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EFFECT OF CADMIUM CHLORIDE ON THE CARDIAC MUSCLE ULTRASTRUCTURE OF RATS

Abstract: Cadmium is a heavy metal and environmental pollutant that plays a significant role in the development of cardiovascular diseases. Chronic exposure to low concentrations of cadmium in experimental animals leads to various biochemical and pathophysiological changes, such as increased blood pressure, accelerated formation of cholesterol plaques in arterial walls, conduction disturbances in the heart, and reduced contractile function of the myocardium. This study aimed to evaluate ultrastructural changes in the heart muscle of rats poisoned with cadmium chloride, as well as to determine the extent of recovery of these changes after cadmium exposure was discontinued. Wistar rats weighing 180 – 200 grams were administered cadmium chloride orally at a dose of 1.5 mg/kg daily. The poisoning lasted for 10 weeks. After the cadmium administration was stopped, heart tissue samples were collected on the first day, one week, and two weeks later for analysis. Following cadmium administration, ultrastructural examination of the cardiac muscle fibers revealed an increased number of mitochondria with significant cristae damage. The number of myofibrils and myofilaments was reduced. Z-discs were partially displaced, and A and I bands were poorly distinguishable. Intercalated discs were irregularly positioned, and the sarcolemma was damaged. Two weeks after cadmium withdrawal, these structural changes were partially reduced. Thus, exposure to cadmium chloride is associated with ultrastructural alterations in the heart that may underline physiological dysfunctions, and it is suggested that these changes are partially reversible after the cessation of cadmium exposure.

Keywords: cadmium chloride, cardiac muscle, ultrastructure, myofibrils, myofilaments, rat.

Introduction

Cadmium (Cd) – is a ubiquitous, non-essential, toxic metal that has harmful effects on the environment and human health upon exposure. These effects have been the focus of research for several decades. Cd occurs naturally in ore form. Its release into the environment from natural or anthropogenic sources can lead to contamination of soil and food products. Although acute Cd intoxication is now rare due to international regulations, people are continuously exposed to low levels of Cd, primarily through food and water consumption, cigarette smoke, polluted air, and occupational contact (Järup & Hazards, 2003). Once absorbed, Cd is not effectively eliminated and thus accumulates in the human body over a lifetime, with a long biological half-life of 15–30 years (Thevenod & Lee, 2013). Cd mainly accumulates in the kidneys, liver, and lungs. However, with chronic exposure, Cd can also accumulate in other parts of the body, including the heart, aorta, bones and intestines (Tai, et al., 2022b), leading to various diseases. Cadmium toxicity causes kidney problems (tubular and glomerular damage), osteomalacia, osteoporosis, testicular dysfunction, and cancer (Honda et al., 2003).

Furthermore, epidemiological studies have demonstrated a link between Cd exposure and the risk of cardiovascular diseases, such as heart failure, stroke, myocardial infarction, and diseases of the coronary and peripheral arteries (Barregard et al., 2016; Deering et al., 2018; Everett & Frithsen, 2008; Peters et al., 2010; Satarug et al., 2010; Tellez-Plaza et al., 2013; Tinkov et al., 2018). For example, Tellez-Plaza et al. (2013), reported an increased risk of ischemic heart disease (hazard ratio [HR]: 1.22; 95% confidence interval [CI]: 1.08–1.38), stroke (HR: 1.75; 95% CI: 1.17–2.59), and heart failure (HR: 1.39; 95% CI: 1.01–1.94) in individuals exposed to high Cd levels (80th vs. 20th percentile of urinary Cd concentration) (Tellez-Plaza et al., 2013). Additionally, Barregard et al. (2016) compared individuals with the highest and lowest quartiles of blood Cd levels and found that

those in the highest quartile had an increased risk of acute coronary events (HR: 1.8; 95% CI: 1.2–2.7) and stroke (HR: 1.9; 95% CI: 1.3–2.9) (Barregard et al., 2016). In the aforementioned studies, the association between Cd exposure and cardiovascular risk was consistent among never-smokers; therefore, this link cannot be entirely attributed to the confounding effects of smoking. As a major toxin in cigarettes, Cd may partially mediate the pro-atherosclerotic effects of smoking. Mediation analysis showed that Cd contributed to approximately 50% of the total increase in cardiovascular risk among current smokers (Andersson et al., 2018; Li et al., 2019).

