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Effect of Thiocin On Cholesterol Metabolism During the Progression of Experimental Atherosclerosis

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Abstract

The effect of Thiocin on cholesterol metabolism parameters in experimental atherosclerosis was investigated. Experimental atherosclerosis was induced in rabbits by daily administration of cholesterol for three months. Experimental atherosclerosis was found to be associated with marked hypercholesterolemia and decreased serum cortisol and vitamin D levels. Thiocin exerted a pronounced dose-dependent hypocholesterolemic effect and promoted an increase in cortisol levels. The most pronounced therapeutic effect was observed with Thiocin administered at a dose of 70 mg/kg and in combination with Levazo. The effect of Thiocin on vitamin D levels was less pronounced.

Keywords: Atherosclerosis, Thiocin, cholesterol, cortisol, vitamin D, hypercholesterolemia, lipoic acid, zinc

Introduction

Atherosclerosis is one of the leading causes of morbidity, disability, and mortality worldwide [9]. Despite significant advances in the prevention and treatment of cardiovascular diseases, the prevalence of atherosclerosis continues to increase [12]. This trend is associated with population aging, changes in lifestyle, and the growing incidence of obesity, diabetes mellitus, metabolic syndrome, and other cardiovascular risk factors. According to current concepts,

atherosclerosis is a chronic, progressive, multifactorial disease [12,15,13].

Disorders of cholesterol metabolism represent a key pathogenetic factor in the development of atherosclerosis. Elevated concentrations of total cholesterol and low-density lipoprotein cholesterol (LDL-C) promote lipid accumulation within the arterial intima, followed by oxidative modification and progression of atherosclerotic lesions [8,15,16].

In recent years, increasing attention has been paid to the role of the neuroendocrine system in the pathogenesis of cardiovascular diseases. Cortisol, one of the principal hormones involved in the physiological response to stress, regulates not only metabolism but also exerts significant effects on immune function, vascular tone, and energy homeostasis. Alterations in cortisol levels during chronic diseases are considered one of the mechanisms underlying impaired adaptive capacity [14,3,4].

Vitamin D also plays an important role in the development of cardiovascular diseases, with physiological functions extending far beyond the regulation of calcium-phosphorus metabolism [11]. Vitamin D has been shown to participate in the regulation of innate and adaptive immunity, inflammatory processes, endothelial function, renin-angiotensin system activity, and cellular proliferation and differentiation. Vitamin D deficiency has been associated with arterial hypertension, metabolic syndrome, type 2 diabetes mellitus, and atherosclerosis. Reduced vitamin D levels are accompanied by enhanced vascular inflammation, endothelial dysfunction, and an increased risk of cardiovascular complications [11, 2,16].

Thus, the current understanding of atherosclerosis extends well beyond disturbances in lipid metabolism alone. The disease is characterized by complex metabolic, hormonal, and inflammatory alterations. Therefore, the development of therapeutic agents capable of simultaneously targeting multiple pathogenetic mechanisms represents a promising strategy for the treatment of atherosclerosis.

The aim of the present study was to investigate the effect of Thiocin on cholesterol metabolism during the progression of experimental atherosclerosis.

Methods

Experimental atherosclerosis was induced in rabbits by daily intragastric administration of cholesterol at a dose of 0.2 g/kg body weight for three months [1]. After the three-month cholesterol administration period, the animals were divided into six groups:

Group 1– intact (normal control);

Group 2 – rabbits with experimental atherosclerosis;

Group 3 – Levazo treatment (0.057 mg/kg body weight);

Groups 4 and 5 – Thiocin treatment at doses of 35 mg/kg

70 mg/kg body weight, respectively;

Group 6– combination therapy.

Animals in Groups 3–6 received treatment for 30 days. Throughout the treatment period, all animals except those in the intact group continued to receive cholesterol.

During the progression of experimental hypercholesterolemia and following treatment with the indicated agents, plasma total cholesterol levels were determined using a colorimetric method. Serum cortisol and vitamin D concentrations were measured by electrochemiluminescence immunoassay (ECLIA) using a cobas e 411 analyzer (Switzerland).

