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METHAMPHETAMINE-ASSOCIATED MYOCARDIAL INJURY AND ITS MODIFICATION BY VITAMIN E IN AN EXPERIMENTAL RAT MODEL

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ABSTRACT

The aim of this study was to determine the toxic effects of methamphetamine with regards to the histological structure of cardiac muscle in adult male white rats, and to see whether Vitamin E could offer a protective effect against the toxic effects of methamphetamine. The study was conducted in the Animal Facility and the Laboratory of the College of Veterinary Medicine, Tikrit University from October 1st, 2025 till November 1st, 2025. Thirty-two adult male white Sprague–Dawley rats were randomly divided into 4 main groups (n=8/group), each of which was split into 2 subgroups (15- vs 30-day treatment). The control group was Group 1 while methamphetamine at a dose of 0.1 mg/kg and 1 mL/day was administered to Group 2, Vitamin E at a dose of 0.1 mL/day to Group 3 and a combination of Vitamin E 0.1 mL/day and methamphetamine 0.1 mg/kg to Group 4. Animals treated with methamphetamine exhibited hyperactivity, increased cage movement, increased agitation, and decreased food and water consumption. Hearts were removed at the conclusion of each experimental period for histopathologic analysis. Histological changes in coronary blood vessels, infiltration of inflammatory cells, hemorrhage, atrophy of myofiber with loss of nuclei and expansion of intramuscular connective tissues were observed, and lesion severity increased with the duration of exposure. The Vitamin E group also showed some minor amount of changes in the histological picture, this might be due to the dosage or length of administration. Despite the fact that methamphetamine/VE treatment was not effective at producing complete lesions, it did show a relative decrease in the severity of the lesions compared to methamphetamine alone. The researchers conclude that methamphetamine exposure causes chronic, dose-dependent toxicity to cardiac muscle, suggesting that exposure causes a slowly progressive damage to cardiac tissue. Moreover, Vitamin E provided partial protection from methamphetamine-induced cardiotoxicity but was not enough to reverse all histological changes, highlighting the importance of further research to determine an optimal dosage and elucidate the mechanism of protection in chronic methamphetamine exposure.

Keywords: Methamphetamine, Cardiotoxicity, Vitamin E, Cardioprotection, Histopathology, Myocardial Injury.

1 INTRODUCTION

Methamphetamine is one of the most powerful psychostimulants and is highly permeable to the blood brain barrier making it very effective in producing great volumes of release of neurotransmitters, specifically dopamine and norepinephrine, which has a broad effect on the central nervous system and many other systems of the body. Its widespread use worldwide and its potential for addiction have led researchers to study its detrimental effects on vital organs (UNODC, 2024; Cruickshank & Dyer, 2009; Darke et al., 2020). Recent studies have shown that methamphetamine is a toxic substance that exert multiple effects on the organs and the more sensitive organs that are more prone to "the toxic effects of methamphetamine are the organs of the heart" (Somma et al., 2023; Kevil et al., 2019; Paratz et al., 2016).

The heart pumps blood regularly to ensure oxygen and nutrient supply to the body's tissues and its normal function may impact the efficiency of the entire cardiovascular system; abnormalities in the heart muscle may cause cardiac arrhythmias, decreased heart's systolic efficiency, or result in diseases like cardiomyopathy and heart failure (Paratz et al., 2016; Schürer et al., 2017). Experimental studies of the direct histological effects of methamphetamine on the heart are limited but growing, and provide some evidence that usage of the drug is associated with cardiovascular disease; however, they are still relatively few in number and only partially describe the pathological changes in the heart associated with the duration and dose of its use, and provide limited insight into the molecular mechanisms underlying drug-induced cardiac damage (Paratz et al., 2020; Won et al., 2013). Many studies have shown that one of the most significant pathological mechanisms contributing to "methamphetamine-induced cardiac toxicity is oxidative stress, which causes methamphetamine to increase the production of reactive oxygen species (ROS) and to promote lipid peroxidation and damage to cell membranes, mitochondrial dysfunction, and activation of inflammatory and apoptotic pathways, in all of which" affect cardiac tissue integrity and function (Ramli et al., 2025; Nazari et al., 2023).