Despite epidemiological data linking Cd exposure to cardiovascular risk, the underlying mechanisms remain unclear. Cd induces cell apoptosis and tissue damage by causing DNA damage, oxidative stress, mitochondrial injury, and endoplasmic reticulum stress (Genchi et al., 2020). The toxic effects of Cd on cardiomyocytes, vascular endothelial cells, and smooth muscle cells have been described both *in vivo* (animal studies) and in vitro (Ghosh & Indra, 2018; Messner et al., 2016; Shen et al., 2018; Washington et al., 2006). In the present study, we investigated the toxicity of Cd in the cardiovascular system of mice, evaluating its impact on baseline hemodynamics, cardiac function, and histology and ultrastructure of cardiac and arterial tissues. Matrix metalloproteinases (MMPs) influence heart failure and atherosclerosis by regulating extracellular matrix (ECM) turnover (Johnson, 2017; Olejarz et al., 2020; Spinale et al., 2013). Therefore, we further examined the effect of cadmium on the expression of cardiac and arterial MMPs, particularly MMP-2, MMP-9, and MMP-14, and their significance in cardiovascular diseases.

Ozturk et al. (2009) in his research, the systemic hemodynamics induced by acute and chronic cadmium (Cd^{2+}) intoxication in the cardiovascular system of rats using thoracic electrical bioimpedance were examined and the acute and chronic effects of Cd^{2+} intoxication on the activities of antioxidant enzymes and malondialdehyde (MDA) were compared. Also, in this study, ultrastructural changes in the heart and aorta of rats were evaluated. Thirty-eight male Wistar albino rats were randomly divided into control, acute, and chronic groups. Chronic group was administered by oral gavage an aqueous solution of $CdCl_2$ for 60 days, at dose of 15 mg Cd^{2+}/kg/day. Acute group was administered by oral gavage an aqueous solution of $CdCl_2$ with a single dose of 15mg Cd^{2+}/kg. Cadmium increased the stroke volume and cardiac output of rats in the chronic group but did not change the heart rate significantly. Antioxidant enzymes activities and MDA level significantly increased in the chronic group. In ultrastructural examination, there were widespread degenerative changes in heart muscle cells of the chronic group but endothelial cells and smooth muscle cells in the aorta tissue samples had normal morphological features in all groups. All of the findings indicate that Cd^{2+} toxication can cause deformation in heart muscle cells due to an increase in free radicals and lipid peroxidation. Also, this study has confirmed that a long-term-Cd^{2+} exposure increased stroke volume (SV) and cardiac output (CO) but did not change the heart rate (HR).

The novelty of the study lies in demonstrating that subchronic cadmium exposure induces a mitochondria-driven structural destabilization of cardiomyocytes, resulting in sarcomeric disorganization secondary to impaired bioenergetic support. The observed mitochondrial – sarcomeric dissociation represents a morphological substrate of toxic cardiomyopathy, highlighting disruption of the energetic – mechanical continuum in myocardial tissue. By incorporating post – exposure recovery intervals, the study further establishes that toxic myocardial injury is a dynamic and partially reversible process, redefining cadmium cardiotoxicity as a structurally phased pathology rather than a static degenerative condition.

This study aimed to evaluate the effects of subchronic cadmium chloride exposure on the ultrastructure of the rat myocardium and to determine whether these alterations are reversible during a post-exposure recovery period.

Materials and methods

The experimental animals were Wistar white rats that had been bred for several generations in the university laboratory to ensure genetic homogeneity. Healthy male rats weighing 180–200 grams were used in the study. The animals were divided into two groups: a control group (6 rats) and an experimental group, subdivided into three time points with 6 rats each. Rats in the experimental group were administered cadmium chloride orally at a dose of 1.5 mg/kg of body weight, dissolved in 0.2 ml 0.9% physiological saline, daily for 10 weeks. The control group received 0.2 ml of 0.9% NaCl solution orally on the same schedule. After completing cadmium administration, rats from the experimental group were euthanized at three time points: on the first day, 1 week, and 2 weeks after cessation of cadmium exposure (6 animals per time point). The left ventricular myocardium was collected from all animals for analysis (Table 1).

The experimental animals were male Wistar albino rats obtained from the animal vivarium at the B. Atchabarov Institute of Fundamental and Applied Medicine (Almaty, Kazakhstan). Healthy rats aged 3-4 months, weighing 180–200 g, were used in the study. The animals were bred under controlled conditions over several generations to ensure genetic homogeneity and the reproducibility of experimental results.