Results and Discussion

Evaluation of plasma total cholesterol levels during the progression of experimental atherosclerosis demonstrated a significant increase at all observation time points (Figure 1).

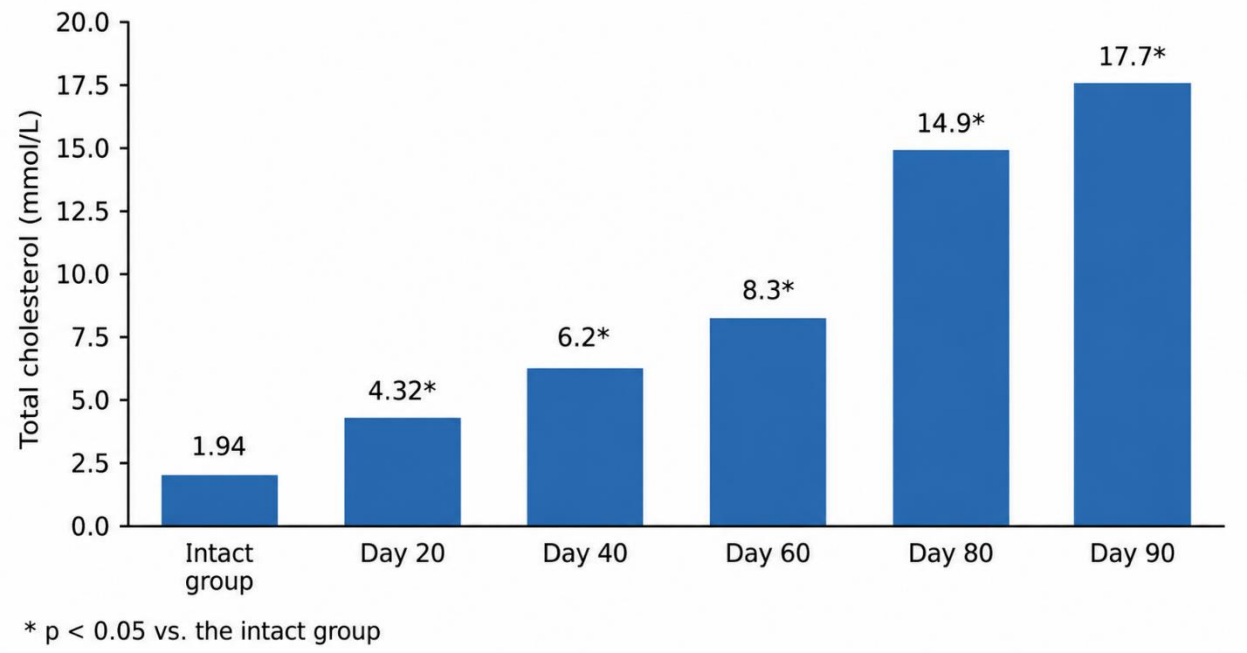

Figure 1. Changes in plasma total cholesterol levels during the progression of experimental atherosclerosis (mmol/L)

In the intact animals, the plasma total cholesterol concentration was 1.94 ± 0.14 mmol/L. On Days 20 and 40 following cholesterol administration, plasma total cholesterol increased 2.23-fold and 3.19-fold, respectively, compared with the intact group. By Day 60, the cholesterol concentration had increased 4.28-fold relative to the intact animals. The most pronounced and sustained elevation in plasma total cholesterol was observed on Days 80 and 90, reaching 7.7-fold and 9.1-fold, respectively, compared with the intact group.

These findings indicate the persistent development of hypercholesterolemia in experimental rabbits following three months of exogenous cholesterol administration.

Along with disturbances in lipid metabolism, serum cortisol levels were also evaluated at different stages of experimental atherosclerosis (Figure 2).

