Modeling Multifocal Atherosclerosis in Rabbits for Gender Influence and Lipid Profile Effects

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Abstract

Background: Circulatory diseases (CD) show a significant health risk globally, particularly in countries like Uzbekistan, where mortality rates from non-infectious diseases, including CD, are alarmingly high. Despite advancements in treatment methods, mortality from CD continues to rise. It emphasizes the need for deeper understanding and effective treatment strategies for multifocal atherosclerosis. Method: A study was conducted using Chinchilla rabbits to simulate multifocal atherosclerosis. The influence of gender and diet on atherosclerosis was studied, along with the impact of blood lipid composition on the coagulation system. Ultrasound examinations of the aorta and its large branches were performed to monitor the dynamics of atherogenesis. Result: The study revealed that a cholesterol-enriched diet led to significant increases in blood lipid parameters, indicating hyperlipidemia. Coagulogram parameters shifted towards hypercoagulation, accompanied by increased platelet count and signs of systemic inflammation. Ultrasound examinations identified early manifestations of atherosclerosis, with male rabbits exhibiting higher lipid profile indicators and inflammatory markers compared to females. Conclusion: The study showed the pronounced effects of a cholesterol-enriched diet on blood lipid parameters and coagulogram parameters in rabbits, particularly in males, highlighting their susceptibility to atherosclerosis. Ultrasound monitoring proved valuable in detecting early signs of atherosclerosis. These findings underscore the importance of developing interventions targeting multifocal atherosclerosis, with rabbit models providing a platform for future drug development and treatment strategies, including potential therapies for atherosclerosis.

Keywords: Atherosclerosis, Rabbits, Gender, Lipid Profile, Multifocal Atherosclerosis

Significance | This study demonstrated a rabbit models as drug development and understanding atherosclerosis dynamics, which is vital for combating cardiovascular diseases globally.

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Introduction

According to WHO research results, the Republic of Uzbekistan is one of the countries with a high risk of developing circulatory diseases (CD). Statistical studies indicate that the mortality rate in Uzbekistan from non-infectious diseases in 2019 exceeded 83.5%, amounting to 702.8 per 100 thousand population, of which the mortality rate from CD accounts for 60.3% (World Health Organization, 2021). The mortality rate from CD in 2021 was 61.7% (107,666 out of a total of 174,500), with the number of deceased patients aged 18-74 years being twice as high in men compared to

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women (World Health Organization, 2021; Nizamov, 2021). CD, such as acute ischemic stroke and acute myocardial infarction, are the leading causes of death both in Uzbekistan and globally. The basis of these diseases is vascular atherosclerosis, which has a multifocal nature of the lesion. Despite improvements in surgical methods for treating multifocal atherosclerosis (MFA), mortality from CD is not decreasing but shows a clear tendency to increase and affect younger populations. These facts underscore the importance of studying the etiology and pathogenesis of multifocal atherosclerosis and developing effective pharmacological treatments. From this perspective, an in-depth study of existing models and the selection of the most effective models of MFA formation in animals, along with the investigation of new drugs at both early stages of atherosclerosis and during atherocalcinosis, remains an urgent problem.

Atherosclerosis is a multifocal disease characterized by the formation of atherosclerotic plaques in large and medium caliber vessels, primarily at their bifurcation points. The main sites of plaque localization are various parts of the aorta, especially the abdominal aorta and iliac arteries, followed by the carotid arteries and then the coronary arteries. The atherosclerotic process is a systemic disease based on lipid metabolism disorders, which manifest as the deposition of lipids in the form of individual foci or plaques in the inner lining of the arteries, primarily of the elastic type. This is followed by the reactive development of connective tissue, leading to thickening of the arterial walls, narrowing their lumen, and often the formation of blood clots. Consequently, dystrophic, necrotic, and sclerotic changes develop in the organs supplied by the affected arteries (Ragino, Chernyavsky, Volkov, Volkova, & Voevoda, 2011, Anastasia et al. 2024a, Anastasia et al. 2024b, Zainab et al. 2024).

There are many hypotheses explaining the occurrence of atherosclerosis. Most of them attribute it to damage to the vascular endothelium (caused by mechanical, chemical, and infectious agents), changes in the lipoprotein profile, increased activity of the immune system, and neoplastic changes in the vessel wall (Hu et al., 2011; Leiderman, 2016; Luczak et al., 2011; Santos & Fonseca, 2009). However, there is still no generally accepted picture of the pathogenesis of the atherosclerotic process.

