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# Colchicine modulates structural and histopathological remodeling in a calcium phosphate-induced rat model of abdominal aortic aneurysm

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## ABSTRACT

**Objectives:** Abdominal aortic aneurysm carries a substantial risk of rupture, and no drug therapy has yet been validated to slow aneurysm enlargement. Colchicine, an established anti-inflammatory agent with proven benefit in coronary artery disease, may also modulate vascular remodeling. This study evaluated the impact of colchicine on geometric and histopathological changes in a calcium phosphate ($CaPO_4$)–induced rat model of abdominal aortic aneurysm.

**Methods:** Twenty-two male Wistar albino rats were randomized into three groups: Sham-operated controls (n=6), $CaPO_4$-induced abdominal aortic aneurysm (aneurysm, n=8), and $CaPO_4$–induced abdominal aortic aneurysm treated with colchicine (n=8). Experimental aneurysms were induced by periadventitial application of 0.5 mol/L calcium chloride and phosphate-buffered saline to the infrarenal aorta. The treatment group received colchicine 0.5 mg/kg/day for 30 days. On day 30, morphometric measurements of lumen diameter and aortic cross-sectional area, together with semiquantitative histological scores for Caspase-3, Caspase-9, elastic fiber fragmentation, and calcium accumulation, were obtained.

**Results:** Compared with sham animals, aneurysm rats exhibited marked increases in lumen diameter and aortic area, higher Caspase-3 and Caspase-9 expression, pronounced elastin fragmentation, and greater calcium deposition. Colchicine significantly reduced lumen diameter and aortic area versus untreated aneurysm rats and lowered Caspase-3 and Caspase-9 scores while attenuating elastin fragmentation. In contrast, calcium scores remained elevated in both aneurysm and colchicine groups relative to sham, without a significant difference between the two aneurysm groups.

**Conclusion:** Colchicine partially limited early aneurysmal remodeling by improving geometric parameters and mitigating apoptosis and elastin degradation, whereas vascular calcification was not substantially modified. These data support further investigation of colchicine as a potential adjunctive therapy in abdominal aortic aneurysm.

**Keywords:** Abdominal aortic aneurysm, colchicine, calcium phosphate model, elastin degradation, apoptosis.

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Abdominal aortic aneurysm (AAA) is a progressive dilation of the abdominal aorta associated with a high risk of rupture and mortality. Despite major advances in surgical and endovascular management, there remains no approved pharmacological therapy capable of effectively preventing aneurysm expansion.[1] This therapeutic gap has directed attention toward anti-inflammatory and tissue-protective agents targeting the molecular mechanisms of aneurysm formation.[2]

The pathogenesis of AAA involves chronic inflammation, degradation of extracellular matrix components (particularly elastin), loss and apoptosis of vascular smooth muscle cells, and medial calcification.[3,4] Calcium-phosphate-based experimental models in rodents reproduce these features rapidly and reproducibly, making them useful for evaluating potential pharmacological interventions.[5] Such models demonstrate accelerated aneurysmal dilatation, elastin fragmentation, macrophage infiltration, and calcium deposition within a short experimental window.

Colchicine is a long-established anti-inflammatory alkaloid that acts by disrupting microtubule polymerization and thereby suppressing various inflammatory processes. Through its cytoskeletal effects, colchicine can reduce leukocyte migration, attenuate oxidative stress, and stabilize vascular tissue responses to injury.[6,7] In addition to its traditional clinical indications such as gout and pericarditis, low-dose colchicine has demonstrated cardiovascular benefits by reducing systemic inflammation and improving vascular outcomes in large randomized controlled trials.[8,9] These broad anti-inflammatory and cytoprotective actions suggest that colchicine may also exert protective effects in the development of AAA.

Therefore, this study aimed to investigate the effects of colchicine on structural remodeling, elastin integrity, apoptosis, and medial calcification in a calcium phosphate ($CaPO_4$)-induced AAA model in rats.