Because of oxidative stress's central role in the pathogenesis of these pathological processes, antioxidants have become a growing interest for their potential protective effects in mitigating methamphetamine-induced damage. One of the most significant fat-soluble antioxidants is vitamin E (α-Tocopherol), which can effectively inhibit lipid peroxidation reactions and prevent cell membranes from being damaged by peroxidation, as well as reduce the inflammatory response and keep cells and tissues in normal condition. Many experimental studies have demonstrated that vitamin E administration can alleviate various parameters of cardiac toxicity and result in improvements in histological changes in different drug toxicity models, including cardiac toxicity, thus suggesting it as a protective agent against methamphetamine-induced cardiac toxicity (Shabani et al., 2023; Traber & Atkinson, 2007; Niki, 2014; Kumar et al., 2021). In order to better understand the pathophysiology of methamphetamine-induced cardiac damage and to help develop new therapeutic and preventive strategies to lessen methamphetamine-induced complications in the future, the current study was designed to estimate the protective consequence of vitamin E against cardiac histological changes persuaded by methamphetamine in male white rats and to confirm its anti-oxidative effect and ability to reduce cardiac damage caused by oxidative stress.

2 MATERIALS AND METHODS

2.1 Laboratory animals

In this study, 32 healthy female Sprague-Dawley rats (150-200g, 2-4 months old) were used. Animals were kept under controlled temperature of 25°C and fed with the nutrients and water.

2.2 Experimental design

In this case, four main groups of animals (8 animals per group) with two sub-groups within each experimental group "(4 animals per sub-group) were randomly allocated for assessing treatment after 15 and 30 days. The initial body weights of all animals were recorded as thoroughly as possible before starting the study. The standard nourishment and water without any treatment were given to group 1 (G1, control) for 30 days. Group 2 (G2) was divided into two subgroups (n = 4 each), 0.1 mg/kg of body weight of methamphetamine was administered orally for 15 and 30 days in each group, respectively. Group 3 (G3) was also subdivided into two subgroups (n=4) which received two different doses of Vitamin E (0.1mL) 15 days and 30 days, respectively. There were two subgroups in Group 4 (G4), the first group (n=4) was treated with methamphetamine (0.1 mg/kg) and Vitamin E (0.1 mL) for 15 days and the second group (as originally described, n=12) were treated for 30 days". During the experimental period, all experimental groups received food and water.

2.3 Preparation of Histological Sections

The histology lab prepared the tissue sections. Science College, Tikrit University. The procedures outlined by Al-Hajj (2015) for processing microscopical sections included the following steps:

In order to repair the removed heart segments, they were immediately submerged in 10% neutral buffered formalin for a whole day. "The tissues were then dehydrated in a series of ethanol (70, 80, 90 and 100%), treated with xylene and embedded in paraffin wax at 60°C.A rotary microtome was then used to segment the paraffin blocks at a thickness of 6µm. Haematoxylin and eosin (H&E) was used to stain the resultant sections, which were subsequently mounted onto slides using D.P.X. and coated with cover slips". Lastly, a light microscope was used to view the produced slides, and a digital camera designed for microscopic imaging was used to take pictures of them.

3 RESULTS

A histological analysis of the heart muscle in the control group (G1) showed no pathological alterations and a normal histological structure with regularly arranged cardiac muscle fibres, distinct central nuclei within the cardiomyocytes and fibroblasts within the endomysium, and a few dispersed white blood cells (Figure 1). "In comparison to the control group", the methamphetamine group (G2) showed a distinct disruption in the regularity of the cardiac muscle fibres after 15 days of treatment, along with their fragmentation, degeneration, and rupture of some cardiac muscle fibres, as shown in Figure (2). After 30 days of treatment, the severity of the histological changes increased, with marked congestion in the coronary blood vessels, clear infiltration of inflammatory white blood cells, and aggregation of cardiac muscle fibers as demonstrated in Figure (3).In the vitamin E (G3) group, histological sections taken after 15 days revealed severe focal hemorrhage surrounded by inflammatory cells, accompanied by perinuclear vacuolar degeneration in the cytoplasm of cardiac myofibers as observed in Figure (4). In addition to fragmentation and disruption of the continuity of the cardiac muscle fibres, as shown in Figure (5), atrophy of the cardiac muscle fibres was noted after 30 days, along with loss of nuclei in some muscle cells, expansion of the intramuscular connective tissue, and infiltration of blood cells into it. After 15 days, "the group treated with methamphetamine and vitamin E" (G4) displayed compaction of the cardiac muscle fibres, cytoplasmic degeneration in many muscle fibres, intramuscular haemorrhage accompanied by haemolysis between the muscle fibres, and white blood cell and macrophage infiltration into the intramuscular connective tissue, as shown in Figure (6). As seen in Figure (7), the histological alterations continued after 30 days and included atrophy of cardiac muscle fibres, loss of nuclei in some cells, growth of the intramural connective tissue with blood cell infiltration, and endocardial haemorrhage.