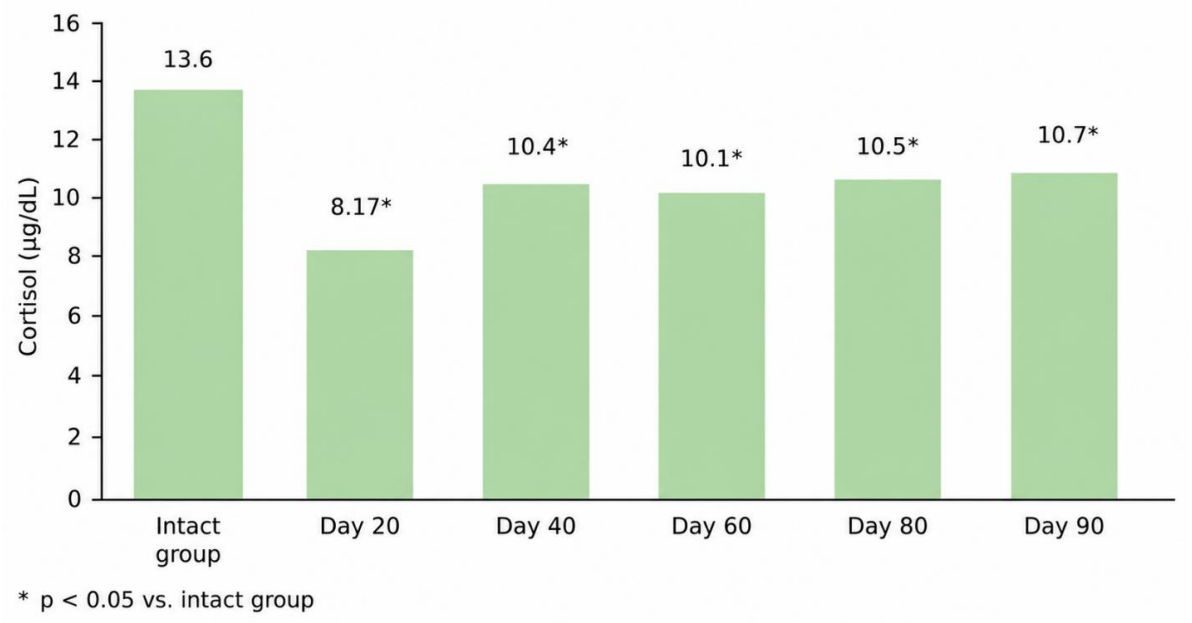

Figure 2. Changes in serum cortisol levels during the progression of experimental atherosclerosis (nmol/L)

As shown in Figure 2, the serum cortisol concentration in the intact animals was 13.6 ± 1.0 ng/mL. On Day 20 following cholesterol administration, the most pronounced decrease in cortisol levels was observed, amounting to 39.93% compared with the intact group. On Days 40, 60, 80, and 90 of experimental atherosclerosis, serum cortisol levels remained reduced by 21.3–25.7% compared with the intact group.

These findings indicate impaired functional activity of the hypothalamic–pituitary–adrenal (HPA) axis during the progression of experimental atherosclerosis. Reduced cortisol levels may contribute to the weakening of endogenous anti-inflammatory mechanisms, enhancement of oxidative stress, progression of endothelial dysfunction, and destabilization of atherosclerotic plaques. In addition, decreased cortisol bioavailability may be associated with increased activity of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), the enzyme responsible for cortisol inactivation in peripheral tissues.

The results of the analysis of vitamin D levels during the progression of experimental atherosclerosis are presented in Figure 3.

