Original paper

Effect of colchicine administration on interleukin-1β and nitric oxide expression at the early stage of atherosclerosis in atherosclerosis Wistar rat model

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Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2025;62(6):1125–1130

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Funding sources
None declared

Conflict of interest
None declared

Acknowledgements
None declared

Received on April 1, 2022
Reviewed on June 11, 2022
Accepted on June 28, 2022

Published online on December 22, 2025

Abstract

Background. The basic mechanisms underlying early atherosclerosis remain controversial. Several theories centered on lipid accumulation have been proposed, but increasing evidence highlights the central roles of inflammation and endothelial dysfunction in the initiation of the disease. Two major processes – chronic lipid-driven injury and maladaptive inflammatory and cellular responses – are closely involved in early atherogenesis and offer potential targets for new management strategies in atherosclerotic cardiovascular disease (ASCVD).

Objectives. The aim of the present study was to evaluate the effects of colchicine compared with atorvastatin on the expression of interleukin-1β (IL-1β), a key pro-inflammatory cytokine, and nitric oxide (NO), a protective mediator, both of which play important roles at the early stages of atherosclerosis.

Material and methods. This was an in vivo experimental study. A total of 20 male Wistar rats (*Rattus novergicus*) were divided into 4 groups: the control (normal) group (N); the dyslipidemia group fed an atherogenic diet (DL); the dyslipidemia group receiving both an atherogenic diet and colchicine (DLK); and the dyslipidemia group receiving both an atherogenic diet and atorvastatin (DLA). All kinds of treatment were administered for 14 days.

Results. The results showed that colchicine and atorvastatin were equally effective in terms of IL-1β reduction ($p > 0.05$). Yet, the data also showed that the NO levels were significantly higher in the DLK group as compared to the DLA group ($p < 0.05$).

Conclusions. In the early development of atherosclerosis, colchicine was significantly more effective than atorvastatin in increasing the NO levels and demonstrated a comparable ability to reduce the IL-1β levels. These findings suggest that colchicine may offer superior benefits as a primary preventive therapy in populations at risk for ASCVD.

Keywords: atherosclerosis, nitric oxide, interleukin-1β, colchicine

Cite as
Febrianda L, Heriansyah T, Gani BA, Mudatsir M. Effect of colchicine administration on interleukin-1β and nitric oxide expression at the early stage of atherosclerosis in atherosclerosis Wistar rat model. *Dent Med Probl.* 2025;62(6):1125–1130. doi:10.17219/dmp/151657

DOI
10.17219/dmp/151657

Highlights

- Colchicine shows superior effectiveness in increasing the NO levels as compared to atorvastatin, offering potential benefits for early atherosclerosis prevention.
- Colchicine demonstrates comparable ability to reduce the IL-1β levels, suggesting its potential as a primary preventive therapy for populations at risk of atherosclerotic cardiovascular disease (ASCVD).

Introduction

Cardiovascular disease (CVD) remains a major global health threat and is the leading cause of death worldwide. Among its forms, atherosclerotic cardiovascular disease (ASCVD) continues to account for the largest share of cases, contributing substantially to global morbidity and mortality.[1] The basic mechanisms underlying early atherosclerosis remain controversial.[2] Statins have long been the cornerstone of atherosclerosis prevention and treatment. In addition to their lipid-lowering action, statins exert pleiotropic (cholesterol-independent) effects that contribute to plaque regression. They also help stabilize atheromatous lesions by increasing fibrous cap thickness and enhancing macrocalcification.[3,4] Emerging theories highlight the central roles of inflammation and endothelial dysfunction in the development of atherosclerosis, offering new insights and potential strategies for the management of ASCVD.[2,5] Nitric oxide (NO) functions as a vasodilator and possesses antiplatelet, antiproliferative, anti-inflammatory, and antioxidant properties. Reduced NO bioavailability leads to endothelial dysfunction, a key early causal factor in the development of atherosclerosis.[6] Inflammation plays a crucial role in atherogenesis through the activation and proliferation of macrophages, endothelial cells and vascular smooth muscle cells. Macrophage-driven inflammatory responses involve the release of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and interleukin-12 (IL-12), and they serve as a major source of reactive oxygen species (ROS) within atherosclerotic lesions.[7,8] During the progression of atherosclerosis, IL-1β plays a dominant role in inducing endothelial dysfunction, and activating leukocytes and proteases. At the complication stage, IL-1β contributes to platelet activation, which can trigger the rupture of atheromatous plaques, and subsequently lead to thrombosis.[9,10]