## METHODS

A total of 22 male Wistar albino rats weighing approximately 300 g were used in this experimental study. Animals were housed in standard laboratory conditions (22±2 °C, 55±10% humidity, 12-hour light/dark cycle) with free access to food and water. All procedures were approved by the Dokuz Eylül University Animal Experiments Ethics Committee (protocol no: 32/2021, date: 02.08.2021) and performed in accordance with institutional and international guidelines for animal care. Rats were randomly assigned into three groups:

Sham group (n=6): Surgical exposure without aneurysm induction.

AAA group (n=8): Calcium phosphate-induced aneurysm.

Drug group (AAA + colchicine treatment group) (n=8): Aneurysm induction followed by colchicine therapy.

### Surgical Procedure

Anesthesia was induced by intraperitoneal administration of ketamine (50 mg/kg) and xylazine (10 mg/kg). After sterile preparation, a midline laparotomy was performed, and the infrarenal abdominal aorta was exposed by gentle retroperitoneal dissection. Experimental AAA performed in the AAA group and drug group was created using the modified $CaPO_4$ periadventitial injury technique. The exposed aorta was first wrapped with a sterile sponge saturated with 0.5 mol/L $CaCl_2$ for 10 minutes, followed by application of a phosphate buffered saline-soaked sponge for 5 minutes, promoting localized $CaPO_4$ crystal formation and medial injury.

In the Sham group, the same procedure was performed using a 0.9% NaCl-soaked sponge for 15 minutes. After application, the abdomen was closed in layers and animals were monitored until recovery.

Rats in the treatment group received colchicine 0.5 mg/kg/day, administered by oral gavage once daily beginning on the day of aneurysm induction and continued throughout the 30-day follow-up period, as specified in the approved ethical protocol. Sham and AAA groups did not receive any pharmacological treatment.

### Tissue Collection and Processing

On postoperative day 30, all rats were re-anesthetized using the same ketamine-xylazine protocol as for the index surgery. A midline laparotomy was reopened, and the infrarenal abdominal aorta, including the segment subjected to periadventitial chemical injury, was carefully dissected free from surrounding tissues and excised en bloc. Animals were then euthanized by exsanguination under deep anesthesia.

The harvested aortic specimens were immediately immersed in 10% neutral buffered formalin and fixed for 48-72 hours. After fixation, tissues were dehydrated through graded ethanol, cleared in xylene, and embedded in paraffin blocks according to routine histological procedures. Transverse sections of 5 µm thickness were obtained using a rotary microtome and mounted on poly-L-lysine-coated glass slides for histological and immunohistochemical evaluation.

### Histopathological and Immunohistochemical Evaluation

For general structural assessment and morphometric measurements, sections were stained with hematoxylin&eosin (H&E). Two additional special stains were used for targeted evaluation of wall components:

Van Gieson's staining was employed to visualize elastic fibers and to grade elastic fiber fragmentation in the aneurysmal segment. Elastin integrity was scored semiquantitatively on a four-point scale (1-4), where higher scores indicated more pronounced disruption and loss of elastic lamellae.

Alizarin Red staining was used to detect medial calcium deposition. Calcification was evaluated semiquantitatively under light microscopy and graded on a 0-3 scale, from no visible deposits (0) to extensive, diffuse calcification involving large areas of the vessel wall (3).

Apoptotic activity within the aortic wall was assessed immunohistochemically using primary antibodies against Caspase-3 and Caspase-9. After antigen retrieval and blocking of endogenous peroxidase, sections were incubated with the primary antibodies, followed by a biotinylated secondary antibody and a streptavidin-peroxidase detection system. The reaction was visualized with a chromogenic substrate and counterstained with hematoxylin.

