The Effect of Eight Weeks of Aerobic Exercise Combined with Curcumin Supplementation on Endoplasmic Reticulum Stress in the Liver of Cadmium-Exposed Rats

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Abstract

Background and purpose: Cadmium (Cd) is a toxic heavy metal known to induce oxidative and endoplasmic reticulum (ER) stress, particularly in hepatic tissue. Curcumin, a natural polyphenol, and aerobic exercise have been independently shown to mitigate cellular stress. This study aimed to investigate the combined effect of curcumin supplementation and aerobic training on ER stress markers in the liver of Cd-exposed rats.

Materials and Methods: 40 male Wistar rats aged 8-10 weeks (n=8 in each group) were allocated into five groups: control (C), cadmium (Cd), cadmium+curcumin (Cd+Cu), cadmium+training (Cd+AT), and cadmium+curcumin+exercise (Cd+Cu+AT). The Cd groups received 5 mg/kg of cadmium daily via drinking water. The AT groups underwent running sessions for eight weeks, five times per week, with each session lasting 30-60 minutes at a speed of 15 m/min on a 15-degree incline. Additionally, the daily intake of curcumin was 160 µL/kg administered orally.

Results: Cadmium (Cd) administration significantly increased hepatic expression of GRP78 and CHOP genes compared to the control group ($p < 0.001$). Co-treatment with curcumin (Cd+Cu), aerobic training (Cd+AT), and particularly their combination (Cd+Cu+AT) significantly reduced the expression of GRP78 ($p < 0.05$) and CHOP ($p < 0.05$) compared to the Cd group. Additionally, the Cd+Cu+AT group showed significantly lower CHOP expression than both the Cd+Cu and Cd+AT groups ($p < 0.05$), indicating a potential synergistic effect.

Conclusion: Eight weeks of aerobic exercise combined with curcumin supplementation effectively attenuates cadmium-induced ER stress in the liver. These findings suggest that the combined intervention may offer enhanced protection against heavy metal-induced hepatic injury.

Keyword: Cadmium Toxicity, Curcumin, Exercise, Endoplasmic Reticulum Stress, Liver.

Introduction

Endoplasmic reticulum (ER) stress is a critical cellular adaptive response implicated in various pathological conditions, including liver diseases and heavy metal toxicity (1-3). The ER plays a pivotal role in protein folding, modification, and transport, and its homeostasis is essential for cell survival and function 3. When the ER's capacity to handle protein folding is overwhelmed, misfolded proteins accumulate, triggering the unfolded protein response (UPR) (2, 3). While the UPR initially aims to restore ER homeostasis, prolonged or severe ER stress can lead to inflammation, oxidative stress, and ultimately, programmed cell death (apoptosis), contributing to tissue damage and disease progression (2, 3).

Cadmium (Cd), a highly toxic heavy metal widely distributed in the environment, poses a significant threat to human and animal health due to its accumulation in various organs, particularly the liver and kidneys (4, 5). Cd exposure has been unequivocally linked to the induction of ER stress, oxidative stress, and mitochondrial dysfunction, contributing to hepatotoxicity and nephrotoxicity (5). For instance, studies have shown that Cd exposure activates key UPR pathways, including PERK, ATF6, and IRE1, leading to the accumulation of unfolded proteins and cellular damage (2). In the liver, Cd-induced ER stress can disrupt lipid metabolism and cause histological changes, contributing to liver injury (6).

Curcumin, a natural polyphenolic compound derived from Curcuma longa, has garnered substantial scientific interest due to its diverse pharmacological properties, including antioxidant, anti-inflammatory, and hepatoprotective effects (4, 7, 8). Research indicates that curcumin can mitigate ER stress in various cellular and animal models by modulating UPR pathways, reducing oxidative stress, and inhibiting apoptosis (7, 8). Specifically, curcumin has been shown to decrease the expression of ER stress markers such as PERK, BiP, ATF6, eIF2α, ATF4, and CHOP, thereby alleviating ER stress-mediated cellular damage (9). Moreover, curcumin's antioxidant capacity, including its ability to scavenge reactive oxygen species (ROS) and enhance endogenous antioxidant enzymes, directly counteracts Cd-induced oxidative stress, which often co-occurs with ER stress (4, 9).