Numerous studies have investigated the effects of anti-inflammatory drugs on ASCVD and their association with major adverse cardiac events (MACE), including colchicine. Colchicine exerts its therapeutic effects by targeting multiple stages of the inflammatory process. Unlike other anti-inflammatory drugs or glucocorticoids, colchicine operates independently of the arachidonic acid pathway. It inhibits neutrophil adhesion to the vascular endothelium, increases the leukocyte cyclic adenosine monophosphate (cAMP) levels, suppresses IL-1 production by activated neutrophils, and blocks TNF-α receptors in macrophages and endothelial cells.[11–13] However, the potential benefits of colchicine, particularly its effects at the molecular level during the early phase of atherosclerosis and its role as a primary preventive therapy in populations at risk for ASCVD, still require further investigation.

The present study aimed to evaluate the effects of colchicine on the concentration of the inflammatory marker IL-1β, which plays a key role at the early stages of atherosclerosis, and on NO, a vasodilator that protects endothelial cells. These effects were compared with those of atorvastatin, a well-established therapeutic agent.

Material and methods

This experimental study involved twenty 4-week-old male Wistar rats (*Rattus norvegicus*), weighing 150–200 g, obtained from Bogor Agricultural University (IPB), Indonesia. The rats were housed in sterile stainless steel cages in a temperature-controlled environment (23°C) with a 12-hour light/dark cycle. They were kept in a well-ventilated area with ad libitum access to tap water and a standard pellet diet. The rats were randomly assigned to 4 groups, each consisting of 5 animals: the control (normal) group (N); the dyslipidemia group fed an atherogenic diet (DL); the dyslipidemia group receiving both an atherogenic diet and colchicine (DLK); and the dyslipidemia group receiving both an atherogenic diet and atorvastatin (DLA).

After a 2-week acclimation period, 5 rats were fed a normal diet, while 15 rats were given an atherogenic diet ad libitum for 8 weeks. The atherogenic diet consisted of vitamin D3, 0.2% cholic acid, 2% egg yolk, 5% goat fat, and 92.8% corn rice. Following the 8-week feeding period, the low-density lipoprotein (LDL) levels were assessed to evaluate the effects of atherosclerosis induction. A previous study showed that an 8-week atherogenic diet significantly increased the LDL levels and induced foam cell formation in male Sprague–Dawley albino rats, thereby impacting their lipid profile.[14]

The treatment phase began in week 9, when the rats were 15 weeks old. During this phase, the animals were fed according to the study design described above. The rats in the treatment groups received therapeutic doses of colchicine (0.5 mg/day) or atorvastatin (40 mg/day) for

14 days. At the end of the treatment period, euthanasia was performed by the researchers and the laboratory staff through the intraperitoneal administration of ketamine (Ilium Ketamil; Troy Laboratories, Sydney, Australia) and xylazine (Xyla; Interchemie, Venray, the Netherlands). Blood samples were collected directly from the heart and transferred into Venoject® tubes. Plasma was separated by centrifugation, using a microcentrifuge (MC-12; Benchmark Scientific Inc., Sayreville, USA) at 3,000 rpm for 10 min, and then immediately stored at –80°C. The plasma samples were later used to measure the IL-1β and NO concentrations.

Measurement of the IL-1β and NO concentrations

The measurement of the IL-1β and NO concentrations in the rat plasma samples was performed using the enzyme-linked immunosorbent assay (ELISA) method. The IL-1β levels were quantified using the Rat IL-1β ELISA Kit (cat. No. E-EL-R0011; Elabscience®, Wuhan, China), and the NO concentrations were measured using the Rat NO ELISA Kit (cat. No. E-BC-K035-M; Elabscience).

