

# Histopathological Analysis of the Inhibitory Effect of Ibuprofen on Amyloidogenesis in a Mouse Model

## Key words

amyloid A;  
amyloidosis;  
casein;  
ibuprofen;  
mouse model

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**Abstract:** Amyloidosis represents a group of diseases, all characterized by the deposition of protein fibrils with a  $\beta$ -sheet structure. To evaluate the effects of ibuprofen on the inhibition of amyloid deposition, we used an animal model of experimental amyloid A amyloidosis. BALB/c mice ( $n = 30$ ) were divided into two groups ( $n = 15$  mice/group). Both the treatment and control groups received casein solution for 3 weeks to induce experimental amyloidosis, and ibuprofen was added to the drinking water of the treatment group simultaneously. After 3 weeks, all mice were euthanized. Tissue samples of various organs were collected, fixed, and processed for routine histopathological examination. This revealed amyloid deposition as an amorphous, homogenous, and eosinophilic substance in the control group's renal glomeruli, hepatic parenchyma, and splenic vascular walls. In the treatment group, only mild amyloid deposition was observed in renal glomeruli and occasionally in the vascular wall of other tissues. The amount of amyloid deposition in the liver and kidneys in the treatment group was significantly lower than in the control group. Our results suggest that ibuprofen may prevent amyloid formation and accumulation in mice, especially in the kidneys and liver.

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## Introduction

Amyloidosis encompasses a diverse group of diseases that occur when amyloid fibrils, with a characteristic cross- $\beta$  structure, accumulate in various organs and tissues throughout the body (1–3). Normally, amyloid fibrils are broken down and eliminated by the body's immune system. However, owing to numerous human diseases, amyloid fibrils can aggregate in various organs (e.g., the heart, kidneys, liver, spleen, and nervous system), interfering with their normal function and resulting in amyloidosis (4).

Amyloidosis can be classified into different types, each with its distinct cause, symptoms, and treatment options (5). Some forms of amyloidosis are hereditary, whereas others develop as a result of underlying medical conditions, such as multiple myeloma or rheumatoid arthritis (6). Amyloid A (AA) fibrils originate from an N-terminal cleavage fragment of serum amyloid A (SAA) protein (an acute-phase reactant)

(7). A major factor contributing to the development of AA-amyloidosis is the increased synthesis and subsequent degeneration of SAA during chronic inflammatory or infectious conditions. Renal manifestations, such as proteinuria (progressing to renal failure), are observed very frequently (in approximately 90 % of AA-amyloidosis cases). Less frequent manifestations of AA-amyloidosis include autonomic neuropathy, hepatomegaly, and cardiomyopathy (8).

Treatment options for AA-amyloidosis depend on the type and severity of the disease. They may include medications to decrease the production of amyloid fibrils, chemotherapy, stem cell transplants, or organ transplants in severe cases (7). Although there is no definitive cure for amyloidosis, early diagnosis and treatment can help manage symptoms, slow the progression of the disease, and improve the quality of life for patients. Anti-inflammatory treatments

have been reported to reduce the risk of developing secondary AA-amyloidosis, and certain drugs (e.g., terbutaline, aminophylline, and colchicine) have been reported to inhibit experimental amyloidosis in mice (9, 10).

Currently, non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used anti-inflammatory therapeutic agents in the world, among which ibuprofen is one of the most well-known. Ibuprofen is a core medicine on the World Health Organization's "Essential Drugs List", which outlines the minimum medical requirements for basic healthcare systems (11). Ibuprofen exerts its effects by inhibiting cyclooxygenase (COX) and prostaglandin synthesis. At least three variants of COX exist (COX-1, COX-2, and COX-3), and ibuprofen inhibits both COX-1 and COX-2. It is believed that COX-2 inhibition is the primary mechanism of action underlying the anti-inflammatory activity of ibuprofen (12).

Based on the known anti-inflammatory properties of ibuprofen, we investigated the potential preventive effects of ibuprofen on experimentally induced amyloid deposition in a mouse model.

## Material and methods

This study was conducted in the Department of Pathobiology at the Faculty of Veterinary Medicine, Ferdowsi University of Mashhad, Iran. All experiments adhered to the guidelines of the animal experimentation committee within the same department, under project license 2009/294.