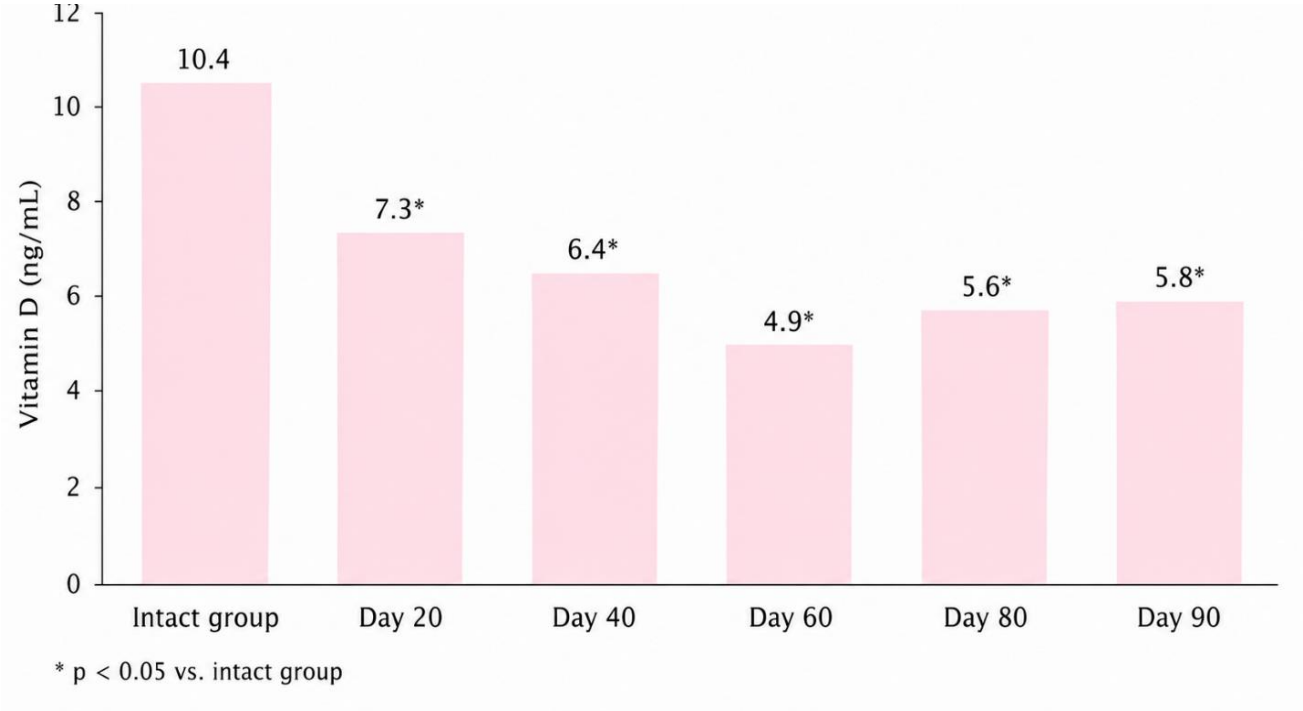

Figure 3. Changes in serum vitamin D levels during the progression of experimental atherosclerosis (ng/mL)

As shown in Figure 3, a decrease in serum vitamin D levels was observed as early as Day 20 of the experiment. The most pronounced reduction occurred on Day 60 of experimental atherosclerosis, when the serum vitamin D concentration reached 4.9 ± 0.5 ng/mL.

The simultaneous development of hypercholesterolemia, reduced cortisol levels, and vitamin D deficiency indicates the formation of interrelated metabolic and endocrine disturbances. These findings confirm that the progression of atherosclerosis is accompanied not only by impaired lipid metabolism but also by marked alterations in hormonal regulation and vitamin D status.

To correct hypercholesterolemia, we used Thiocin, a preparation synthesized by researchers at the Tashkent Pharmaceutical Institute, containing zinc and lipoic acid. As shown in Table 1, Levazo reduced plasma total cholesterol levels by 10.7%, 19.8%, and 31.6% on Days 10, 20, and 30 of treatment, respectively, compared with the untreated control group.

Table 1

Effect of Thiocin on plasma total cholesterol levels (mmol/L) in rabbits with experimental atherosclerosis.

Group of animal	Days of study		
	10th day	10th day	10th day
Intact Group	1,94 ± 0,14	1,94 ± 0,14	1,94 ± 0,14
Control Group	17,7±0,33	17,7±0,33	17,7±0,33
Received Levazo	15,8±0,50*	14,2±0,32*	12,1±0,37*
Received Thiocin 35 mg/kg	14,9±0,68*	12,4±0,63*	7,8±0,14*
Received Thiocin 70 mg/kg	11,6±0,35*	9,1±0,33*	5,3±0,18*
Received Thiocin 70 mg/kg + Levazo	8,4±0,13*	6,9±0,45*	4,2±0,41*

Note: In all cases, $p < 0.05$ compared with the control group.