The competitive ELISA procedure began with coating the wells with the antigen. A total of 100 µL of the standard and the test sample was added to each well, except for the blank. The plates were incubated at 37°C for 1 h, followed by the addition of 50 µL of substrate A and 50 µL of substrate B to each well. The plates were then incubated for 10–15 min at 37°C, protected from light. The reaction was terminated by adding 50 µL of a stop solution to each well. After 5 min, absorbance was measured at 450 nm, using a microplate reader (xMark™ Microplate Absorbance Spectrophotometer; Bio-Rad, Hercules, USA).

Statistical analysis

Data normality and the homogeneity of variances were assessed using the Shapiro–Wilk test ($p > 0.05$) and Levene's test, respectively. The one-way analysis of variance (ANOVA) was used to evaluate the effects of colchicine and atorvastatin administration on the IL-1β and NO concentrations. Post-hoc analysis was subsequently performed to determine pairwise differences among the groups. Statistical analysis was conducted using IBM SPSS Statistics for Windows, v. 20.0 (IBM Corp., Armonk, USA).

Results

Atherosclerosis was induced by administering an atherogenic diet for 8 weeks. The Shapiro–Wilk test confirmed that the data was normally distributed ($p > 0.05$). As shown in Table 1, the mean LDL levels after atherosclerosis induction in the DL, DLK and DLA groups were 72.3 ±8.9 mg/dL, 74.0 ±10.6 mg/dL and 73.8 ±9.9 mg/dL, respectively. In contrast, the normal group had a mean LDL level of 23.8 ±5.3 mg/dL.

Effect of colchicine on the LDL levels

The study also evaluated the effect of colchicine on reducing the LDL levels. The results demonstrated that administering 0.5 mg of colchicine for 14 days effectively lowered the LDL levels in rats with atherosclerosis. The mean reduction in the LDL levels in the DLK group was 32.8 ±6.2 mg/dL ($p < 0.05$), as presented in Table 2.

Effect of colchicine on the IL-1β levels

The results showed that the mean IL-1β levels were 56.5 ±19.6 µ/mmol in the DL group, 32.4 ±5.7 µ/mmol in the DLK group and 39.7 ±11.5 µ/mmol in the DLA group ($p < 0.05$), as presented in Table 3. These findings indicate a significant difference in the IL-1β levels among the treatment groups. In contrast, IL-1β was not detected in the N group.

Table 1. Mean low-density lipoprotein (LDL) levels after atherosclerosis induction

Group	LDL level [mg/dL]
N	23.8 ±5.3
DL	72.3 ±8.9
DLK	74.0 ±10.6
DLA	73.8 ±9.9

Data presented as mean ± standard deviation (*M ±SD*).
Groups: N – control (normal) group; DL – dyslipidemia group with an atherogenic diet; DLK – dyslipidemia group (atherogenic diet + colchicine); DLA – dyslipidemia group (atherogenic diet + and atorvastatin).

Table 2. Comparison of the low-density lipoprotein (LDL) levels before and after colchicine administration in the DLK group

Colchicine administration in DLK	LDL level [mg/dL]	Mean difference [mg/dL]	95% *CI*	*p*-value
Before	74.0 ±10.6	32.8 ±6.2	25.0–40.5	<0.000*
After	41.2 ±4.4			

Data presented as *M ±SD*.
DLK – dyslipidemia group (atherogenic diet + colchicine); *CI* – confidence interval. * statistically significant.

Table 3. Mean interleukin-1β (IL-1β) levels for each treatment group

Group	Number of samples	IL-1β level [µ/mmol]	*p*-value
DL	5	56.5 ±19.6	0.004*
DLK	5	32.4 ±5.7	
DLA	5	39.7 ±11.5	

Data presented as *M ±SD*.
Groups: DL – dyslipidemia group with an atherogenic diet; DLK – dyslipidemia group (atherogenic diet + colchicine); DLA – dyslipidemia group (atherogenic diet + and atorvastatin). * statistically significant.

Post-hoc analysis was conducted to identify which group had the lowest IL-1β levels. As shown in Table 4, there was no significant difference in the mean IL-1β levels between the DLK and DLA groups ($p > 0.05$). However, a significant difference of 24.1 µ/mmol was observed between the DL and DLK groups ($p < 0.05$). In contrast, no significant difference was found between the DL and DLA groups ($p > 0.05$).