Aerobic training is a well-established non-pharmacological intervention known to confer numerous health benefits, including improvements in metabolic homeostasis, cardiovascular function, and stress resilience (10, 11). Emerging evidence suggests that aerobic exercise can positively influence ER stress responses, particularly in metabolic disorders and chronic diseases (11, 12)). For instance, aerobic exercise training has been shown to rescue cardiac protein quality control and blunt ER stress in heart failure models (11). In the context of liver health, aerobic exercise can improve diet-induced metabolic-associated fatty liver disease by affecting hepatic ER stress markers 24. Lifelong exercise is also associated with reduced ER stress and can counteract age-related pathologies and lipid metabolism disorders (10).

Given the individual protective effects of both curcumin and aerobic training against ER stress and associated pathologies, particularly in the context of heavy metal toxicity, investigating their combined impact is a logical next step. While both interventions have been studied separately or in combination for other conditions like polycystic ovary syndrome (PCOS) (12, 13) and diabetes (12), their synergistic potential in mitigating cadmium-induced hepatic ER stress remains to be fully elucidated. Considering that Cd exposure induces severe ER stress and oxidative damage in the liver (13), and both curcumin and aerobic exercise target these pathways, a combined approach may offer a more comprehensive and effective therapeutic strategy. This study, therefore, aims to investigate the effects of an eight-week regimen of

aerobic training combined with curcumin supplementation on endoplasmic reticulum stress in the liver of rats exposed to cadmium. Such research could provide valuable insights into novel strategies for protecting against heavy metal-induced hepatotoxicity and contribute to a better understanding of the interplay between lifestyle interventions and natural compounds in modulating cellular stress responses.

Materials and Methods

In this experimental study, 40 male Wistar rats, aged 8-10 weeks and weighing approximately 190-220 grams, were sourced from the laboratory animal breeding and reproduction centre. To facilitate adaptation to their new environment, the rats were housed in the laboratory for one week. They were maintained under standard conditions, including a 12:12 hour light-dark cycle, a relative humidity of 55%, a temperature range of 22 to 24°C, with unrestricted access to water and food. Following this acclimatization period, the rats were randomly allocated into eight groups: control (C), cadmium (Cd), cadmium+curcumin (Cd+Cu), cadmium+exercise (Cd+AT), and cadmium+curcumin+exercise (Cd+Cu+AT). This research received approval from the ethics committee at the Islamic Azad University, Ayatollah Amoli branch, under the code IR.IAU.AMOL.REC.1403.175.

Cadmium supplementation

Pure Cd chloride was sourced from Sigma Aldrich. Based on the number and weight of the rats, 35 mg of Cd was dissolved in the daily water intake of the groups receiving Cd. The rats were administered 5 mg/kg of Cd dissolved in their drinking water daily (14).

Aerobic training protocol

The rats were familiarized with the treadmill for a week, running for 10 minutes each day at a speed of 8 m/min with a 0-degree incline. Subsequently, they ran daily for 60 minutes at a speed of 15 m/min on a 15-degree slope for eight weeks, with five sessions each week. To adhere to the principle of overload, the exercise duration was set at 30 minutes in the first to fourth week, then increased to 60 minutes from the fourth to the eighth week (15).

Curcumin supplementation

Initially, curcumin was sourced from Sigma Aldrich in America. Subsequently, each mouse was administered a solution of 160 µl of curcumin (dissolved in dextrose) per kilogram of body weight using small bottles (16).

Dissection and sampling

Forty-eight hours after the final training and supplementation session, the rats were anaesthetized using ketamine (50 mg/kg) and xylazine (20 mg/kg) following a 12-hour fasting period. Once full anesthesia was achieved, the liver tissue was dissected, weighed, and rinsed with saline. The tissue was then placed in tubes containing RNA Later to prevent RNA degradation, and after being frozen with liquid nitrogen, it was stored in a refrigerator at -80°C. To mitigate the influence of circadian rhythms, the tissue collection commenced at 8:00 AM and concluded at 11:30 AM.

Data analysis

The Shapiro-Wilk test was used to investigate the normal distribution of the data of the present study. Regarding inferential statistics, one-way analysis of variance was performed to examine the differences between the groups and Tukey's post hoc test was performed to evaluate the differences between the groups in SPSS software. Also, a significance level of $p \geq 0.05$ was considered for data analysis.

Results

Data analysis revealed a statistically significant difference in hepatic GRP78 gene expression changes among the experimental groups (F = 7.274, p = 0.0001). Post hoc analysis indicated a significant increase in GRP78 expression in the Cd group compared to the control group (p = 0.001). Furthermore, a significant decrease in GRP78 expression was observed in the Cd+Cu (p = 0.001), Cd+AT (p = 0.047), and Cd+Cu+AT (p = 0.013) groups compared to the Cd group (Figure 1).