Caspase-3 and Caspase-9 immunoreactivity was scored semiquantitatively on a 0-3 scale (0= no staining, 1= mild, 2= moderate, 3= strong and diffuse staining). Each slide was evaluated independently by two observers who were blinded to group allocation, and the mean of their scores was used for statistical analysis. The histopathological outcomes reported in the manuscript (elastic fiber fragmentation,

calcium accumulation, Caspase-3, and Caspase-9) correspond directly to these scoring systems.

### Morphometric Analysis

Morphometric measurements were performed on H&E-stained cross-sections using a computer-assisted image analysis system (ImageJ software, National Institutes of Health, Bethesda, MD, USA). For each animal, images were acquired at standardized magnification from the region of maximal dilation of the infrarenal aorta. At least three non-overlapping sections per animal were analyzed, and the mean value was used for further comparisons.

In line with the final study dataset, two primary morphometric parameters were evaluated:

Lumen diameter-defined as the maximal internal diameter of the aortic lumen measured perpendicular to the long axis of the vessel.

Aortic area-defined as the total cross-sectional area of the aortic wall and lumen within the external contour of the vessel.

### Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Continuous morphometric variables were assessed for normality using the Shapiro-Wilk test and expressed as mean ± standard deviation. Normally distributed variables were compared among the three experimental groups using One-Way Analysis of Variance. When a significant overall difference was detected, pairwise group comparisons were performed with Student's t-test. Because the study had an exploratory design and included a limited number of animals, no formal adjustment for multiple pairwise testing was applied; therefore, raw p-values were reported.

Histopathological scoring variables were evaluated as ordinal data and summarized using the median with interquartile range. Group differences were examined using the Kruskal-Wallis test. For parameters demonstrating significant global differences, pairwise comparisons were carried out with the Mann-Whitney U test. Similar to continuous variables, no correction for multiple comparisons was used, and raw p-values were presented. A p-value <0.05 was considered statistically significant.

## RESULTS

Lumen diameter differed significantly among the three groups. The aneurysm group exhibited a notable increase in lumen diameter compared with the sham group (p=0.005), consistent with aneurysmal dilatation following $CaPO_4$-induced injury. Colchicine treatment substantially limited this enlargement, resulting in significantly smaller lumen diameters relative to untreated aneurysm rats (p<0.001). No significant difference was observed between the sham and colchicine groups (p=0.195).

Aortic area showed a similar pattern. Aneurysm formation led to a marked increase in aortic area compared with the sham group (p<0.001). Colchicine-treated rats demonstrated significantly smaller aortic areas than untreated aneurysms (p<0.001). All pairwise comparisons among the three groups reached statistical significance (p<0.001 for all), indicating clear differences in structural expansion across conditions (Table 1).

Caspase-3 expression was considerably higher in the aneurysm group compared with the sham group (p=0.001). Colchicine treatment reduced Caspase-3 levels significantly when compared with untreated aneurysm animals (p=0.003). A significant difference was also present between the sham and colchicine groups (p=0.019).

Caspase-9 scores increased markedly following aneurysm induction, with significantly higher values in the aneurysm group than in the sham group (p=0.002). Colchicine administration resulted in significantly lower Caspase-9 scores compared with untreated aneurysms (p=0.006). The sham and colchicine groups also differed significantly (p=0.009).

Elastic fiber fragmentation was substantially greater in the aneurysm group than in the sham group (p=0.001). Colchicine treatment attenuated elastin degradation, producing significantly lower fragmentation scores than those seen in untreated aneurysm animals (p<0.001). The sham versus colchicine comparison showed a trend toward increased fragmentation in the treatment group but did not reach statistical significance (p=0.058).

Aneurysm induction resulted in increased calcium accumulation, with significantly higher scores in the aneurysm group compared with the sham group (p=0.003). Colchicine-treated rats displayed higher calcium levels than shams (p=0.015). However, no statistically significant difference was detected between the aneurysm and colchicine groups (p=0.116) (Table 2, Figure 1).