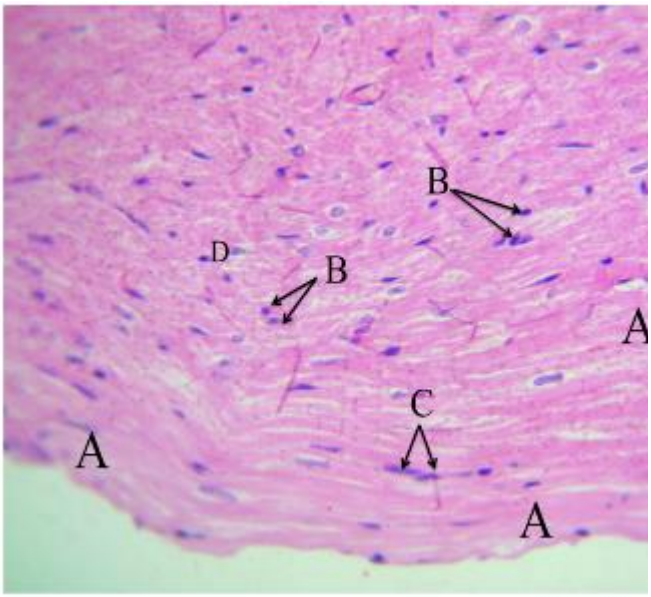

Figure 1: Photomicrograph of a G1 showing normal cardiac tissue, regularly arranged myocardial fibers (A), centrally located nuclei of cardiac muscle cells (B), fibroblasts within the endomysial connective tissue (C), and a few scattered leukocytes (D). (H&E, 40×).

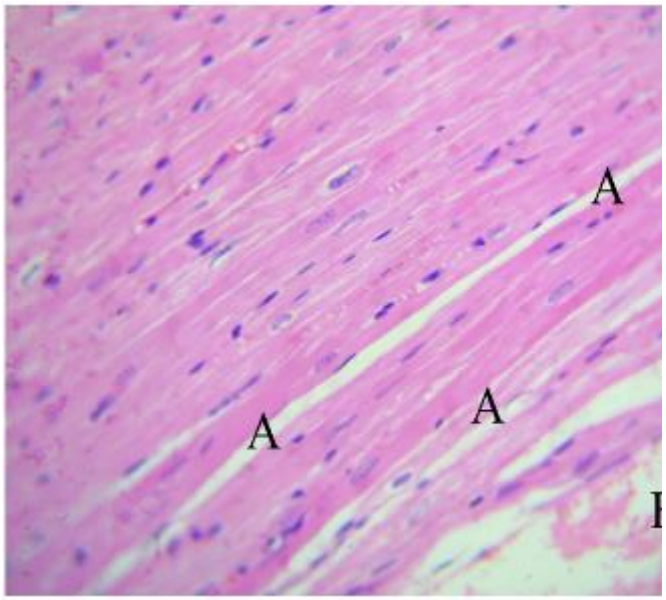

Figure 2: Photomicrograph of a rat cardiac tissue from G2 showing disorganization and fragmentation of the cardiac muscle fibers (A), accompanied by degeneration and disruption of some myocardial fibers (B). (H&E, 40×).