Analysis of more than 100 years of experience in modeling the atherosclerotic process allows us to identify several main directions in the study of this pathology, the development of which was associated primarily with the reproduction of atherogenic damage to blood vessels and organs in experimental animals:

The development of atherosclerosis is closely linked to several key factors. Firstly, the role of an atherogenic diet in the development of hypercholesterolemia and the atherosclerotic process is significant. Diets high in cholesterol and saturated fats contribute to elevated cholesterol levels in the blood, which is a major risk factor for atherosclerosis. Secondly, there is substantial evidence substantiating the cause-and-effect relationship between hypercholesterolemia and the formation of lipid plaques in blood vessels. Elevated cholesterol levels lead to the accumulation of lipids in the arterial walls, forming plaques that can restrict blood flow. Thirdly, understanding the molecular mechanisms of atherogenic damage to cellular populations of blood vessels and the formation of atherosclerotic plaques is crucial. This involves studying how lipids infiltrate the endothelium, triggering inflammatory responses and plaque development. Lastly, the development of drugs that reduce blood lipid levels is essential in managing and preventing atherosclerosis. These drugs, such as statins, work by lowering cholesterol levels, thereby reducing the risk of plaque formation and subsequent cardiovascular events.

In 1908, Russian scientist A.I. Ignatovsky first showed the possibility of experimentally modeling atherosclerosis by feeding rabbits egg yolk, which contains a lot of cholesterol. In 1912, N.N. Anichkov and S.S. Khalatov provided experimental confirmation that administering a solution of cholesterol in sunflower oil to rabbits via a gastric tube leads to changes in the aorta of the animals after 3-4 months, similar to those observed in human atherosclerosis. Due to the fact that this model involved the introduction of exogenous cholesterol in a very high dose, scientists wondered whether experimental atherosclerosis in rabbits could be induced by long-term feeding of low doses of dietary cholesterol. By increasing the duration of the experiment to two years, N.N. Anichkov and his colleagues managed to achieve pronounced atherosclerosis using low doses of dietary cholesterol. Through these experiments, N.N. Anichkov concluded that atherosclerosis is an infiltrative-hyperplastic process (Anichkov, 1913; Protasov, 2018, Anastasia et al. 2024c, Anastasia et al. 2024d, Anastasia et al. 2024e, Anastasia et al. 2024f, Anastasia et al. 2024g, Anastasia et al. 2023, Mathangi et al. 2021).

Modeling the atherosclerotic process in rabbits has substantiated the cause-and-effect relationship between hypercholesterolemia and the formation of lipid plaques in blood vessels, detailing the morphogenesis of atherogenic damage to the aorta, coronary vessels, and myocardium (Klimov, 1977). When modeling hypercholesterol damage to the vascular bed and organs in rabbits, it is important to note that a long-term hypercholesterol diet is hepatotoxic and often leads to their death before the end of the experiment. Unlike humans, in rabbits, the atherosclerotic process is accompanied by massive systemic inflammation (Xiangdong et al., 2011; Luczak et al., 2011). The HDL-dominated lipoprotein profile of rabbits is significantly different from that of humans, who have the largest LDL fraction (Xiangdong et al., 2011).

The advantages of using rabbits to study atherogenesis include a visible response to dietary cholesterol, the presence of transgenic lines, a convenient size of the animal, accessibility, and ease of

handling. However, there are several disadvantages: differences in the localization of cholesterol plaques compared to humans (in the aortic arch and descending thoracic aorta in rabbits, as opposed to lesions of the abdominal aorta in humans); most of the circulating cholesterol in rabbits is represented by high-density lipoproteins; the need for very high plasma cholesterol levels for induction of atherosclerosis; absence of progressive lesions; lipase deficiency in the liver; absence of spontaneous atherosclerosis and cholesterol accumulation syndrome when feeding cholesterol; and marked differences in the lipid profile of male and female rabbits (thus, it is preferable to induce experimental atherosclerosis in males) (Voronkova, Kuspanalieva, & Maslova, 2021).

The objectives of the study were multifaceted. Firstly, the research aimed to examine the influence of gender and diet in modeling atherosclerosis in rabbits, recognizing that these factors could significantly impact the development and progression of the disease. Secondly, the study focused on understanding how the composition of blood lipids affects the blood coagulation system, which is crucial for identifying potential therapeutic targets and interventions. Thirdly, the researchers conducted ultrasound studies to monitor the dynamics of atherogenesis in experimental rabbits, providing valuable insights into the temporal progression of the disease. Lastly, the study sought to determine the practical significance of these findings for medicine, aiming to translate the experimental results into clinical applications that could improve the prevention, diagnosis, and treatment of atherosclerosis in humans.