Animals were maintained under standard vivarium conditions: ambient temperature 22 ± 2°C, relative humidity 50–60%, and a 12 h light/12 h dark cycle. Ventilation was provided by a supply and exhaust system with controlled air quality. The animals were housed under barrier system conditions ("clean/dirty zones"). Rats were kept in polycarbonate cages (approximately 40 × 25 × 20 cm), with no more than 6 animals per cage. Animals were fed a standard pelleted diet, with free access to water (ad libitum). The animals were divided into two groups: a control group (6 rats) and an experimental group, subdivided into three time points with 6 rats each. Rats in the experimental group were administered cadmium chloride ($CdCl_2$) orally at a dose of 1.5 mg/kg body weight, dissolved in 0.2 mL of 0.9% physiological saline, once daily for 10 weeks. Animals in the control group received 0.2 mL of 0.9% NaCl solution orally according to the same schedule. After completion of cadmium administration, animals from the experimental group were euthanized at three time points: on day 1, 1 week, and 2 weeks after cessation of cadmium exposure (n = 6 per time point). The left ventricular myocardium was collected from all animals for subsequent analysis. The selected dose of cadmium chloride (1.5 mg/kg body weight) corresponds to a subchronic exposure level commonly used in recent experimental studies to induce organ-specific toxicity without excessive mortality. Subchronic cadmium exposure has been shown to cause cardiotoxic effects, including impaired myocardial contractility and altered hemodynamic parameters associated with oxidative stress and molecular damage (Protsenko et al., 2020).

Experimental data indicate that doses in the range of approximately 1–2 mg/kg/day produce consistent morphological and functional alterations in tissues while maintaining animal viability, which is essential for studying both injury progression and recovery. Similar dosing regimens (e.g., ~2 mg/kg $CdCl_2$) have been successfully used in recent studies to induce oxidative stress and structural tissue damage under subchronic conditions (Hu et al., 2024).

Higher doses (≥5 mg/kg) are associated with severe toxicity and pronounced tissue damage, limiting their suitability for long-term experimental models (Razooqi et al., 2924).

Therefore, the selected dose of 1.5 mg/kg represents a biologically relevant and methodologically justified model of chronic cadmium intoxication.

The duration of cadmium administration (10 weeks) was selected to induce stable chronic intoxication and ensure sufficient accumulation of the toxicant in tissues. Cadmium is characterized by cumulative properties and a long biological half-life; therefore, prolonged exposure is required to produce consistent morphological and ultrastructural alterations.

Post-exposure time points (day 1, 1 week, and 2 weeks after cessation) were included to evaluate the dynamics of tissue injury and recovery following withdrawal of the toxic agent. This design allows assessment of both the persistence and potential reversibility of cadmium-induced myocardial damage.

Euthanasia was performed under deep general anesthesia using Ketamine (80–100 mg/kg) and Xylazine (10 mg/kg), administered intraperitoneally. Adequate depth of anesthesia was confirmed by the absence of pain reflex and corneal reflex. Following induction of surgical anesthesia, euthanasia was completed by decapitation.

All procedures were carried out in accordance with international guidelines for the care and use of laboratory animals and were approved by the local ethics committee (Table 1).

Table 1
Experimental animal group

Group	Condition	Number of animals	Cadmium dose, mg/kg
control	no treatment	6	–
experiment	1st day post-cadmium	6	1.5
	1 week post-cadmium	6	1.5
	2 weeks post-cadmium	6	1.5

Immediately after excision, myocardial tissue samples (~1 mm³) were fixed at 4°C in 0.1 M Millonig's phosphate buffer (pH 7.2) containing 2% glutaraldehyde and 2.5% paraformaldehyde (Sigma-Aldrich, USA). Post-fixation was performed in 1% osmium tetroxide at 4 °C for 2 hours (Electron Microscopy Sciences, USA). The specimens were dehydrated in graded ethanol and acetone (Merck, Germany) and embedded in Epon-812 resin. Ultrathin sections (70–80 nm) were prepared using an AK-VIII ultramicrotome, positioned on copper grids, and stained with 2% uranyl acetate and lead citrate (0.04 M). The samples were processed at the Atchabarov Research Institute of Fundamental and Applied Medicine (Almaty, Kazakhstan).

Ultrastructural analysis was performed using a Hitachi H-600 transmission electron microscope (Japan) at 80 kV at the Kazakh Research Institute of Oncology and Radiology (Almaty, Kazakhstan).

Cadmium chloride ($CdCl_2$, ≥99% purity, analytical grade) was obtained from a certified supplier of chemical reagents in the Republic of Kazakhstan, Lab Time (product code 79037, CAS No. 10108-64-2). A sterile 0.9% sodium chloride solution (physiological saline, pharmaceutical grade) was purchased from a licensed pharmaceutical manufacturer by Kelun-Kazpharm, Kazakhstan. All reagents used in the study were of analytical or pharmaceutical grade and complied with relevant quality standards. Solutions were prepared under standard laboratory conditions in accordance with established protocols.

Ethical considerations

All experimental procedures involving animals were approved by the Local Ethics Committee of Asfendiyarov Kazakh National Medical University (Protocol No. 38 dated 28.01.2026) and were conducted in accordance with international guidelines for the care and use of laboratory animals.