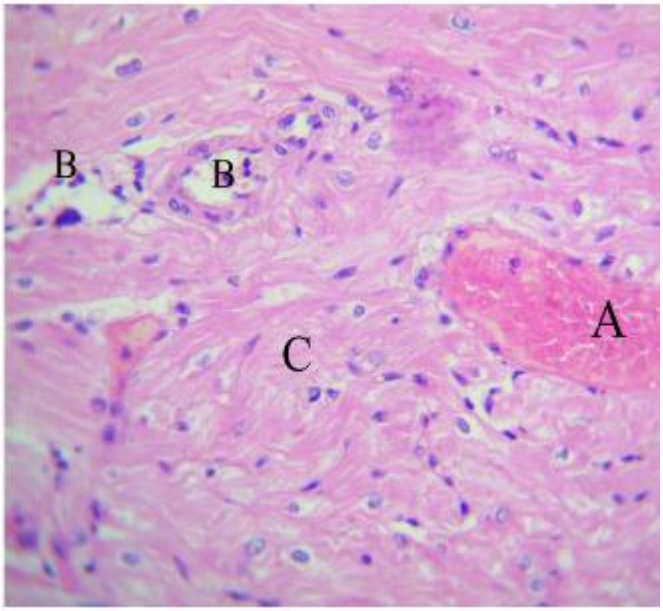

Figure 3: Photomicrograph of a rat cardiac tissue from G2 demonstrating marked congestion of the coronary blood vessels (A), infiltration of inflammatory leukocytes (B), and closely packed myocardial fibers (C). (H&E, 40×).

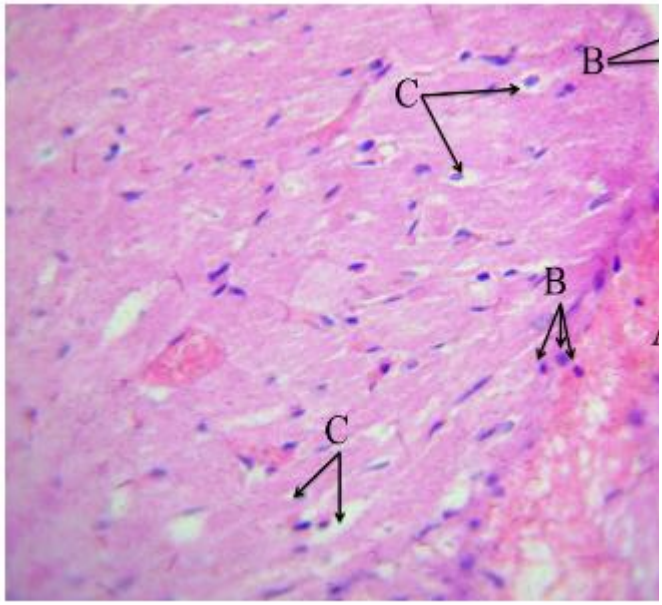

Figure 4: Photomicrograph "a rat cardiac tissue from G3 showing severe focal hemorrhage (A) surrounded by inflammatory leukocytes (B)", together with perinuclear cytoplasmic vacuolar degeneration of the cardiac muscle fibers (C). (H&E, 40×).

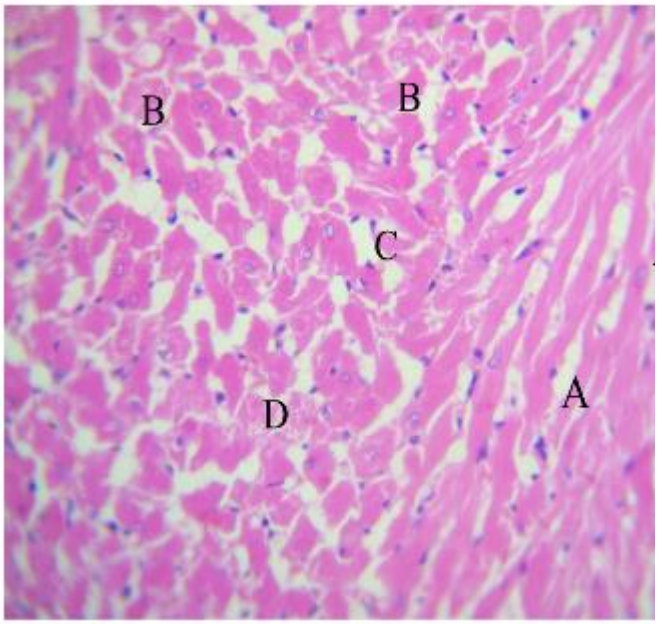

Figure 5: Photomicrograph of a rat cardiac tissue from G3 demonstrating atrophy of the cardiac muscle fibers (A), loss of nuclei in some myocardial fibers (B), expansion of the endomysial connective tissue containing infiltrating blood cells (C), and fragmentation with discontinuity of myocardial fibers (D). (H&E, 40×).