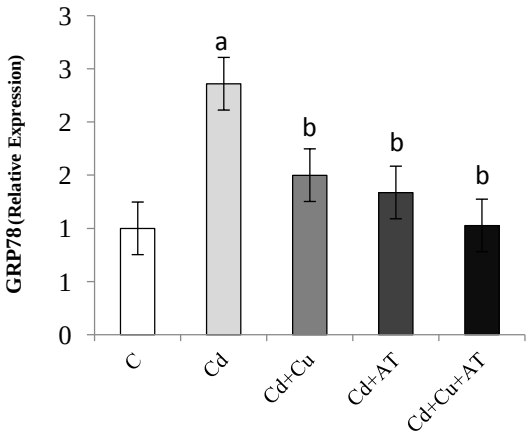

Figure 1. Liver expression of GRP78 in different groups by one-way analysis of variance (p<0.05).
a Difference from the C group, b Difference from the Cd group, c Difference from the Cd+Cu+AT group.
C: control, Cd: cadmium, Cd+Cu: cadmium+curcumin, Cd+AT: cadmium+training and Cd+Cu+AT: cadmium+curcumin+training.

In addition, data analysis showed a statistically significant difference in CHOP gene expression changes in the liver tissue across the different groups (F = 15.142, p = 0.0001). Post hoc tests revealed a significant increase in CHOP expression in the Cd (p = 0.0001), Cd+Cu (p = 0.012), and Cd+AT (p = 0.022) groups compared to the control group. Moreover, a significant reduction in CHOP expression was found in the Cd+Cu (p = 0.035), Cd+AT (p = 0.019), and Cd+Cu+AT (p = 0.0001) groups compared to the Cd group. Additionally, the Cd+Cu+AT group showed a significant decrease in CHOP expression compared to both the Cd+Cu (p = 0.020) and Cd+AT (p = 0.036) groups (Figure 2).

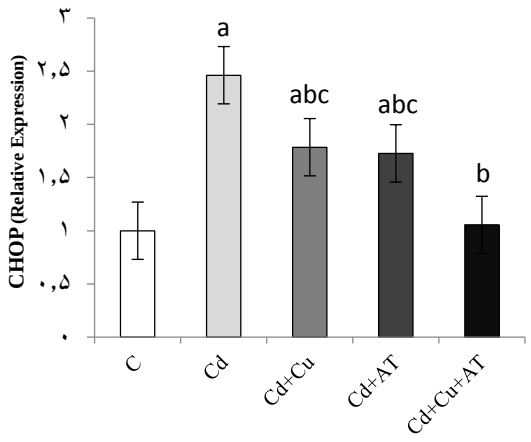

Figure 2. Liver expression of CHOP in different groups by one-way analysis of variance ($p<0.05$).
a Difference from the C group, b Difference from the Cd group, c Difference from the Cd+Cu+AT group.
C: control, Cd: cadmium, Cd+Cu: cadmium+curcumin, Cd+AT: cadmium+training and Cd+Cu+AT: cadmium+curcumin+training.

Discussion

The findings of the present study demonstrate that cadmium (Cd) exposure significantly induces endoplasmic reticulum (ER) stress, as evidenced by the marked upregulation of GRP78 and CHOP gene expression. These molecular responses were significantly attenuated by aerobic exercise and curcumin supplementation, particularly when both interventions were combined, suggesting a protective and potentially synergistic effect against Cd-induced ER stress.

Cd is a well-known environmental toxicant that disrupts cellular redox homeostasis, induces oxidative stress, and interferes with protein folding in the ER, thereby activating the unfolded protein response (UPR) (17, 18). GRP78 (glucose-regulated protein 78), a master chaperone of the ER, is a central regulator of UPR and is rapidly upregulated in response to ER stress (19). CHOP (C/EBP homologous protein), a transcription factor downstream of PERK-eIF2α-ATF4 pathway, is a key mediator of ER stress-induced apoptosis and is often used as a marker of maladaptive UPR activation (20).

The significant increase in GRP78 and CHOP mRNA levels observed following Cd administration is consistent with previous reports demonstrating Cd-induced ER stress in various tissues, including liver, kidney, brain, and testis (21, 22). Cd generates reactive oxygen species (ROS), disrupts calcium homeostasis, and impairs proteostasis, all of which contribute to ER dysfunction and cell death (22). These findings support the hypothesis that Cd triggers a shift from adaptive to apoptotic UPR signaling, leading to cellular injury.

