocysteine vs Control	Relative Efficacy
Gemfibrozil	↓ 1.4-fold	Moderate
Chitosan (25 µg/kg)	↓ 1.73-fold	High
Chitosan (50 µg/kg)	↓ 2.18-fold	Very high
Heparin	↓ 2.05-fold	Very high

Table 5: Comparative Efficacy of Pharmacological Agents.

Chitosan derivatives, especially at 50 µg/kg, demonstrated the most pronounced hypohomocysteinemic effect.

Conclusion

The study confirms that homocysteine plays a pivotal role in the development of endothelial dysfunction and atherosclerosis. Its elevation is closely associated with lipid metabolism disturbances, oxidative stress, and inflammatory activation. Pharmacological correction using chitosan derivatives and heparin effectively reduced homocysteine levels and improved lipid profiles, demonstrating superior efficacy compared to gemfibrozil. Among the tested compounds, the chitosan derivative at 50 µg/kg showed the most significant protective effects. These findings highlight the potential of chitosan-based compounds as promising agents for the комплексной терапии атеросклероза, targeting both lipid abnormalities and homocysteine-mediated endothelial damage. Further studies are required to elucidate the molecular mechanisms of action and to assess the long-term therapeutic potential of these compounds.

Acknowledgments

The author expresses gratitude to Professor J.A. Rizayev for institutional support.

Funding

No external funding was received.

Conflicts of Interest

The author declares no conflicts of interest.

Data Availability

Data are available from the corresponding author upon reasonable request.

References

1. Jakubowski H, Witucki Ł. (2025). Homocysteine metabolites, endothelial dysfunction, and cardiovascular disease. *Int J Mol Sci*.;26(2):746.
2. Yuan D, et al. (2023). Mechanism of homocysteine-mediated endothelial injury and its consequences for atherosclerosis. *Front Cardiovasc Med*.; 9:1109445.
3. Zhang S, et al. (2023). Homocysteine promotes atherosclerosis through macrophage pyroptosis via ER stress. *Mol Med*; 29:73.
4. Gimbrone MA, García-Cardeña G. (2021). Endothelial cell dysfunction and the pathobiology of atherosclerosis. *Circ Res*;118(4):620–636.
5. Smith AD, Refsum H. (2021). Homocysteine, B vitamins, and cardiovascular disease. *Am J Clin Nutr*;113(5):1207–1214.
6. Tousoulis D, et al. (2020). Oxidative stress and endothelial dysfunction: therapeutic approaches. *Eur Heart J*;41(12):1115–1123.
7. Libby P. (2021). The changing landscape of atherosclerosis. *Nature*.;592:524–533.
8. Tsimikas S. (2020). Lipoprotein(a): emerging target in cardiovascular disease. *J Am Coll Cardiol*.;76(23):2720–2732.
9. Mach F, et al. (2020). ESC Guidelines for the management of dyslipidaemias. *Eur Heart J*.; 41:111–188.
10. Wald DS, et al. (2021). Homocysteine and cardiovascular disease: meta-analysis. *BMJ*.;373: n2180.
11. Li J, et al. (2022). Homocysteine induces endothelial dysfunction via oxidative stress pathways. *Redox Biol*.; 52:102294.
12. Getz GS, Reardon CA. (2021). Animal models of atherosclerosis. *Arterioscler Thromb Vasc Biol*.;41(1): e1–e15.

DOI:10.31579/2690-4861/1100