Effect of colchicine on the NO levels

The results (Table 5) showed that the mean NO levels were 216.04 ±20.39 µ/mmol in the DLK group and 141.44 ±18.05 µ/mmol in the DLA group. Meanwhile, the NO levels in the N and DL groups were 263.00 ±16.18 µ/mmol and 107.44 ±8.71 µ/mmol, respectively ($p < 0.05$). These findings indicate a significant difference in the NO levels among the groups. As expected, the N group, serving as the negative control, exhibited relatively higher NO levels, with a mean value of 250.55 ± 8.05 µ/mmol.

Table 4. Post-hoc analysis of the interleukin-1β (IL-1β) levels among the treatment groups

Pairwise comparisons	Mean difference [µ/mmol]	95% *CI*		*p*-value
		min	max	
DL vs. DLK	24.1	0.35	47.99	0.046*
DL vs. DLA	16.8	6.99	40.65	0.219
DLK vs. DLA	7.3	16.49	31.15	1.000

Groups: DL – dyslipidemia group with an atherogenic diet; DLK – dyslipidemia group (atherogenic diet + colchicine); DLA – dyslipidemia group (atherogenic diet + and atorvastatin). min – minimum; max – maximum; * statistically significant.

Table 5. Mean nitric oxide (NO) levels for each treatment group

Group	Number of samples	NO level [µ/mmol]	*p*-value
DL	5	107.44 ±8.71	
DLK	5	216.04 ±20.39	0.000*
DLA	5	141.44 ±18.05	

Data presented as *M* ±*SD*.
Groups: DL – dyslipidemia group with an atherogenic diet; DLK – dyslipidemia group (atherogenic diet + colchicine); DLA – dyslipidemia group (atherogenic diet + and atorvastatin). * statistically significant.

Table 6. Post-hoc analysis of the nitric oxide (NO) levels among the treatment groups

Pairwise comparisons	Mean difference [µ/mmol]	95% *CI*		*p*-value
		min	max	
DL vs. DLK	108.60	79.59	137.62	0.000*
DL vs. DLA	34.00	4.98	63.02	0.021*
DLK vs. DLA	74.60	45.58	103.62	0.000*

Groups: DL – dyslipidemia group with an atherogenic diet; DLK – dyslipidemia group (atherogenic diet + colchicine); DLA – dyslipidemia group (atherogenic diet + and atorvastatin). * statistically significant.

Post hoc analysis revealed a significant difference in the NO levels of 74.60 µ/mmol between the DLK and DLA groups ($p < 0.05$). Similarly, a significant difference of 108.60 µ/mmol was observed between the DLK and DL groups ($p < 0.05$). Additionally, the mean NO level in the DLA group was significantly higher than in the DL group, with a difference of 34.00 µ/mmol ($p < 0.05$) (Table 6).

Discussion

Normally, male Wistar rats (*Rattus norvegicus*) have the LDL levels ranging from 10 to 54 mg/dL.[15] An increase in the LDL fraction in plasma, as observed in the atherogenic model group, leads to dyslipidemia. Elevated LDL levels are a major risk factor for atherosclerosis, as they promote the accumulation of lipoproteins in the intimal layer, stimulate macrophage and monocyte adhesion, and trigger the migration of sub-endothelial smooth muscle cells, thereby accelerating the formation of atheromatous plaques.[16,17] A previous study showed similar results, demonstrating that an 8-week high-fat diet significantly increased the triglyceride and LDL levels, decreased the high-density lipoprotein (HDL) levels, and induced the formation of aortic atheromatous plaques in male Sprague–Dawley albino rats.[14]

The mean decrease in the LDL levels in the DLK group was 32.8 ±6.2 mg/dL ($p < 0.05$) after administering 0.5 mg of colchicine for 14 days, indicating that colchicine effectively lowers the LDL levels. The precise mechanism underlying this effect remains unclear. Notably, the consistent reduction in LDL across all DLK group samples is an interesting finding, suggesting that colchicine plays a significant protective role against the endothelial cell damage caused by cholesterol crystals. Colchicine has been shown to reduce the formation of cholesterol crystal-induced ROS, thereby inhibiting the activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome and the associated inflammatory response, ultimately ameliorating endothelial cell pyroptosis. These effects highlight the potential of colchicine as a promising therapeutic agent for the prevention and treatment of atherosclerosis.[18]

This finding is consistent with a previous study conducted on 24 Sprague–Dawley rats used as a model of atherosclerosis with a high-fat diet.[19] In that study, the administration of 0.5 mg colchicine for 5 weeks resulted in decreased triglyceride and LDL levels, along with a significant increase in the HDL levels.[19]

Data analysis showed no significant difference in the mean IL-1β levels between the DLA and DLK groups ($p > 0.05$). Based on these results, it can be concluded that colchicine and atorvastatin exhibited similar efficacy in suppressing IL-1β expression during the early stages of atherosclerosis in this study.