All procedures were carried out in accordance with the Order of the Ministry of Health of the Republic of Kazakhstan dated December 11, 2020, №. Ministry of Health of the Republic of Kazakhstan-248/2020. The movement of personnel and materials was ensured through sanitary airlocks with the mandatory use of personal protective equipment. To prevent bacterial contamination, cleaning procedures, feeding, and animal care were performed strictly in accordance with the established regulations.

Housing and care of laboratory animals were organized according to barrier system principles, with strict separation of "clean" and "dirty" flows. The maintenance, care, and use of laboratory animals were conducted based on the following regulatory documents: the sanitary rules approved by the Order of the Ministry of Health of the Republic of Kazakhstan dated December 25, 2020, №. Ministry of Health of the Republic of Kazakhstan-331/2020; generally accepted international guidelines for working with laboratory animals (GLP, *Guide for the Care and Use of Laboratory Animals*); and the internal standard operating procedures (SOPs) of the vivarium.

Results and discussion

Electron microscope findings of the control white mouse myocardial cells. The nucleus and nucleus of the spindle type are clearly observed and the nuclear membrane of the double membrane was easily observed. Myofibril was distributed in large numbers and between the myofibril, the circumferential privates were distributed bearing the privates (Figure 1a). Myofibrils were clearly separated by sarcomere due to the limit of the Z-line and I band (1), A band and H band were observed. Some T tubules were also observed. M lines were observed in the center of eradication. myofilaments were arranged regularly at regular intervals and sharpened at each root (Figure 1b).

Electron microscopic findings of white rat cardiomyocytes in the experimental group in the myocardium of white rats sacrificed on the first day after daily administration of cadmium for 10 weeks, most of the myofibrils were shrunk or reduced, and the sarcoplasmic reticulum was proliferated between the myofibrils, but some of the sarcoplasmic reticulum was damaged or reduced (Figure 2a). The Z lines of the root fibers show an irregular arrangement and the myofibrils are reduced or damaged. Distinctions between bands and bands were rarely observed. The structure of the sarcoplasmic reticulum (interdisc) was observed to be irregular and the fascicle (in the sarcolemma) was observed to have disconnected phases (Figure 2b).

Figure 1
Electron micrographs of cardiac muscle fibers in control rat (a) X 8000 and (b) X 20000)
Round oval nucleus (N) of a cardiac cell is clearly seen. Numerous myofibrils (m) and myofilaments are clearly arranged. A few mitochondria (M) are located at interfibrillar region and adjacent nucleus. In myofibril, Z-line, A-band, I-band and H-line showed their fine structures.
Mitochondria contains numerous cristae.