### Animals

A total of 30 young adult (5-week-old) male BALB/c mice, weighing 28–30 g, were selected from the laboratory animal house of the Faculty of Veterinary Medicine, Ferdowsi University of Mashhad. The mice were randomly divided using a simple randomization method into two groups: the treatment group (n=15) and the control group (n=15). They were kept in six cages (three cages per group with five mice per cage) and given 2 weeks to acclimatize to the environment (25 °C, 12 h light/dark cycle). Throughout the study, the mice had continuous access to commercial chow (Javaneh Khorasan®, Mashhad, Iran) and tap water. Food and water consumption were recorded twice a day to assess any changes in intake that could indicate health issues or treatment effects. The mice were monitored daily to assess general health; any signs of distress, pain, or illness; and behavior, including grooming, vocalization, activity levels, and posture. These observations were consistently conducted throughout the study to ensure accurate and reliable data collection. Our observations confirmed that the procedures did not cause significant pain or stress, and thus no pain relief medication was administered.

### Induction of amyloidosis

Amyloidosis was induced in the control and treatment groups through the injection of casein solution. A modified version of the protocol by Shirahama and Cohen (13, 14) was performed, in which the concentration of casein was increased from 10 % to 15 %, and the number of injections was decreased from 21 to 15 injections. Injections consisted of 0.5 ml of 15 % casein solution (Sigma-Aldrich®, Germany) dissolved in 0.05 N sodium hydroxide and were administered at 2.5 mg/kg/day subcutaneously into the loose skin of the neck five times a week for 3 weeks (15 injections).

### Administration of ibuprofen

Throughout the 3 weeks of casein injections, the treatment group received 10 mg/kg/day of ibuprofen, dissolved in their drinking water; this mode of administration was chosen based on the literature (15). Measures were implemented to prevent any waste of water. Specifically, we adhered to the following procedure based on the Bachmanov et al. study and our previous experience (16). The daily water consumption was estimated at 5 ml per mouse (25 ml/cage). The drinking water for the treatment group was prepared daily to achieve a final ibuprofen concentration of 0.06 mg/ml using tablets (Motrin®, McNeil Incorporation, Canada). By contrast, the control group received the same amount of tap water without added medication.

### Tissue collection and preparation

Upon completion of the animal experiments, mice were sacrificed using the cervical dislocation method. A systematic necropsy was performed, and detailed macroscopic observations were documented. Furthermore, tissue samples were collected from the liver, spleen, kidneys, brain, heart, stomach, and lungs. All samples were fixed in 4 % paraformaldehyde and processed using an automatic tissue processor (Leica TP1020, Leica Biosystem®, Wetzlar, Germany). Subsequently, the samples were sectioned at a thickness of 5 µm and underwent staining with Hematoxylin-Eosin, and Congo Red methods.

### Histopathological analysis

The histological sections were analyzed using light microscopy (Nikon-Eclipse TE200, Nikon®, Tokyo, Japan) by two researchers in a double-blind manner to evaluate the extent of amyloid deposition and other histological changes. Visualization of the deposits with Congo Red staining enabled amyloid deposition to be semi-quantitatively graded on a scale of negative (–) to strongly positive (+++) (Table 1).

**Table 1:** Grading of amyloid deposition. The amount of amyloid deposition was semi-quantitatively graded from negative (-) to strongly positive (+++) based on the visualization of amyloid deposits using Congo Red staining and light microscopy

Grade	Description
- (Negative)	Absence of amyloid deposits
+ (mild)	Amyloid deposits with limited distribution, and observed in up to 25% of the microscopic fields of view
++ (moderate)	Amyloid deposits were intermediately distributed, and observed in 25-75% of the microscopic fields of view
+++ (Severe)	Amyloid deposits were extensively distributed, and observed in more than 75% of the microscopic fields of view

### Statistical analyses

Descriptive statistics and statistical tests were performed using SPSS software (IBM SPSS Statistics version 23; IBM Corporation, Armonk, New York, USA). The normality of the outcome variables was checked using the Shapiro-Wilk test. The Mann-Whitney U-test was used to compare the amount of amyloid deposition between the control and treatment groups.  $P < 0.05$  was considered statistically significant.

## Results

All the mice survived amyloidosis induction and ibuprofen treatment.

### Macroscopic findings

Enlarged and pale kidneys were predominantly observed in the control group (Figure 1A). The livers in the control group exhibited moderate enlargement in 46 % of the cases

(Figure 1B). A pale and enlarged spleen was observed only in one case in the control group (Figure 1C). No significant anatomical changes were observed in the stomach, lung, heart, or brain samples.