Administration of Thiocin at a dose of 35 mg/kg body weight reduced plasma total cholesterol levels by 15.8%, 29.95%, and 55.93% on Days 10, 20, and 30 of treatment, respectively, compared with the control group. In the group receiving Thiocin at 70 mg/kg body weight, plasma cholesterol levels decreased by 34.5%, 48.6%, and 70.1%, respectively, compared with the control group. These findings indicate that Thiocin at a dose of 70 mg/kg exerts a more pronounced hypocholesterolemic effect.

Combined administration of Thiocin and a statin produced an even greater reduction in plasma cholesterol levels, amounting to 52.54%, 61.0%, and 76.3% on Days 10, 20, and 30, respectively, compared with the control group. These results demonstrate a marked dose-dependent hypocholesterolemic effect of Thiocin, which was most pronounced when administered in combination with a statin.

The effects of these treatments on serum cortisol levels are presented in Table 2.

Table 2

Effect of Thiocin on serum cortisol levels (ng/mL) in experimental atherosclerosis.

Group of animal	Days of study		
	10th day	10th day	10th day
Intact Group	13,6 ± 0,5	13,6 ± 0,5	13,6 ± 0,5
Control Group	10,7 ± 0,3	10,7 ± 0,3	10,7 ± 0,3
Received Levazo	12,3 ± 0,1*	14,4 ± 0,8	15,8 ± 0,5
Received Thiocin 35 mg/kg	14,1 ± 0,6	15,1± 0,2	16,6 ± 0,2
Received Thiocin 70 mg/kg	15,0 ± 0,2	17,3 ± 0,3	18,3± 0,2
Received Thiocin 70 mg/kg + Levazo	13,0 ± 0,3*	14,2 ± 0,4	15,4 ± 0,4

Note: In all cases, $p < 0.05$ compared with the control group.

Treatment of experimental animals with Levazo resulted in a significant increase in serum cortisol levels on Days 20 and 30 of the study by 34.6% and 47.6%, respectively, compared with the control group.

Administration of Thiocin at a dose of 35 mg/kg body weight significantly increased serum cortisol levels by 31.7%, 41.1%, and 55.1% at all observation time points compared with the control group. A more pronounced increase in

cortisol levels was observed in animals treated with Thiocin at a dose of 70 mg/kg body weight, reaching 40.2%, 61.7%, and 71.0%, respectively, compared with the control group.

Combined administration of Levazo and Thiocin (70 mg/kg body weight) also produced a significant increase in serum cortisol levels on Days 20 and 30, amounting to 32.7% and 43.9%, respectively, compared with the control group. However, the magnitude of this effect was lower than that observed with Thiocin (70 mg/kg) administered as monotherapy.

To correct the observed disturbances in vitamin D levels, Levazo was used as the reference drug, while Thiocin was administered at doses of 35 mg/kg and 70 mg/kg body weight. The effects of the investigated treatments on serum vitamin D levels are presented in Table 3.

Table 3

Effect of Thiocin on serum vitamin D levels (ng/mL) in experimental atherosclerosis.

Group of animal	Days of study		
	10th day	10th day	10th day
Intact Group	10,4 ± 0,6	10,4 ± 0,6	10,4 ± 0,6
Control Group	5,8 ± 0,05	5,8 ± 0,05	5,8 ± 0,05
Received Levazo	6,3 ± 0,05	6,7 ± 0,02	7,1 ± 0,01
Received Thiocin 35 mg/kg	5,6 ± 0,02	4,8 ± 0,01	3,9 ± 0,01
Received Thiocin 70 mg/kg	4,4 ± 0,02	4,3 ± 0,01	4,1 ± 0,02
Received Thiocin 70 mg/kg + Levazo	3,5 ± 0,01	4,1 ± 0,02	4,8 ± 0,01

Note: In all cases, $p < 0.05$ compared with the control group.

As shown in Table 3, animals treated with Levazo demonstrated a significant increase in serum vitamin D levels. On Days 20 and 30 of the study, vitamin D concentrations increased by 15.5% and 22.4%, respectively, compared with the control group.