Materials and Methods

Subjects

To simulate multifocal atherosclerosis (MFA), four Chinchilla rabbits with a body weight of 3.0-3.5 kg were selected for the experiment. The group included three females and one male.

Ethical Considerations

The care and use of the animals were conducted in accordance with international regulations, specifically Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes (September 22, 2010). The protocol was designed to minimize animal suffering and ensure ethical treatment throughout the study.

Diet and Hyperlipidemia Induction

The rabbits were maintained on a standard vivarium diet predominantly consisting of wheat. Hyperlipidemia was induced by oral administration of a 10% fat emulsion for parenteral nutrition, "Sepid," produced by Sichuan Kelun Pharmaceutical Co., Ltd. (China), for two months. The emulsion was administered using an automatic pipette at a dose of 0.5 ml/kg.

Enhancement of Atheromatosis

After one month of Sepid administration, vitamin D2 (ergocalciferol) was added to the animals' diet to enhance aortic atheromatosis. It was provided in the form of a 0.0625% oil solution at a dose of 0.256 ml/kg for 30 days. Additionally, one month after starting Sepid, adrenaline was injected intravenously at a dose of 0.04 mg/kg every five days for 30 days (total of six injections) to further enhance atheromatosis and reduce the induction time of atherosclerosis.

Laboratory Tests

During the study, laboratory blood tests and ultrasound examinations of the aorta and its large branches were performed. Blood tests were conducted three times: at the beginning (baseline), at the end of the second month, and at the end of the third month. Biochemical blood tests included:

- Total protein (g/l)
- Glucose (mmol/l)
- C-reactive protein (CRP Latex) (mg/l)
- Triglycerides (TG) (mmol/l)
- Cholesterol (CH) (mmol/l)
- High-density lipoprotein (HDL) (mmol/l)
- Low-density lipoprotein (LDL) (mmol/l)

These tests were performed using a biochemical analyzer with CYPRESS DIAGNOSTICS kits (Germany).

Coagulogram Parameters

The following coagulogram parameters were studied using a coagulometer RT 2201 C (Germany) with kits from CYPRESS DIAGNOSTICS:

- Prothrombin time (PT), sec
- Activated partial thromboplastin time (APTT), sec
- Plasma recalcification time (RP), sec
- Thrombin time, sec
- Fibrinogen (F), g/dL
- Ultrasound Diagnostics

Ultrasound diagnostics to measure the diameter, wall thickness, and blood flow velocity in the abdominal aorta were performed using a portable Chison ultrasound machine Ebit 60 CW (China).

Blood Pressure and Heart Rate

Blood pressure and heart rate were monitored on the hind leg of the rabbits using an automatic digital blood pressure monitor LD 8 (Germany), specifically designed for animals.

Platelet Count

The number of platelets in peripheral blood was manually counted under a ZEISS binocular microscope (Germany).

Statistical analysis

Statistical analysis was conducted using SPS v 15 with paired t-tests for within-group comparisons, and ANOVA for between-group differences, analyzing biochemical, coagulogram, and ultrasound data.

Table 1A. Indicators of coagulogram, platelets, blood pressure and heart rate levels and weight of rabbits with a model of atherosclerosis (M ± m , n = 6). Note: *p=0.001 in relation to the intact group; **p in relation to the control group

Tests	Data from intact rabbits	Indicators in the 2nd month of feeding Sepid	3 month (Sepid was stopped)
Prothrombin time, (PT), sec	13.2±1.2	11.1±1.0	
Activated partial thromboplastin time (aPTT), sec	39.8±2.6	24.4±2.3	24.4±2.3
recalcification , sec	84.7 ±3.6	32.3±2.6	56.1±3.4
Thrombin time	20.2±1.6	12.4±1.0	6.0±0.5
Fibrinogen, mg/ dl	420.0±31.0	604.6±44.0*	734.3±45.0
Platelets, 10^9/l	322.0±24.0	625.0±42.0*	676.8±40.0
Systolic pressure	91.0±7.4	104.0±8.6	105.4±8.6
Diastolic pressure	33±2.5	74.8±3.7*	53.8±3.7
Pulse rate	78.1±6.3	105±8.2	103.9±8.1
Animal weight, kg	3.4±0.22	3.0-±0.21	2.9±0.20

Table 1B.