The kidneys were less pale and smaller in the treatment group, indicating milder lesions. No other abnormal changes were observed macroscopically.

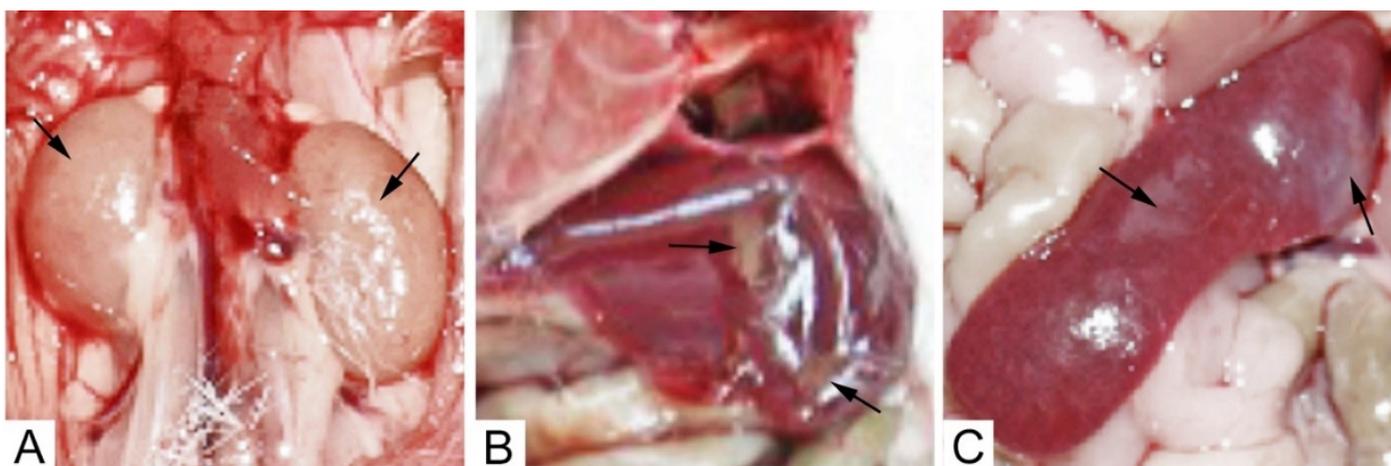
### Microscopic findings

Light microscopy revealed amyloid deposits as either a homogenous eosinophilic or orange substance after staining with Hematoxylin-Eosin or Congo Red, respectively (Figure 2).