Importantly, both curcumin and aerobic exercise were found to reduce the expression of GRP78 and CHOP in this model. Curcumin, a polyphenolic compound derived from Curcuma longa, has been extensively studied for its antioxidant, anti-inflammatory, and cytoprotective properties. Several studies have demonstrated that curcumin can mitigate ER stress by modulating UPR signaling pathways and reducing ROS production (23). For instance, in a study by Wang et al., curcumin was shown to attenuate tunicamycin-induced ER stress in hepatocytes by inhibiting the PERK-eIF2α-CHOP pathway (24). Similarly, curcumin reduced GRP78 and CHOP expression in models of myocardial ischemia-reperfusion injury and metabolic syndrome (25).

Aerobic exercise is another non-pharmacological strategy that exerts systemic protective effects through enhancement of antioxidant defense systems, improvement of mitochondrial function, and reduction of chronic inflammation—all of which contribute to reduced ER stress burden

(26). Physical activity has been shown to modulate UPR signaling and decrease GRP78 and CHOP expression in tissues affected by metabolic disorders and neurodegenerative diseases (27). For example, Liu et al. reported that regular aerobic exercise reduced ER stress and apoptosis in the hippocampus of rats exposed to chronic stress (28).

Notably, the combination of curcumin and aerobic training resulted in the most pronounced reduction in ER stress markers, suggesting a potential additive or synergistic effect. This observation aligns with previous findings showing that combining antioxidant supplementation with physical activity can amplify their individual benefits in models of oxidative and ER stress (29). In a study by Zhang et al., the combination of curcumin and exercise significantly downregulated ER stress-related genes and improved ovarian function in a polycystic ovary syndrome (PCOS) model (30). These combined interventions may target different but complementary pathways, such as enhancing proteostasis, improving mitochondrial function, and suppressing inflammatory mediators, thereby conferring greater resilience to cellular stressors.

Overall, the present findings underscore the pivotal role of ER stress in mediating Cd-induced toxicity and highlight the therapeutic potential of curcumin and aerobic training as protective strategies. While the current study focused on gene expression changes, future investigations should explore the downstream functional consequences of these molecular alterations, including protein-level validation, cellular apoptosis assays, and histopathological analysis. Additionally, dose-response relationships, timing of interventions, and long-term outcomes warrant further investigation.

While the present study provides valuable insights into the protective effects of aerobic exercise and curcumin on cadmium (Cd)-induced endoplasmic reticulum (ER) stress, several limitations should be acknowledged. First, the analysis was limited to the gene expression levels of GRP78 and CHOP, without corresponding assessment of protein expression or downstream signaling activity. Future studies should include Western blot or immunohistochemistry to confirm changes at the protein level and to better understand post-transcriptional regulation. Second, the study was conducted in an animal model, which, while useful for mechanistic exploration, may not fully replicate the complexity of human responses to Cd exposure and intervention. Translational studies in human populations are necessary to validate these findings. Third, the study focused primarily on ER stress pathways; other interconnected mechanisms such as mitochondrial dysfunction, inflammation, or autophagy were not evaluated and may also contribute to the observed outcomes. Additionally, the dosage and duration of curcumin supplementation and exercise intervention were fixed, and dose-response or time-course effects were not explored.

Conclusion

In conclusion, this study demonstrates that cadmium exposure significantly induces ER stress, as evidenced by increased expression of GRP78 and CHOP genes. Both curcumin supplementation and aerobic exercise, particularly when combined, attenuated these stress markers, indicating a potential protective role against Cd-induced cellular dysfunction. These findings highlight the therapeutic potential of non-pharmacological interventions in mitigating the harmful effects of environmental toxins. Future studies should expand upon these findings by including protein-level validation, exploring additional cellular pathways, and assessing long-term functional outcomes in both sexes and across various exposure models. Collectively, the data provide a promising foundation for further research into integrative strategies for reducing the burden of heavy metal toxicity and ER stress-related diseases.

Declarations

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of the Islamic Azad University, Ayatollah Amoli Branch, with the code IR.IAU.MAMOL.REC.1403.175.

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Authors' contributions

Concept/Design- A. Barari/ Sh. Alishan. Acquisition of Data- A. Abdi/ Sh. Alishan. Data Analysis/Interpretation- A. Barari. Drafting of the manuscript- A Barari/ Sh. Alishan/ A. Abdi. All authors approved the final version of the manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

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