## DISCUSSION

In this experimental study, we investigated the effects of colchicine on structural and histopathological alterations in a calcium phosphate-induced AAA model in rats. The principal findings of our study were that colchicine attenuated aneurysmal dilatation, limited aortic wall expansion, reduced apoptotic activity, and mitigated elastic fiber degradation. These results collectively suggest that colchicine exerts a measurable protective influence on the aortic wall during $CaPO_4$ induced aneurysm formation.

The marked differences observed in lumen diameter and aortic area across the experimental groups indicate that structural remodeling occurred rapidly in this $CaPO_4$-induced model. The finding that

**Table 1.** Morphometric comparison

| Parameter | Sham | Aneurysm | Drug | p-values | | | |
|---|---|---|---|---|---|---|---|
| | | | | ANOVA | Sham-aneurysm | Sham-drug | Aneurysm -drug |
| Lumen diameter | 651.75±93.23 | 788.57±56.05 | 581.70±95.31 | **<0.001** | **0.005** | 0.195 | **<0.001** |
| Aortic area | 434068.55±81284.07 | 835417.32±28269.16 | 626651.69±75027.21 | **<0.001** | **<0.001** | **<0.001** | **<0.001** |

Morphometric parameters were expressed as mean ± standard deviation. Group differences were evaluated using One-Way Analysis of Variance (ANOVA). Pairwise comparisons were performed with Student's t-test. Significant p-values are shown in bold. A p-value <0.05 was considered statistically significant.

**Table 2.** Comparison of histopathological scores

| Parameter | Comparison | Group 1 median (Q1-Q3) | Group 2 median (Q1-Q3) | p-value |
|---|---|---|---|---|
| Caspase-3 | Sham *vs.* aneurysm | 1.0 (1.0-1.0) | 3.0 (2.75-3.0) | **0.001** |
| | Sham *vs.* drug | 1.0 (1.0-1.0) | 2.0 (1.0-2.0) | **0.019** |
| | Aneurysm *vs.* drug | 3.0 (2.75-3.0) | 2.0 (1.0-2.0) | **0.003** |
| Caspase-9 | Sham *vs.* aneurysm | 0.5 (0.0-1.0) | 3.0 (2.0-3.0) | **0.002** |
| | Sham *vs.* drug | 0.5 (0.0-1.0) | 2.0 (1.0-2.0) | **0.009** |
| | Aneurysm *vs.* drug | 3.0 (2.0-3.0) | 2.0 (1.0-2.0) | **0.006** |
| Elastic fiber fragmentation | Sham *vs.* aneurysm | 1.0 (1.0-1.0) | 3.0 (3.0-4.0) | **0.001** |
| | Sham *vs.* drug | 1.0 (1.0-1.0) | 1.5 (1.0-2.0) | 0.058 |
| | Aneurysm *vs.* drug | 3.0 (3.0-4.0) | 1.5 (1.0-2.0) | **<0.001** |
| Calcium accumulation | Sham *vs.* aneurysm | 0.5 (0.0-1.0) | 2.0 (2.0-3.0) | **0.003** |
| | Sham *vs.* drug | 0.5 (0.0-1.0) | 1.5 (1.0-2.0) | **0.015** |
| | Aneurysm *vs.* drug | 2.0 (2.0-3.0) | 1.5 (1.0-2.0) | 0.116 |

Pairwise comparisons of apoptotic markers (Caspase-3 and Caspase-9), elastic fiber fragmentation, and calcium accumulation among Sham, aneurysm, and drug-treated groups. Data are expressed as median (Q1-Q3). Comparative analyses were performed using the Mann-Whitney U test. Multiple comparison adjustment was not applied due to the exploratory nature of the study. A p-value <0.05 was considered statistically significant.