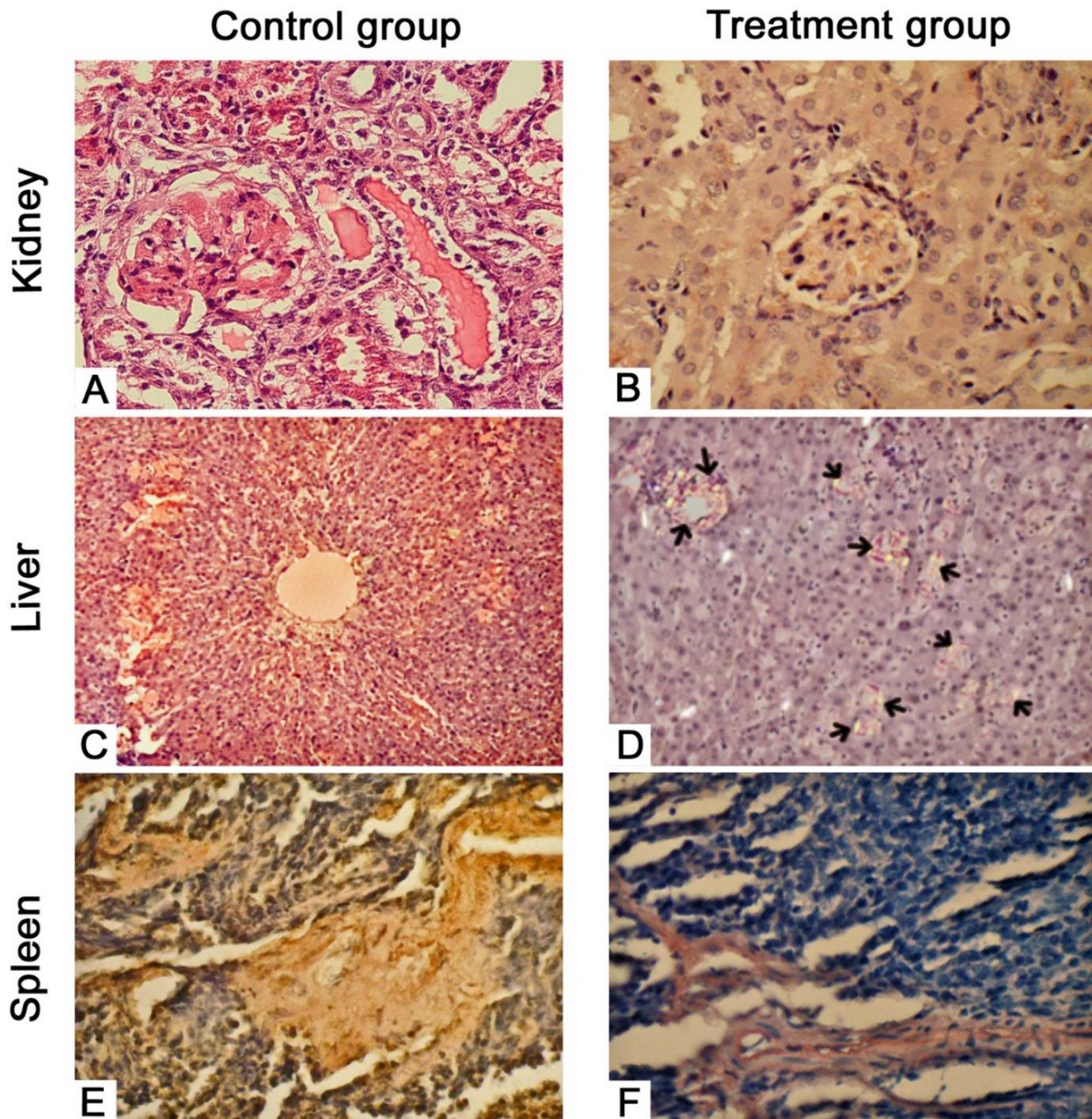
**Kidney:** Various degrees of amyloid deposition were observed in the kidney samples of the control and treatment groups (Table 2) (Figures 2A and B). In the control group, in all cases, amyloid deposits were present in the glomeruli, predominantly in the mesangium. Amyloid deposition was mild in 11 samples (73 %), moderate in 3 samples (20 %), and severe in 1 sample (7 %) (Table 2). The presence of amyloid in the glomeruli caused a reduction in the cell population, leading to a hypocellular appearance of the tissue (Figure 2A). Moreover, hyperemia was observed in the kidneys in the cases of mild to moderate amyloid deposition.

Hyaline casts were observed in the renal tubules in cases of moderate and severe amyloid deposition (Figure 2A). Additionally, amyloid deposits were observed on the epithelial side of the glomerular basement membrane and in blood vessels.

In the treatment group, we observed mild amyloid deposition in the kidneys of 5 mice (33 %) (Table 2). Amyloid deposits and hyperemia were observed within the mesangium of the glomeruli (Figure 2B).



**Figure 1:** Macroscopic view of the samples in the control group. A: Large, pale kidneys (arrows) could be observed in the control group. B: Liver with focal pale areas. C: Enlarged and multifocally pale spleen (arrows) in the control group.



**Figure 2:** Histosections of the kidney, liver, and spleen in control and treatment groups. Hematoxylin-Eosin staining: A. Congo Red Staining: B-F.

A and B: Histosections of the kidney sample. A: Presence of hypocellular appearance of renal tissue followed by glomerular amyloid deposits and Hyaline casts in renal tubules ( $\times 400$ ). B: Mild degrees of amyloid deposition in the renal glomeruli of the treatment group ( $\times 400$ ). C and D: Histosections from the liver in the control and treatment groups. C: The liver parenchyma is diffusely involved by amyloid depositions (amorphous pale orange material) predominantly within the sinusoidal spaces ( $\times 400$ ). D: Amyloid depositions appear apple-green by polarized microscopy (arrows) ( $\times 400$ ). E and F: Histosections from the spleen in the control and treatment groups. Amyloid depositions are observed in the arterial walls of the red pulp ( $\times 400$ ).