Colchicine inhibits the activation of NLRP3 inflammasomes in macrophages in response to stimuli such as cholesterol crystals and ROS, leading to reduced production of IL-1β and other pro-inflammatory cytokines, including TNF-α and IL-6, in atherosclerotic lesions, thereby preventing disease progression.[20,21] Similarly, atorvastatin suppresses IL-1β expression by inhibiting NLRP3 inflammasome activity through phagolysosomal pathways.[22] This shared mechanism explains the comparable effectiveness of colchicine and atorvastatin in suppressing IL-1β expression, as observed in this study.

Immunofluorescence staining has demonstrated that the assembly of the NLRP3 inflammasome into its active complex requires microtubule-mediated transport. Colchicine inhibits microtubule polymerization and promotes microtubule degradation, thereby effectively suppressing the inflammatory response.[23,24]

This study supports previous findings on the effectiveness of colchicine in reducing the monocyte IL-1 levels in patients with acute coronary syndrome (ACS) by lowering the protein levels of pro-caspase-1 and caspase-1.[11] Caspase-1 plays a key role in the NLRP3-mediated inflammatory response, including the activation of IL-1β and IL-6. It cleaves pro-IL-1 and pro-IL-18 into their active forms, so the inhibition of caspase-1 naturally reduces the downstream levels of active IL-1.[24]

The highest mean NO level was observed in the DLK group, at 216.04 ±20.39 μ/mmol. These results suggest that colchicine is more effective than atorvastatin in increasing the NO levels, a key mediator of vasodilation that protects endothelial cells during the early stages of atherosclerosis.

Colchicine significantly increases the expression of phosphorylated AMP-activated protein kinase (AMPK), a critical regulator of energy metabolism. In the prevention and treatment of atherosclerosis, AMPK promotes cholesterol excretion, enhances fatty acid oxidation and inhibits inflammatory processes.[18] The activation of the AMPK pathway also modulates vascular endothelial function, suppresses ROS production and reduces oxidative stress during the early stages of atherosclerosis. This mechanism helps explain the observed increase in the NO levels, a vasodilator that protects endothelial cells in the early development of atherosclerosis in this study.[18,25]

A similar study reported comparable results, showing that a single therapy with colchicine administered to hyperlipidemic rats at the early stages of atherosclerosis improved both inflammation and endothelial function, even independently of the lipid-lowering effects.[22]

An in vitro study reported similar findings, showing that colchicine reduced ROS formation and increased the NO levels, thereby alleviating oxidative stress.[26] These effects create a favorable environment for preventing the formation and progression of atherosclerotic lesions. In other words, colchicine exerts beneficial effects in both the primary and secondary prevention of coronary heart disease (CHD).

Conclusions

In the early development of atherosclerosis, colchicine was significantly more effective than atorvastatin in increasing the NO levels and demonstrated a comparable ability to reduce the IL-1β levels. These findings suggest that colchicine may offer superior benefits as a primary preventive therapy in populations at risk for ASCVD.

Limitations

This study focused solely on the effects of colchicine on the IL-1β and NO levels during the early development of atherosclerosis, without conducting histopathological examinations to assess atherosclerotic lesion formation and progression. Further studies are warranted to evaluate the relationship between colchicine administration, the functions of other organs and potential adverse effects.

Ethics approval and consent to participate

The study was evaluated and approved by the Research Ethics Committee at the Faculty of Veterinary Medicine of the Syiah Kuala University, Banda Aceh, Indonesia (132/KEPH/V/2021).

Data availability

The datasets supporting the findings of the current study are available from the corresponding author on reasonable request

Consent for publication

Not applicable.

Use of AI and AI-assisted technologies

Not applicable.

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