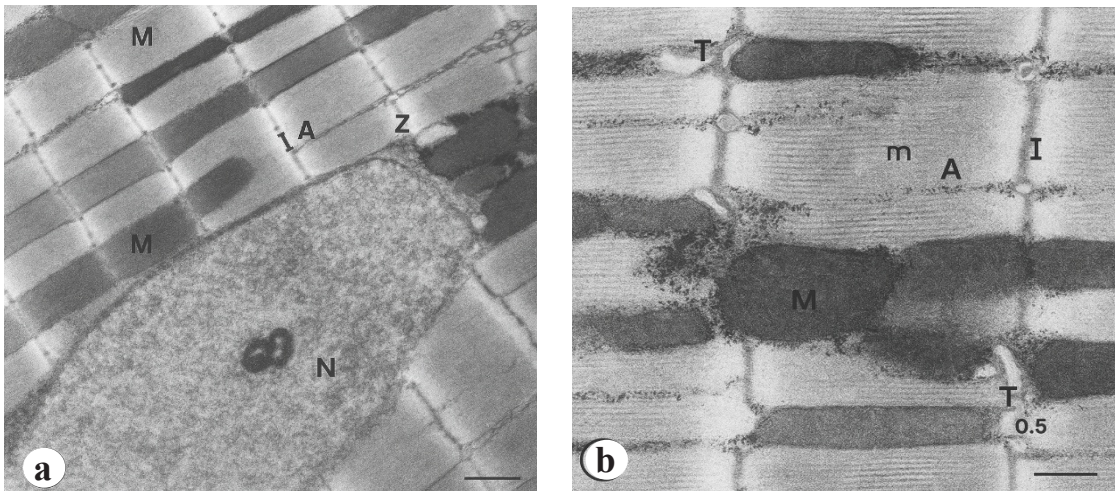
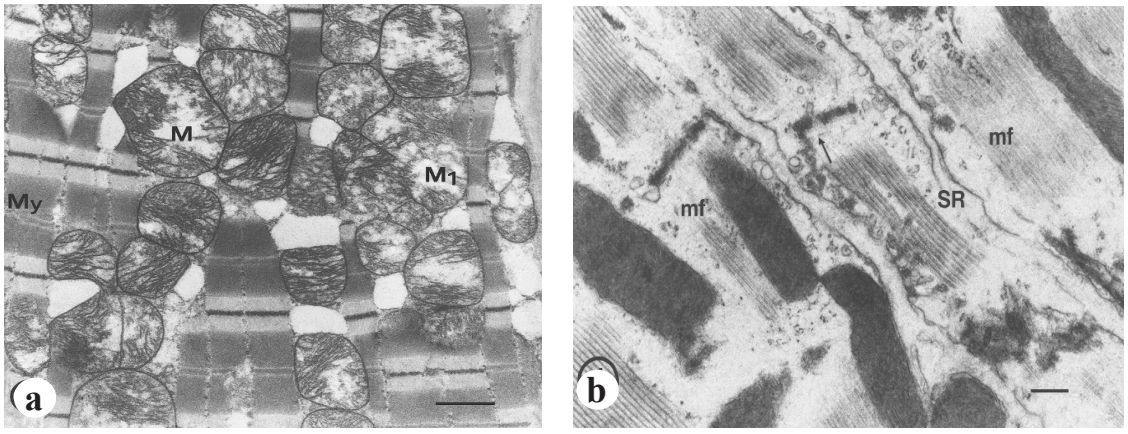
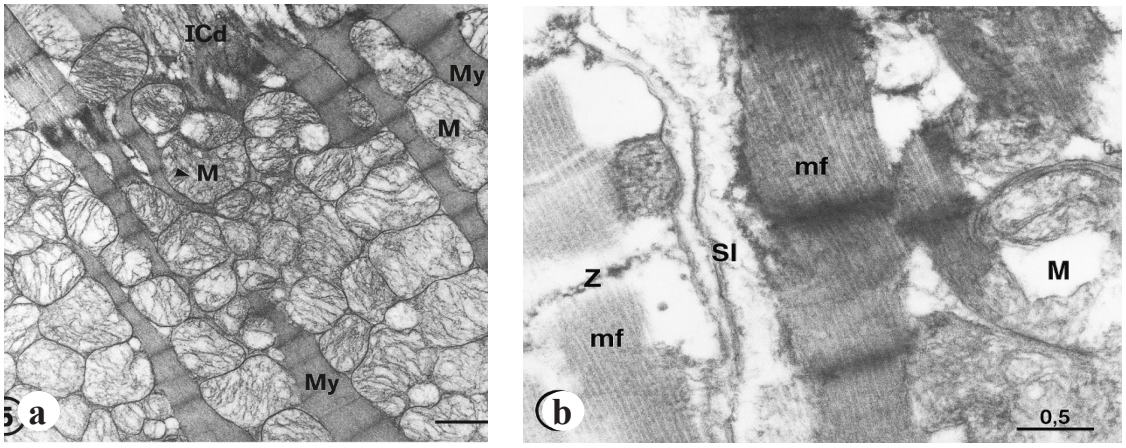


Figure 2
Electron micrographs of rat cardiac muscle fibers at 1st day after cadmium chloride administration of 10 weeks (a) X 8000 and (b) X 20000)
The number of mitochondria (M) is increased, and their cristae are severely damaged. Consequently, cardiac myofibrils (My) are decreased, and few myofilaments (mf) are observed. The Z-discs show irregular structures and are partially dislocated. Additionally, irregularly arranged intercalated discs (Ic) and a disrupted sarcolemma are visible.



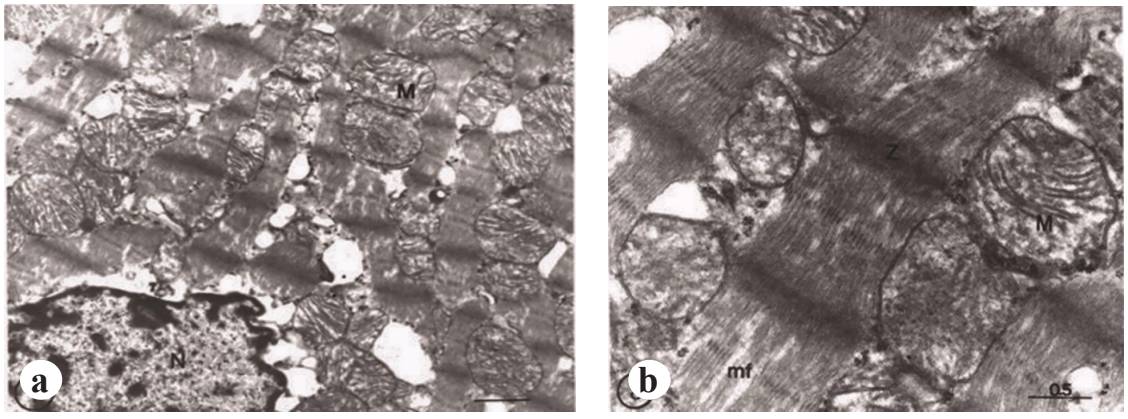
In the cardiomyocytes of white rats treated with cadmium 10 for a week and recovered after 1 week, the number of myofibrils is significantly reduced, numerous private bodies are observed, the connection of sarcolemmal plates is disrupted, and some of the myofilaments are lost, and the loss of private bodies and the loss of A and h bands are also observed (Figure 3a, 3b).