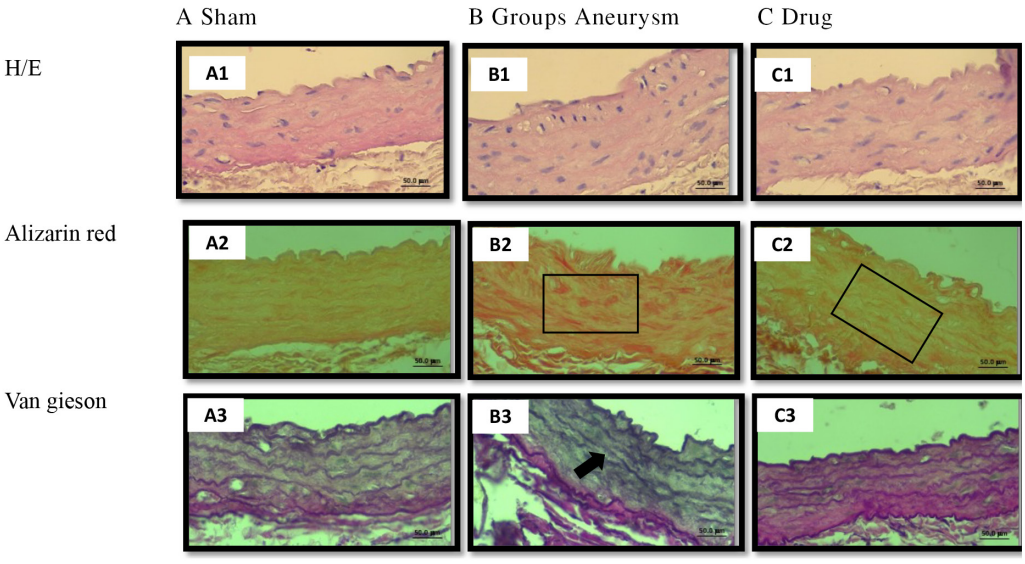


**Figure 1.** Histological sections of groups (hematoxylin&eosin stain, 40X) A1- Sham group, B1- Aneurysm group, C1- Drug group. Histological sections of groups (alizarin red stain, 40X): A2- Sham group, B2- Aneurysm group, C2- Drug group. Calcium accumulation in the groups is shown in the square. Histological sections of groups (Van Gieson stain, 40X): A3: Sham group, B3- Aneurysm group, C3- Drug group. Deteriorations in elastic fibers in the tunica media layer were seen with the black arrov.

colchicine-treated animals exhibited values closer to physiological dimensions suggests that the drug may interfere with the processes driving pathological wall expansion. Similar attenuation of aneurysmal growth with colchicine has been reported in recent preclinical studies, supporting the notion that pharmacological intervention can modify early aneurysmal remodeling of the aortic wall.[10] Nevertheless, contrasting findings also exist, and some models have shown limited structural response to colchicine treatment, highlighting that its effects may vary depending on the underlying mechanism of aneurysm induction.[11]

Aneurysm induction resulted in marked elastic fiber fragmentation, reflecting the early deterioration of medial architecture typical of experimentally induced AAAs.[12] Preservation of elastin is fundamental to maintaining aortic wall stability.[13] In the present study, colchicine-treated animals demonstrated substantially lower elastin fragmentation scores compared with untreated aneurysm rats, suggesting that the drug may exert a stabilizing effect on the medial layer of the vessel wall. This aligns with recent reports indicating that elastin degradation is a critical driver in aneurysm progression and that pharmacological modulation of inflammatory and proteolytic pathways may help preserve medial elastin structure.[12]

Apoptotic signaling is regarded as an important contributor to structural deterioration in AAA, and experimental models consistently demonstrate increased activation of caspase-dependent pathways in aneurysmal

segments.[14] In our study, aneurysm induction was associated with higher Caspase-3 and Caspase-9 scores, indicating activation of intrinsic apoptotic mechanisms within the aortic wall. Colchicine treatment reduced both caspase markers, implying a potential attenuation of apoptotic activity in the aortic tissue. These findings are in line with previous reports showing that modulation of apoptosis-related pathways can influence the structural trajectory of aneurysm development without necessarily restoring cellularity itself.[15,16]