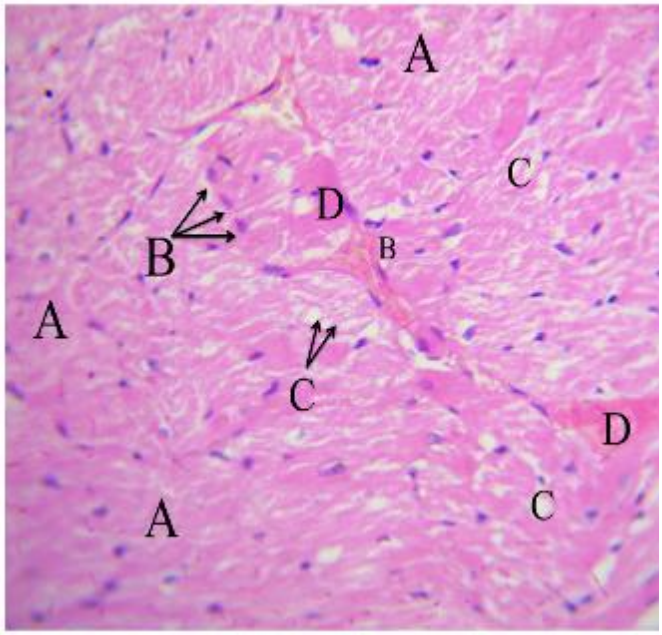

Figure 6: Photomicrograph of a rat cardiac tissue from G4 and Vitamin E (0.1 mL/day) for 15 days), showing closely packed myocardial fibers (A), infiltration of scattered leukocytes and macrophages within the endomysial connective tissue (B), cytoplasmic degeneration of numerous cardiac muscle fibers (C), and interstitial hemorrhage with erythrocyte degradation between the myocardial fibers (D). (H&E, 40×).

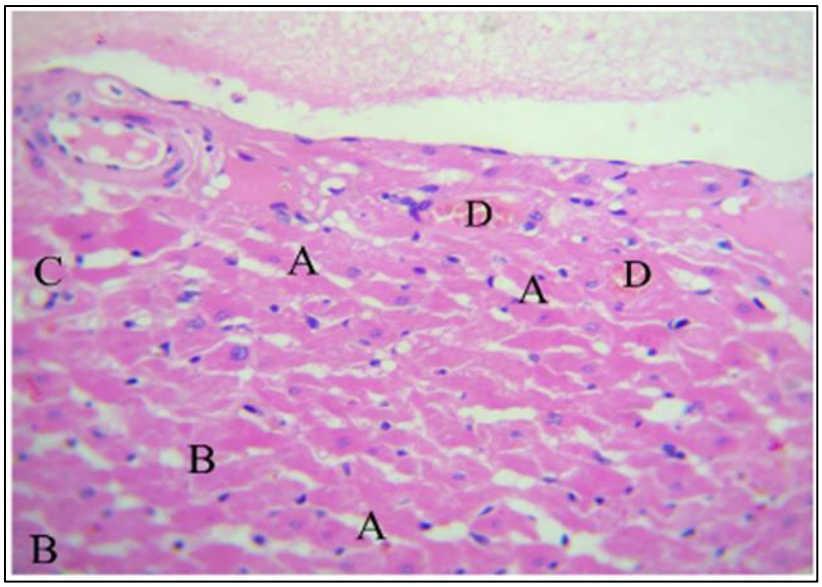

Figure 7: Photomicrograph of the cardiac tissue of the rat from G4 showing atrophy of the cardiac muscles fibers (A), disappearance of the nuclei from some cardiac fibers (B), enlargement of endomysial connective tissue with infiltration of blood cells (C), and hemorrhage in the endocardial region (D). (H&E, 40×).