Treatment with Thiocin at doses of 35 mg/kg and 70 mg/kg was associated with lower serum vitamin D levels. The most pronounced reduction was observed on Day 30, amounting to 29.3% and 32.8%, respectively, compared with the control group. In animals receiving combined therapy with Thiocin and Levazo, the serum vitamin D level remained 17.3% lower than that of the control group. The lowest vitamin D concentrations were recorded on Days 10 and 20 of treatment, reaching 3.5 ± 0.01 ng/mL and 4.1 ± 0.02 ng/mL, respectively. These findings indicate that alterations in vitamin D levels persisted throughout the treatment period of experimental atherosclerosis. Different pharmacological treatment regimens produced distinct changes in vitamin D levels, suggesting differential effects of the investigated drugs on vitamin D metabolism.

The obtained results demonstrate that the investigated treatments exert different effects on serum vitamin D levels. The greatest increase in vitamin D concentration was observed in the Levazo-treated group. Administration of Thiocin at either dose did not restore vitamin D levels to those of the control group, whereas combined treatment with Thiocin and Levazo resulted in a partial recovery of vitamin D concentration by Day 30 of therapy.

The present findings indicate that the development of experimental atherosclerosis is accompanied by disturbances in cholesterol metabolism and alterations in biologically related metabolites. Elevated plasma total cholesterol levels were associated with reduced serum cortisol and vitamin D concentrations, reflecting impairment of both lipid and steroid metabolism during atherosclerosis [7,9].

The observed increase in plasma total cholesterol is consistent with current concepts of atherosclerosis pathogenesis. Excessive cholesterol accumulation promotes endothelial dysfunction, activation of inflammatory processes, and progression of atherosclerotic vascular lesions. These findings confirm the validity of the experimental model used in this stu

Simultaneously with the development of hypercholesterolemia, a reduction in serum cortisol levels was observed. Cortisol is one of the principal hormones regulating

metabolism and inflammatory responses. Therefore, decreased cortisol concentrations may contribute to enhanced inflammation and progression of vascular injury during atherosclerosis [16].

A concomitant decrease in serum vitamin D levels was also detected. Vitamin D is currently recognized as an important regulator of immune responses, inflammation, and endothelial function. Its deficiency has been associated with an increased risk of cardiovascular diseases. Thus, the observed reduction in vitamin D levels further confirms the presence of profound metabolic disturbances during experimental atherosclerosis.

The present study demonstrated that Thiocin possesses a pronounced hypocholesterolemic effect. The greatest reduction in plasma total cholesterol was observed at a dose of 70 mg/kg, while the maximum effect was achieved when Thiocin was administered in combination with a statin. This effect is likely attributable to the antioxidant properties of lipoic acid and the role of zinc in regulating enzymatic processes involved in lipid metabolism.

Treatment with Thiocin was also associated with an increase in serum cortisol levels, which was most pronounced at the 70 mg/kg dose. These findings suggest a partial restoration of impaired steroid metabolism under conditions of experimental atherosclerosis.

A different pattern was observed for vitamin D levels. Despite the marked reduction in plasma cholesterol and the increase in cortisol concentrations, recovery of vitamin D levels was less pronounced. This finding suggests that vitamin D metabolism is regulated by additional mechanisms that are not directly dependent on changes in total cholesterol concentration.

Thus, the present results demonstrate that Thiocin exerts a marked hypocholesterolemic effect and contributes to the partial restoration of impaired steroid metabolism in experimental atherosclerosis. However, its influence on vitamin D metabolism requires further investigation.

Conclusion

1. Experimental atherosclerosis is associated with hypercholesterolemia and reduced serum cortisol and vitamin D levels.
2. Thiocin exhibits a pronounced dose-dependent hypocholesterolemic effect.
3. Administration of Thiocin promotes an increase in serum cortisol levels in experimental atherosclerosis.
4. The most pronounced hypocholesterolemic effect is achieved by the combined administration of Thiocin and Levazo.
5. The effect of Thiocin on vitamin D levels is less pronounced than its effects on cholesterol metabolism and cortisol concentrations.

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