Liver: Mild degrees of amyloid deposition were observed in the liver samples from the control and treatment groups (Table 2) (Figures 2 C and D). In the control group, mild degrees of amyloid deposition were detected in 7 out of 15 cases (46.6 %) (Table 2). The amyloid deposits appeared as homogenous eosinophilic substances among hepatocytes

or within the sinusoidal spaces (Figure 2 C). These deposits occupied space and induced mild cellular alterations in adjacent hepatocytes. Additionally, hyperemia was observed in 8 liver samples. Furthermore, infiltration of mononuclear inflammatory cells was observed in the hepatic portal areas in one case.

**Table 2:** The number of mice in the control and treatment groups and the degree of amyloid deposition in different tissues

Study Group	Tissue sample	Amyloid positive			Amyloid negative (-)	
		Total	+	++	+++	Total
<b>Control</b>	Kidney	15	11	3	1	0
	Liver	7	7			8
	Spleen	9	5	4		6
	Heart	0				15
	Lung	1		1		14
	Brain	2	2			13
	Stomach	0				15
<b>Treatment</b>	Kidney	5	5			10
	Liver	1	1			14
	Spleen	5	5			10
	Heart	0				15
	Lung	0				15
	Brain	0				15
	Stomach	0				15

In the treatment group, mild amyloid depositions were observed in 1 liver (6 %) (Table 2) and the amyloid depositions were detected predominantly within the sinusoidal spaces (Figure 2 D).

**Spleen:** Mild and moderate degrees of amyloid depositions were observed in the spleen samples of the control and treatment groups (Table 2) (Figures 2 E and F). Amyloid deposition was observed in 9 out of 15 mice (60 %), it was mild in 5 mice (33 %) and moderate in 4 mice (27 %) (Table 2). Amyloid deposits appeared as a homogeneous substance predominantly in the red pulp, particularly around the walls of the blood vessels (Figure 2 E). Furthermore, hyperemia was observed only in 1 spleen sample.

In the treatment group, we observed mild amyloid deposition in 5 spleen samples (33 %) (Table 2). Amyloid deposits were observed in the same areas as in the control group (Figure 2F).

**Other tissues:** In lung samples from the control group, hyperemia was evident, and amyloid deposition was observed only in one case in the wall of a blood vessel with moderate intensity. In brain samples of the control group, amyloid deposits were observed in two cases in the walls

of cerebral blood vessels; however, no signs of hyperemia were detected in the samples (Table 2). No amyloid deposits were observed in the heart and stomach samples of the control group. No signs of amyloidosis were detected in the heart, lung, brain, and stomach tissue samples harvested from the treatment group.

### Statistical analysis

Comparisons between the control and treatment groups revealed that the degree of amyloid deposition in the kidney was significantly lower in the treatment group compared to the control group ( $P < 0.001$ ). A similar finding was obtained for liver samples, which showed a significant difference between the studied groups ( $p = 0.015$ ). However, no significant differences were observed between the spleen samples from the studied groups ( $p = 0.065$ ) (Table 3).

### Discussion

In this study, we assessed the inhibitory effect of ibuprofen on AA-amyloidosis. Our findings indicate that ibuprofen can inhibit the induction of amyloidosis in mice, specifically in the kidneys and liver. Amyloid deposits were present in

**Table 3:** Median, first, and third quartile degree of amyloidosis in treatment and control groups of kidney, liver, and spleen

Tissue	Degree of Amyloidosis				
	Group	N	Median	Q1*	Q3**
Kidney	Control	15	1	1	2
	Treatment	15	0	0	1
Liver	Control	15	0	0	1
	Treatment	15	0	0	0
Spleen	Control	15	1	0	2
	Treatment	15	0	0	1

\*First quartile, \*\*Third quartile

kidneys in 100 % of untreated animals, whereas only 33 % of ibuprofen-treated animals showed amyloid deposits in kidneys. Similar findings were obtained in liver tissue, which showed approximately 30 % less amyloid deposition in the treatment group compared to the control group. Although no significant difference was found in spleen samples, the authors cannot claim that the treatment had a less pronounced effect on splenic amyloidosis, as fewer positive cases were observed in the spleen of the treatment group compared to the control samples, increasing the number of samples may better show the difference between the studied groups. Currently, the standard therapeutic strategy for AA-amyloidosis is decreasing the amount of SAA by controlling inflammation. Nakamura et al. revealed that the administration of effective anti-inflammatory drugs decreases or delays the occurrence of amyloidosis in inflammatory diseases such as rheumatoid arthritis (17). The most probable explanation for the anti-inflammatory effect of ibuprofen is the decrease in COX-2 levels. This may decrease SAA precursor levels and thereby decrease amyloid fibril levels (18).