Figure 3
Electron micrographs of rat cardiac muscle fibers at l week after cadmium chloride administration of 10 weeks (a) X 8000 and (b) X 20000)
Few myofibrils (My) are seen, and mitochondria (M) are increased in numbers. Mitochondria lost a lot of cristae. Myofilaments (mf) are reduced and A-bands and I-bands are not clearly defined. Z-disc are partly observed. Sarcolemma (Sl) are segregated from myofibrils (Mf).



In the cardiomyocytes of white rats treated with cadmium 10 for a week and recovered after 2 weeks, the number of myofibrils is similar to that of the control group, but the number of private bodies is slightly increased, and the myofilaments are also recovered.

Figure 4
Electron micrographs of rat cardiac muscle fibers at 2 weeks after cadmium chloride administration of 10 weeks (a) X 8000 and (b) X 20000)
The myofibrils(mf) of cardiac muscle fibers were increased in numbers. Mitochondria (M) are reduced in number similar to control rat mitochondria. Z-disc, I-band and A-band are seen.



Cadmium is a heavy metal widely used for industrial purposes, and in recent years, due to the development of industry in the world, an increase in intake through air pollution, smoking, drinking water and food has been reported.

The results of a study by Reda A. Ali et al. (2024), showed that exposure to various low doses of Cd in chick embryos affects key stages of myocardial development, which may predispose offspring to cardiovascular disease in the future. This study showed that exposure to Cd caused inflammation of embryonic cardiomyocytes, thickening and hyperplasia of the heart muscle. In addition, Cd causes underdevelopment of the heart, as well as microstructural and histopathological damage, which is reflected in a decrease in the efficiency of the heart. The cardio-

toxic effects of Cd on the structure and function of the heart depend on the dose (Reda et al., 2024).

Yu-Ting Tai et al. (2022a) demonstrated the successful establishment of a mouse model of chronic cadmium (Cd) accumulation. Cadmium deposition was detected in multiple tissues, including the spine, femur, aorta, heart, kidneys, lungs, liver, intestines, serum, and urine, confirming systemic distribution following prolonged exposure. The authors reported that Cd accumulation in the kidneys and aorta reached near-saturation levels in the higher-dose group. In addition, calcium concentrations in bone and kidney tissues decreased with increasing Cd exposure, indicating direct toxic effects on mineralized tissues. Although no significant changes in body weight, blood pressure, or heart rate were observed, histological examination revealed pronounced structural alterations in cardiac tissue. These findings suggest that Cd accumulation plays an important role in mediating pathophysiological changes, particularly in the heart and skeletal system (Tai et al., 2022a).

Shing-Hsien Chou et al. (2023) showed epidemiological studies have reported an association between chronic cadmium (Cd) exposure and increased cardiovascular risk; however, their causal relationship remains unclear. The aim of this study is to explore the effects of Cd exposure on the cardiac and arterial systems in mice. According to the concentration of cadmium chloride in drinking water, male mice were randomly divided into control and low-dose and high-dose Cd exposure groups. The intervention duration was 12 weeks. In cardiac tissues, Cd exposure led to focal necrosis, myofibril disarray, perivascular and interstitial fibrosis, and disorganized sarcomere structures. Cd also induced the apoptosis of cardiomyocytes and increased the expression levels of matrix metalloproteinase (MMP)-2 and MMP-14 in cardiac tissues. In the arterial tissues, Cd exposure damaged the intimal and medial layers of the aorta. Cd further reduced the viability of aortic smooth muscle cells in vitro. This study provides evidence for the Cd-induced damage of the cardiovascular system, which may contribute to various cardiovascular diseases (Chou et al., 2023).

Sepulchro Mulher et al. (2024) demonstrated that cadmium, a widespread environmental heavy metal, acts not only as a cardiovascular risk factor but also as a potential metalloestrogen capable of inducing sex-dependent vascular effects. Using isolated aortic preparations from female Wistar rats, the authors investigated the in vitro effects of cadmium chloride ($CdCl_2$, 5 μM) on vascular reactivity. Exposure to $CdCl_2$ resulted in structural damage to the vascular endothelium, increased production and release of reactive oxygen species (O_2), reduced the involvement of potassium (K^+) channels, and enhanced activation of the angiotensin II pathway in response to phenylephrine. In addition, estrogen receptor alpha (ERα) was found to modulate vascular reactivity in the presence of cadmium, supporting the hypothesis that cadmium may function as a metalloestrogen. The study concluded that cadmium exposure promotes endothelial injury and oxidative stress in the isolated aorta of female rats, potentially contributing to the development of vasculopathies (Sepulchro Mulher et al., 2024).