Tests	No. Rabbit and its naming	Data from intact rabbits	Indicators in the 2nd month of feeding Sepid	3 month (Sepid was stopped)
Prothrombin time, (PT), sec	1-gray female	12.2	10.6	14.8
	2-gray female	13.8	11.9	15.6
	3-gray male	13.6	11.9	14.1
	4-white female	13.2	10.2	12.1
Activated partial thromboplastin time (aPTT), sec	1	40.6	26.4	32.1
	2	35.8	23.8	25.8
	3	36.9	21.3	28.9
	4	45.6	26.3	41.8
Recalcification plasma, sec	1	84.8	50.8	70.3
	2	65.6	42.4	43.4
	3	72.0	29.1	48.0
	4	46.5	25.2	63.2
Thrombin time sec.	1	17.2	7.2	5.85
	2	20.1	7.4	5.7
	3	24.7	18.8	-
	4	32.3	20.6	6.35
Fibrinogen, mg/ dl	1	322.0	534.0	352.0
	2	451.5	648.3	702.0
	3	440.0	436.0	1001.0
	4	308.0	515.9	638.1
Platelets, 10^9/l	1	375.0	600.0	682.0
	2	300	725	750
	3	375	575	600
	4	325	775	725
Systolic pressure	1	100	116.5	105.0
	2	88	117.0	90.0
	3	78	100.0	100.0
	4	88	95.0	128.5
Diastolic pressure	1	32	47	53
	2	40	40	50
	3	44	48	55
	4	30	40	56.5
Pulse rate	1	75.5	123	92
	2	89	75.5	93.5
	3	63	85.5	98
	4	75	90	116
Animal weight, kg	1	3.4	3.3	3.5
	2	3.5	3.0	3.3
	3	3.0	2.8	2.7
	4	3.8	3.0	2.8

Table 2A. Biochemical blood parameters of rabbits with a model of atherosclerosis (M ± m , n = 5)

Tests	Data from intact rabbits	Indicators in the 2nd month of feeding Sepid	3 month (Sepid was stopped)
Total protein, g/l	63.2±4.2	60.0±13.2	
Glucose,			
Total cholesterol , , Mmol/l	2.6±2.6	4.0±0.32*	
Triglycerides , mmol/l	1.1±0.06	1.73±0.08*	
Low density lipoproteins (LDL)	0.58±0.45	1.55±1.2*	
High density lipoproteins (HDL)	0.69±0.48	0.76±0.44	

Note: *p=0.001 in relation to the intact group; **p in relation to the control group

Table 2B.

Tests		Data from intact rabbits	Indicators in the 2nd month of feeding Sepid	3 month (Sepid was stopped)
Total protein, g/l	1	50.0	50	48
	2	70	50	75
	3	75	75	110
	4	56	100	100
Glucose,	1	4.4	4.9	4.8
	2	5.0	5.2	5.2
	3	5.1	4.7	5.6
	4	5.0	4.9	5.0
Total cholesterol, , Mmol/l	1	2.0	2.5	2.4
	2	2.4	3.7	2.9
	3	2.5	2.9	Z.7
	4	2.6	4.2	3.7
Triglycerides, mmol/l	1	0.71	2.4	1.19
	2	0.9	2.62	1.67
	3	1.19	2.38	3.05
	4	0.95	2.38	1.47
Low density lipoproteins (LDL)	1	1.2	0.96	1.35
	2	0.77	2.5	1.27
	3	0.78	2.1	2.0
	4	0.77	1.7	1.5