Husebekk et al. reported that treatment with Tenidap (an anti-inflammatory and anti-rheumatoid drug) inhibits the development of AA-amyloidosis by inhibiting cytokines, such as interleukin-6, interleukin-1, and tumor necrosis factor  $\alpha$ , which results in decreased SAA levels (9). Naproxen is another anti-inflammatory drug that has been examined in combination with Tenidap by Sipe et al. They observed that both drugs have an inhibitory effect on increasing interleukin-6 and SAA levels, with Tenidap exerting more significant effects than Naproxen (19). Currently, monoclonal antibody drugs, such as Rituximab, are used to treat AA-amyloidosis and rheumatoid arthritis. Similar to NSAIDs, these drugs exert their effects by decreasing the levels of acute-phase proteins (20). Colchicine is another anti-inflammatory drug of interest. Gateau et al. reported that long-term colchicine treatment prevents inflammatory flares and the development of amyloidosis (21).

Epidemiological data on AA-amyloidosis are rare (14), whereas amyloid beta (A $\beta$ ) amyloidosis, the cause of Alzheimer's disease, has been widely studied (22). Evidence that inflammation contributes to the pathogenesis of Alzheimer's disease has stemmed from 20 retrospective epidemiological studies and one prospective longitudinal study, which demonstrated that NSAID consumption is associated with an up to 50 % reduction in the risk of Alzheimer's disease (19). Moreover, it is reported that a high dose of the NSAID indomethacin, which fully suppresses COX-I activity, was accompanied by a significantly decreased amyloid burden in a mouse model of A $\beta$ -amyloidosis (23). In animal models, it has been shown that ibuprofen can ameliorate Alzheimer's disease by decreasing inflammation and amyloid deposition. Based on Guo and Lim's research on Alzheimer's disease, NSAIDs, such as indomethacin and ibuprofen, may help reduce amyloid deposition and thereby prevent cellular degeneration and improve memory (24, 25).

All the aforementioned studies align with our study, suggesting that ibuprofen, which is widely prescribed for its anti-inflammatory, antipyretic, and pain-relief properties, may also play a preventive role in amyloidogenesis. In conclusion, this study demonstrates the potential efficacy of ibuprofen treatment for secondary AA-amyloidosis and organ-specific amyloidosis, particularly in organs prone to severe amyloidosis, such as the kidneys and liver. Further research is needed to elucidate the mechanisms underlying the differential effects among organs and the long-term efficacy and safety of taking ibuprofen.

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ARM designed the research and performed the anatomical and histopathological diagnosis. ASM performed the animal experiment, drug administration, and sample collection. ASM wrapped up the manuscript. MA performed the statistical analysis. All the authors made critical revisions to the manuscript.

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## **Histopatološka analiza zaviralnega učinka ibuprofena na amiloidogenezo na mišjem modelu**

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**Izveček:** Amiloidoza predstavlja skupino bolezni, za katere je značilno odlaganje beljakovinskih fibril s strukturo  $\beta$ -ploskve. Za oceno učinkov ibuprofena na zaviranje odlaganja amiloida smo uporabili živalski model eksperimentalne amiloidoze amiloida A. Miši BALB/c ( $n = 30$ ) smo razdelili v dve skupini ( $n = 15$  miši/skupina). Tako zdravljena kot kontrolna skupina sta tri tedne prejemale raztopino kazeina za indukcijo eksperimentalne amiloidoze, hkrati pa je bil pitni vodi zdravljene skupine dodan ibuprofen. Po treh tednih so vse miši evtanazirali. Vzorci tkiva različnih organov so bili zbrani, fiksirani in obdelani za rutinsko histopatološko preiskavo. Ta je pokazala odlaganje amiloida kot amorfne, homogene in eozinofilne snovi v ledvičnih glomerulih, jetrnem parenhimu in žilnih stenah vranice kontrolne skupine. V skupini, ki je bila zdravljena, je bilo v ledvičnih glomerulih in občasno v žilni steni drugih tkiv opaženo le blago nalaganje amiloida. Količina odloženega amiloida v jetrih in ledvicah v tej skupini je bila bistveno manjša kot v kontrolni skupini. Naši rezultati kažejo, da lahko ibuprofen prepreči nastajanje in kopičenje amiloida pri miših, zlasti v ledvicah in jetrih.

**Ključne besede:** amiloid A; amiloidoza; kazein; ibuprofen; mišji model