Rossi et al. (2024) reported that chronic cadmium exposure is associated with vascular alterations and increased arterial pressure; however, the short-term cardiovascular effects remain insufficiently characterized. In their experimental study, Wistar rats were exposed to cadmium chloride ($CdCl_2$) at a concentration of 100 mg/L in drinking water for 7 days, which corresponds to an approximate daily intake of ~10–15 mg/kg body weight, depending on fluid consumption. The authors demonstrated that, despite relatively low plasma cadmium levels, the exposed animals exhibited elevated systolic blood pressure and enhanced vascular contractility in response to phenylephrine. Endothelium removal and nitric oxide synthase (NOS) inhibition increased contractile responses in both control and cadmium-treated groups. In the aorta of cadmium-exposed rats, increased phosphorylation of endothelial nitric oxide synthase (eNOS, Ser1177) and elevated basal nitric oxide production were observed. Furthermore, cadmium exposure was associated with decreased catalase expression and increased basal hydrogen peroxide (H_2O_2) release. Catalase incubation attenuated the enhanced contractile response. In vessels pre-contracted with phenylephrine, cadmium-treated rats showed impaired endothelium-dependent (acetylcholine-induced) and endothelium-independent (sodium nitroprusside-induced) relaxation. However, responses to sodium nitroprusside were comparable between groups when pre-contraction was induced by KCl. These findings indicate that even short-term cadmium exposure can induce early alterations in vascular function and blood pressure regulation, potentially mediated by impaired antioxidant defense and increased H_2O_2 bioavailability.

El Bakary et al. (2025) reported that exposure to cadmium (Cd) induces pronounced cardiotoxic effects, primarily mediated by oxidative stress and inflammatory responses. In their experimental study, male albino rats were divided into five groups (con-

trol, Cd, Cd+R, Cd+RES, and Cd+RES+R). Cadmium chloride was administered intraperitoneally at a dose of 2 mg/kg body weight, five times per week for six consecutive weeks. Resveratrol (50 mg/kg/day) was administered for 35 days, starting from the second week of cadmium exposure, and low-dose gamma radiation (0.75 Gy) was applied at the end of the experimental period. The authors demonstrated that cadmium exposure significantly increased serum levels of cardiac injury markers, including creatine kinase-MB (CK-MB), troponin I, and lactate dehydrogenase (LDH), along with alterations in lipid profile parameters. Moreover, a marked downregulation of key metabolic and antioxidant regulators was observed in cardiac tissue, including AMP-activated protein kinase (AMPK), Sirtuin 1 (SIRT1), nuclear factor erythroid 2-related factor 2 (NRF2), and suppressor of cytokine signaling 3 (SOCS3). Notably, resveratrol exerted a protective effect by modulating AMPK-mediated signaling pathways and attenuating oxidative stress and inflammatory responses in cadmium-treated animals.

Raktim et al. (2026) reported that cadmium induces cardiotoxicity even at low doses through endocrine disruption and oxidative stress. This investigation assessed age-related susceptibility in female albino rats by comparing pre-pubertal (30-day-old) and post-pubertal (60-day-old) animals that were administered $CdCl_2$ at a dosage of 5.12 mg/kg body weight per day via oral gavage for 15 days. Despite greater Cd accumulation in pre-pubertal rats, post-pubertal animals exhibited heightened cardiac injury. This paradox correlated with impaired induction of metallothionein (MT), enhanced glutathione and vitamin C depletion, and reduced enzymic antioxidants (SOD, CAT, GPx). Concomitantly, altered adrenal function with increased corticosterone (CORT) and reduced estradiol (E2) reflected differential hypothalamic–pituitary–adrenal (HPA) axis responsiveness, further compromising antioxidant defenses. Biomarkers of cardiac function confirmed this vulnerability: increased serum CK-MB and troponin I, electrocardiographic (ECG) abnormalities (ST elevation, QT prolongation, tachycardia), and larger infarct volume. Collectively, these findings demonstrate that post-pubertal susceptibility is driven by reduced MT inducibility and HPA axis–mediated endocrine dysregulation, which amplify oxidative injury and structural remodeling of ventricular myocardium. From a translational standpoint, our findings identify adolescence and early adulthood as critical windows during which females exhibit heightened vulnerability to environmental $CdCl_2$ exposure. Variations in metallothionein (MT) expression capacity and estradiol levels may serve as informative biomarkers for predicting individual susceptibility. These results also suggest the potential value of targeted interventions such as MT induction, antioxidant therapy, or modulation of hormonal pathways, that merit further investigation. Collectively, the study emphasizes the urgent need for stricter regulation of cadmium exposure, particularly among peripubertal populations, to reduce lifelong cardiovascular risk.