Calcium deposition increased markedly after aneurysm induction in our model, consistent with prior work showing that medial mineralization accompanies chemically induced aortic injury and structural degeneration.[17,18] In the present study, colchicine-treated animals demonstrated calcium scores that were significantly higher than those of sham rats and only modestly lower than those of untreated aneurysm animals, with no statistically significant difference between the latter two groups. These findings suggest that colchicine did not substantially influence early vascular calcification within the 30-day observation period, possibly because mineral deposition may progress relatively independently of short-term anti-inflammatory or cytoskeletal-modulating treatments in this model.

Colchicine has regained prominence in recent years following major cardiovascular outcome trials. Studies in patients with myocardial infarction and in those with stable coronary artery disease have demonstrated that colchicine significantly reduces major adverse cardiovascular events, thereby increasing interest in applying the drug to other chronic vascular pathologies.[19,20] In recent years, colchicine has also been investigated for AAA; several experimental studies have suggested that it may slow aneurysm development, often through mechanisms involving attenuation of cellular stress responses, preservation of elastic fiber integrity, or reduction of inflammasome-related signaling.[10,21,22] However, not all studies have shown consistent results, and some experimental models have reported no significant suppression of aneurysm expansion, implying that its efficacy may depend on model type, treatment timing, and dosing regimen.[11]

In this context, the present $CaPO_4$-induced model provides complementary structural and histopathological insights into colchicine's effects during aneurysm formation. The smaller lumen diameters and reduced aortic areas observed in the colchicine group, together with lower Caspase-3 and Caspase-9 scores and markedly decreased elastin fragmentation, suggest that the drug may partially limit early structural deterioration. In contrast, the lack of a significant reduction in calcium deposition indicates that calcification in this model may be more resistant to short-term colchicine treatment. Overall, these findings suggest that colchicine may serve as an adjunctive pharmacological strategy aimed at stabilizing the aneurysmal aortic wall, although its effects may not extend uniformly across all components of AAA pathobiology.

This study has several limitations. First, mechanistic pathways were not directly assessed, and therefore no conclusions can be drawn regarding the molecular processes through which colchicine may influence aneurysm remodeling. Second, only a single colchicine regimen was evaluated, leaving the dose–response relationship and the effects of alternative treatment schedules undetermined. Third, the $CaPO_4$ model represents an acute chemically induced injury that does not fully recapitulate the chronic and multifactorial nature of human AAA, which may limit translational extrapolation. Finally, the sample size was modest, reducing the power to detect more subtle differences between subgroups and warranting confirmation in larger experimental cohorts.

In this experimental $CaPO_4$-induced AAA model, colchicine treatment was associated with reduced lumen diameter, smaller aortic area, lower apoptotic activity, and attenuated elastin fragmentation compared with untreated aneurysm animals. These findings suggest that colchicine can mitigate early structural deterioration of the aortic wall, although mineralization remained largely unaffected. While the mechanistic basis of these effects was not directly assessed, the overall pattern supports a potential role for colchicine as an adjunctive strategy in limiting early aneurysmal remodeling. Further studies incorporating alternative dosing strategies, longitudinal assessment, and chronic AAA models are needed to clarify its therapeutic relevance and translational potential.

### Ethics

**Ethics Committee Approval:** All procedures were approved by the Dokuz Eylül University Animal Experiments Ethics Committee (protocol no: 32/2021, date: 02.08.2021) and performed in accordance with institutional and international guidelines for animal care.

**Informed Consent:** This experimental study did not involve human participants; therefore, informed consent was not required.

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### Footnotes

### Authorship Contributions

Surgical and Medical Practices: M.B.K., Ç.B., P.A.; Concept: T.G., K.M.; Design: S.B.; Data Collection or Processing: P.A.; Analysis or Interpretation: P.A.; Literature Search: M.B.K., N.U.T.; Writing: M.B.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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