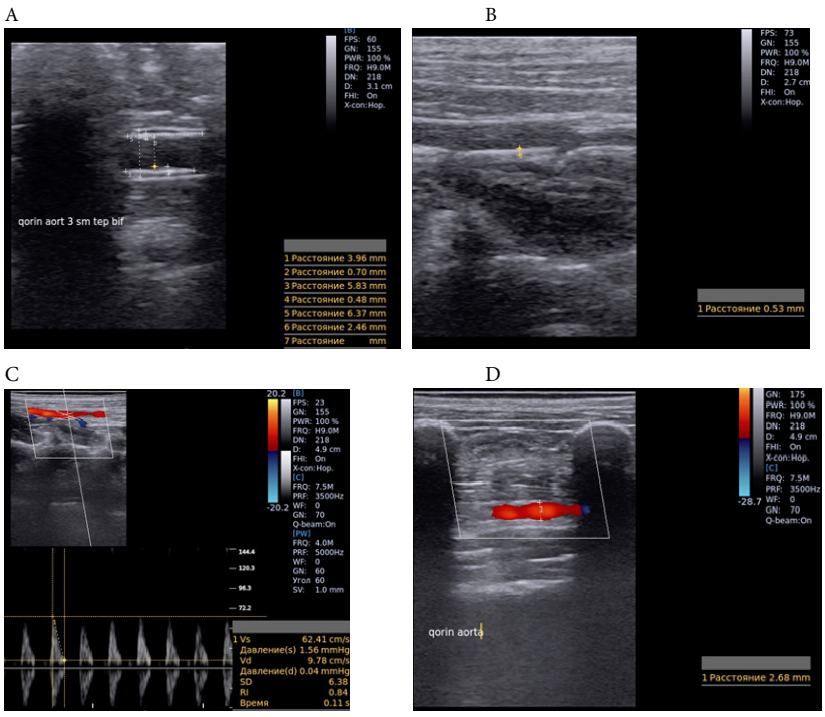

Figure 1. (A) Abdominal aorta of a male rabbit. (B) Abdominal aorta at the level bifurcations. (C) Doppler mode of abdominal ultrasound. (D) Doppler mode of ultrasound aorta of a male rabbit. Measurement of LSSC. studies of the carotid arteries of a male rabbit. Measurement of LSSC.

Table 3. Ultrasound data of the examined rabbits.

Index	No.	Average values for the original rabbits	In the 2nd month of the experiment
Abdominal aorta size (mm)	1	3.2 - 4.8	2.74
	2		2.79- 3.0
	3		3.96
	4		3.17
Wall thickness(mm)	1	0.4 -0.7	0.38
	2		0.43
	3		0.7
	4		0.6
LSSC (cm/sec)	1	80 -130	134
	2		61-74
	3		66
	4		57.9
Local intimal thickening (mm)	1	Absent	No
	2		2.82 length, 0.43 thickness
	3		6.37 length 0.48 thickness
	4		No
Heart rate beats per minute	1	250-450	460
	2		300
	3		300
	4		400

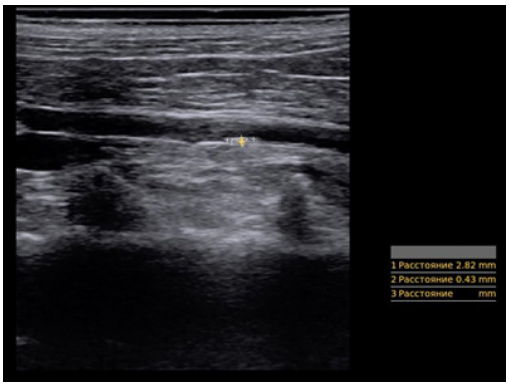

Figure 2. Ultrasound data of the abdominal aorta of rabbit No. 2.

Sepid contains refined soybean oil emulsified with purified egg yolk phospholipids. Soybean oil consists of a mixture of triglycerides, predominantly polyunsaturated fatty acids. Phospholipids are isolated from egg yolk. The size of lipid globules and biological properties are identical to those of chylomicrons (An et al., 2020; Smith et al., 2018).

As shown by the coagulogram data in Table 1, after two months of administering atherogenic substances to the animals, the PT index in the control group decreased by 16%. The APTT shortened by 64% (*p=0.001) compared to the initial blood data of rabbits (39.8±2.6 sec). APTT measures the efficiency of the intrinsic coagulation pathway; a shortened APTT indicates increased coagulation (hypercoagulation), while a prolonged APTT indicates hypocoagulation and is sensitive to plasma coagulation defects, especially to deficiencies of factors XII, XI, IX, VIII, V, and II, as well as to an excess of anticoagulants in plasma.

The plasma recalcification time largely reflects deficiencies in factors involved in the internal mechanism of prothrombinase formation, as well as the amount of fibrinogen, platelets, and their functional activity. In the control group, plasma recalcification time (PR) decreased by 49% (*p=0.001) compared to the data from intact animals (51.3±2.6 sec). Thrombin time characterizes the last phase of blood coagulation and depends on the content of fibrinogen and inhibitors that block the action of thrombin and the conversion of fibrinogen to fibrin. Thrombin time in the control group decreased by 49% (*p=0.001) compared to data from intact animals (20.2±1.6 sec). The studies showed that fibrinogen (F) content in the control group increased by 44% (*p=0.001) compared to data from intact animals (420.0±31g/dL), indicating not only hypercoagulation but also the presence of an extensive inflammatory process.