Xiao et al. (2026) demonstrated that cadmium (Cd^{2+}) exposure exacerbates atherosclerotic lesions through endothelial dysfunction. In their study, a positive correlation was observed between cadmium levels and atherosclerotic plaque burden in human vascular samples. In vivo experiments using apolipoprotein E-deficient ($ApoE^{-/-}$) mice fed a high-fat diet showed that cadmium chloride ($CdCl_2$) exposure led to a dose-dependent increase in atherosclerotic plaque formation. Histological analysis revealed enhanced lipid deposition within the vascular wall, as confirmed by Oil Red O staining, along with increased signs of vascular inflammation. Similarly, in zebrafish models, cadmium exposure intensified high-fat diet–induced vascular lipid accumulation and inflammatory changes. These findings indicate that cadmium contributes to the progression of atherosclerosis by promoting structural and histopathological alterations in the vascular wall.

During the experimental period, no mortality was observed in either the control or cadmium-treated groups. All animals completed the study according to the experimental protocol; therefore, the final sample size remained unchanged (control: n = 6; cadmium-treated: n = 18, with n = 6 per time point). Histological examination revealed no significant differences in the morphology of small arteries, capillaries, or cardiomyocytes between the cadmium-treated and control groups. However, pronounced ultrastructural alterations were observed in the sarcoplasmic reticulum (SR) of papillary muscle cardiomyocytes in the cadmium-treated animals. These changes were characterized by dilatation of the SR cisternae, reflected by an increased intermembrane distance, as well as disruption of junctional complexes. Such structural damage to the SR may impair intracellular calcium handling and, consequently, affect myocardial electrical conductivity and contractile function. In addition, an increase in electron density of the SR in the interventricular septum was observed, suggesting alterations in ionic homeostasis and intercellular signaling. These findings support the hypothesis that cadmium exposure may interfere with cell-to-cell

electrical coupling in myocardial tissue. Minor differences in the degree of SR electron density reported across studies are unlikely to be solely attributable to variations in cadmium dose or duration of exposure.

Subchronic exposure to cadmium for 10 weeks induced degenerative alterations in myocardial myofibrils and myofilaments, suggesting that sarcoplasmic reticulum dysfunction may impair cardiac contractility and electrical conduction. Notably, partial attenuation of these ultrastructural changes was observed after cessation of cadmium administration (1 day, 1 and 2 weeks), indicating a degree of reversibility. However, these findings should be interpreted with caution, as the extent of structural recovery requires further confirmation by quantitative morphometric analysis and additional ultrastructural evidence. These results highlight the need for further studies aimed at elucidating the mechanisms of cadmium-induced myocardial injury and potential strategies for its prevention.

Conclusion

The present study confirms that long-term oral administration of cadmium chloride at a dose of 1.5 mg/kg causes notable degenerative changes in the ultrastructure of myocardial tissue in Wistar albino rats. Morphological alterations were evident as early as one day after the exposure period ended. These included shrinkage and partial loss of myofibrils, disorganization of Z-lines, disappearance of A and I bands, disconnection of the sarcoplasmic reticulum, and proliferation of electron-dense (private) bodies between the myofibrils. Such damage indicates impaired structural integrity and potential compromise of cardiac function.

Interestingly, one week after cadmium withdrawal, the myocardial structure remained abnormal, although some signs of improvement were noted. However, two weeks post-exposure, most of the structural features of the myocardium were restored to a state resembling normal tissue, suggesting that the cadmium-induced damage is, to a significant extent, reversible if exposure is discontinued in time.

These findings suggest that cadmium has a direct toxic effect on myocardial ultrastructure, but the myocardium also possesses a certain regenerative capacity. This highlights the importance of early detection and removal of cadmium exposure to prevent long-term or irreversible cardiac damage. Further studies are recommended to explore the molecular mechanisms of this recovery and its impact on heart function.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Author contributions

Nurzhamal M. Joldasbayeva: Conceptualization, Investigation, Methodology, Writing – Original Draft & Review & Editing.

Zina B. Tungushbaeva: Conceptualization, Supervision, Data Curation, Formal Analysis, Visualization.

Murat B. Zhaksybaev: Conceptualization, Discussion of the research results.

Nariman N. Pravin: Conceptualization, Discussion of the research results.

All authors have read and approved the final version of the manuscript.

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