4 DISCUSSION

The control group showed no pathological alterations and the normal histological structure of the heart muscle, which is defined by the regular arrangement of cardiac muscle fibres and the presence of central nuclei and fibroblasts inside the intramuscular connective tissue. This confirms the integrity of the animal model used and that it was not exposed to any factors that might affect the histological structure of the heart. These results are consistent with the normal histological description of the rat heart muscle reported in the reference studies (Bancroft & Gamble, 2019; Treuting *et al*., 2018)., making them a suitable basis for comparison with the pathological changes observed in the treated groups. The cardiac structural changes caused by methamphetamine can be explained by its stimulation of catecholamine release—particularly norepinephrine and dopamine—which leads to coronary vasoconstriction and increased oxygen consumption in the heart muscle (Kevil *et al*., 2019; Paratz *et al*., 2016; Darke *et al*., 2020)., resulting in ischemia and oxidative stress. This leads to increased production of reactive oxygen species (ROS), lipid peroxidation, and damage to proteins and DNA, as well as impaired mitochondrial function, ultimately resulting in cardiomyocyte degeneration and loss of cellular membrane integrity (Ramli *et al*., 2025; Nazari *et al*., 2023; Somma *et al*., 2023). Inflammatory pathways also get activated and pro-inflammatory cytokines are released due to oxidative stress, which is responsible for the vascular congestion and inflammatory cell infiltration in the cardiac tissue. These findings are in line "through those published by Ramli et al. (2025), who showed that methamphetamine's cardiotoxicity is linked to oxidative stress, mitochondrial dysfunction, and the activation of inflammatory pathways. They are also consistent with the study by Shabani et al. (2023)" that demonstrated that methamphetamine induces production of free radicals and dysfunction of mitochondria, which results in the clear damage to myocardial tissue. Furthermore, the increase in lesion severity with prolonged exposure indicates the cumulative effect of methamphetamine, which is associated with sustained free radical production, disrupted calcium metabolism, activation of apoptosis pathways, and increased collagen deposition, all of which exacerbate structural damage to the heart muscle. The histological changes observed in the vitamin E group may be attributed to the effects of dose and duration of exposure, as some studies suggest that vitamin E may exhibit a pro-oxidant effect (pro-oxidant effect) (Traber & Atkinson, 2007; Niki, 2014), when used in high doses or in cases of an imbalance between antioxidants and oxidizing agents, which may lead to disruption of cell membrane integrity and the occurrence of certain degenerative and hemorrhagic changes. Nevertheless, the results are not compatible with those of numerous studies already conducted, which have shown that vitamin E protects against oxidative stress and integrity of cardiac tissue; this may be due to the differences in the dose, duration of treatment, animal model and experimental conditions of the studies, as showed in the study conducted by Garg and Lee (2022). The findings showed that vitamin E failed to fully protect against the histological changes in the group that was administered both methamphetamine and vitamin E (Nazari et al., 2023; Paratz et al., 2020); indicating that the cardiotoxicity effects of methamphetamine were more severe than the protective effects of the antioxidant administered in this study. It is possible that persistent oxidative stress, inflammation, and mitochondrial dysfunction limited the effectiveness of vitamin E, leading to the persistence of some manifestations of tissue damage. These observations are partially consistent with a study by Shabani *et al*. (2023), which demonstrated that the efficacy of antioxidants in reducing methamphetamine-induced cardiac toxicity depends on their type, dose, and duration of administration. Recent studies have also indicated that antioxidants may mitigate the severity of tissue damage without completely preventing it, particularly in cases of

chronic exposure, suggesting that vitamin E provided partial protection (Shabani *et al*., 2023; Kevil *et al*., 2019; Ramli et al., 2025).; however, this was insufficient to prevent all the pathological effects caused by methamphetamine in cardiac tissue.

5 CONCLUSION

Exposure to methamphetamine led to clear pathological histological changes in the myocardium, manifested as disruption of the normal structure of cardiac muscle fibers, degeneration, vascular congestion, inflammatory exudation, and hemorrhage, The severity of these changes increased with longer duration of exposure, indicating a cumulative effect of methamphetamine on cardiac tissue. The findings of vitamin E group also indicated that the single use of vitamin E supplementation was not sufficient to maintain the normal histological structure of the heart muscle under the experimental conditions of this study. However, combined treatment with methamphetamine and vitamin E did yield partial protection, by decreasing the severity of some tissue lesions, but this had not been enough to prevent all pathological effects resulting from methamphetamine treatment. The cardiac toxicity of methamphetamine appears to involve several pathological mechanisms and the protective effect of vitamin E is dose and administration time dependent, suggesting the need for additional studies to establish the specific dose and protective mechanism of action.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The authors declare no conflicts of interest regarding this manuscript.

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