These data also correlate with a 94% (*p=0.001) increase in the number of platelets in peripheral blood compared to the initial data of rabbits (322.0±24x10^9/L). The increase in platelet count was accompanied by a slight increase in both blood pressure and heart rate. As presented in Table 2, total cholesterol (TC) increased by 54% (*p<0.001) compared to the initial data in rabbits (2.6±2.6 mmol/L), triglycerides (TG) increased by 70% (*p<0.001) compared to the initial data of rabbits (1.73±0.08 mmol/L), and low-density lipoprotein (LDL) increased by 167% (*p<0.001) compared to the initial data of rabbits (0.58±0.45 mmol/L).

Despite the rabbits' diet being enriched with fats, their weight remained practically unchanged and even decreased in rabbit No. 4. Ultrasound examination of the blood vessels of rabbits was carried out twice: in intact rabbits in the control group before the experiment and at the second month of the experiment. The average values of blood vessel and blood flow indicators in intact rabbits were determined, including the average diameter and wall thickness of the abdominal aorta, intimal thickness, and blood flow velocity. At the second month of the study, pronounced ultrasound changes were noted in a male rabbit. The thickness of the abdominal aorta wall was 0.7 mm, with the thickness and length of the local thickening being 0.48 mm and 6.37 mm, respectively. The thickness at the level of the origin of the renal arteries was 0.53 mm (see Figures 1A and 1B). Doppler mapping data showed no changes in the linear velocity of systolic blood flow (Figures 1C and 1D). Local changes were also detected in the wall of the abdominal aorta in female gray rabbit No. 2, with local intimal thickening measuring 2.82 mm in length and 0.43 mm in thickness (see Figure 2). These indicators suggest changes in the vascular wall characteristic of the atherosclerotic process.

A cholesterol-enriched diet for two months resulted in a significant increase in blood lipid parameters, indicating hyperlipidemia, as well as changes in coagulogram parameters toward hypercoagulation and an increased number of platelets, suggesting an elevated risk of acute vascular events in the blood supply organs. Despite discontinuing the Sepid fat emulsion at the third month, blood counts did not return to baseline levels, indicating persistent biochemical and hemostasiological changes due to the high-fat diet. The high level of fibrinogen indicates a systemic inflammatory process in the rabbits. Ultrasound of the aorta and its branches can determine early manifestations of suspected atherosclerosis in rabbits (Table 3). Notably, in the male rabbit, fibrinogen, total cholesterol, triglycerides, and lipoproteins were significantly higher compared to females, emphasizing the gender characteristics of the atherosclerotic process.

Conclusion

The utilization of a 10% Sepid fat emulsion has been demonstrated to induce significant alterations in blood lipid parameters in rabbits, underscoring its efficacy in initiating hyperlipidemia, a pivotal factor in atherosclerosis research. Moreover, male rabbits exhibited markedly elevated lipid profile indicators and inflammatory markers compared to their female counterparts, suggesting a heightened susceptibility to atherosclerosis in males. This observed increase in triglycerides, total cholesterol, and various lipoprotein fractions was concomitant with elevated levels of fibrinogen and platelets, alongside a reduction in prothrombin time (PT), thrombin time (TT), and a shortened activated partial thromboplastin time (APTT), indicative of blood hypercoagulation. The imperative role of ultrasound in monitoring the progression of atheromatosis in the aorta and its branches in rabbits cannot be overstated. Unlike previous studies primarily reliant on clinical and biochemical blood tests, ultrasound enables dynamic assessment of vascular changes, enhancing the quality of the atherosclerosis model. Furthermore, the development of multifocal atherosclerosis (MFA) models in rabbits holds promise for advancing therapeutic interventions. This innovation paves the way for the exploration and application of herbal or chemical

preparations capable of modulating atheromatosis across its developmental spectrum, potentially culminating in the creation of drugs capable of dissolving atherocalcinosis in vivo, thus presenting a transformative outlook for combating atherosclerosis.

Author contributions

M.M.A., K.T.M., N.L.V., A.V.F., R.N.J., D.R.J., N.M.V., I.T.A., S.S.S. developed the study design, and wrote, reviewed, and edited the paper.

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Competing financial interests

The authors have no conflict of interest.

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