ORIGINAL ARTICLE

HISTOPROTECTIVE EFFECTS OF COQ_{10} AGAINST VITAMIN D_3 INDUCED CARDIOTOXICITY IN ALBINO RATS

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ABSTRACT

Background: Vitamin D_3 toxicity is increasing due to its easy availability and unprescribed use of vitamin D_3 supplements. With the increasing awareness about vitamin D_3 deficiency and increase in number of prescriptions by physician without proper laboratory investigation may leads to increased risk of vitamin D_3 toxicity.

Objectives: To determine the toxic effects of Vitamin D_3 on cardiac muscles and to evaluate the cardioprotective effects of Coenzyme Q_{10} on Vitamin D_3 induced cardiotoxicity in albino rats.

Methodology: Animals were randomly divided into four groups with 10 animals in each group. Group I (Control), Group II (Vitamin D_3 at 2 mg/kg/day for 4 weeks), Group III (Vitamin D_3 + CoQ_{10} 10mg/kg/day simultaneously for 4 weeks) and Group IV (Vitamin D_3 for 2 weeks followed by CoQ_{10} 10mg/kg/day for 2 weeks). Histological features such as nuclear status, branching pattern, mononuclear infiltrates, calcium deposition and fibrosis in cardiomyocytes using hematoxylin-eosin, Masson's trichrome, and Von Kossa staining were studied.

Results: Group II showed significantly deranged cardiomyocyte architecture, fibrosis and calcification. Group III showed normal cardiomyocyte architecture. Group IV showed partial histological recovery, suggesting reduced efficacy with delayed intervention.

Conclusion: Combined use of Coenzyme Q_{10} and Vitamin D_3 prevented myocardial tissue injury, and ultimately maintaining proper functioning of cardiac tissue

Key words: cholecalciferol, cardioprotective, cardiotoxicity, Coenzyme Q10, Fibrosis, Calcification.

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INTRODUCTION

Vitamin D_3 (cholecalciferol) is a fat-soluble secosteroid hormone essential for calcium and phosphate metabolism, bone mineralization, and regulation of immune responses.[1] It plays a pivotal role in maintaining skeletal health and modulating various cellular functions. However, the increasing awareness of vitamin D_3 benefits, there has been a parallel rise in its unsupervised and excessive use. The easy availability and common practice of self-medication have significantly contributed to vitamin D_3 toxicity (VDT).[2,3] VDT leads to serious systemic consequences, most prominent effect is hypercalcemia, which promotes pathological calcification in soft tissues including the kidneys, blood vessels, and cardiac muscle.[4]

This situation is concerning regarding the global burden of cardiovascular diseases (CVDs), which remain the leading cause of death worldwide, responsible for

approximately 32% of all fatalities as of 2019.[5] Multiple factors such as oxidative stress, mitochondrial dysfunction, and chronic low-grade inflammation are recognized contributors to myocardial injury and progression of cardiac disease.[5] In experimental models, high doses of vitamin D_3 have been linked to myocardial hypertrophy, fibrosis, microcalcifications, and vascular calcification. These structural changes compromise cardiac function, increasing the risk of arrhythmias, heart failure, and sudden cardiac death.[6]

Regarding these concerns, there is growing scientific interest in identifying potential cardioprotective agents that can mitigate or reverse myocardial injury. One such promising agent is Coenzyme Q_{10} (CoQ_{10}), a naturally occurring lipophilic quinone that functions as a key component of the mitochondrial electron transport chain, facilitating ATP production.[8] CoQ_{10} is a powerful antioxidant that protects mitochondrial and cellular membranes by neutralizing reactive oxygen species (ROS).[9] Through antioxidative, anti-inflammatory, and membrane-stabilizing properties, CoQ_{10} has demonstrated protective effects in various cardiovascular conditions, including myocardial infarction, drug-induced cardiotoxicity and heart failure.[6,7]Given the increasing misuse of vitamin D_3 and potential to induce cardiac damage, it is critical to explore effective interventions. This study was designed to investigate whether CoQ_{10} supplementation can prevent or attenuate vitamin D_3-induced myocardial damage. This study will contribute to understanding the cardiotoxic risks associated with unregulated vitamin D_3 use and highlight the role of CoQ_{10} in cardioprotection. Ultimately, this study aims to raise awareness about the cautious and informed use of vitamin D_3 supplements, and to explore CoQ_{10} as a potential adjunct therapy in preventing vitamin D_3-induced cardiotoxicity.

METHODS

This controlled experimental study was conducted using forty healthy adult albino Wistar rats, aged 8–12 weeks and weighing between 150–200 g. The animals were procured from an accredited facility and housed under standardized laboratory conditions. Environmental conditions included a controlled temperature of 22 ± 2 °C, a 12-hour light/dark cycle, humidity (60± 5 %) and free access to commercially prepared food and water. Ethical approval for the study was obtained from the Institutional Review Board (IRB) of King Edward Medical University (Approval No. 475/RC/KEMU, dated 13/11/2023).

After a one-week acclimatization period, the animals were randomly assigned into four experimental groups (n = 10 per group). Throughout the study duration, the rats were monitored daily and remained healthy without any signs of distress or illness.

Group I (Control): Received distilled water (1 ml/day, orally) for four weeks.

Group II (Vitamin D_3): Received Vitamin D_3 at a dose of 2 mg/kg/day intraperitoneally for four weeks.

Group III (Vitamin D_3 + CoQ_{10}): Received Vitamin D_3 (2 mg/kg/day, intraperitoneally) and Coenzyme Q_{10} (10 mg/kg/day, orally) simultaneously for four weeks.

Group IV (Sequential Vitamin D_3 and CoQ_{10}): Received Vitamin D_3 (2 mg/kg/day, intraperitoneally) for the first two weeks, followed by Coenzyme Q_{10} (10 mg/kg/day, orally) for the subsequent two weeks.

At the end of the experimental period, all animals were euthanized under isoflurane anaesthesia. The hearts were carefully excised and fixed in 10% neutral buffered formalin. Standard histological procedures were followed for tissue processing, sectioning, and staining.

Hematoxylin and Eosin (H&E) Stain: Used for assessment of fragmented nucleus, cardiomyocyte branching pattern, and presence of mononuclear inflammatory infiltrates.

Von Kossa Stain: Utilized to detect calcium deposits as blackish spots. Calcification was scored on a scale of 0 to 3 (0 = no calcification; 1 = 1–2 fields; 2 = 3–6 fields; 3 = ≥7 fields of calcification).

Masson's Trichrome Stain: Applied to evaluate myocardial fibrosis. Fibrosis was semi-quantitatively graded as 0 (no fibrosis), 1+ (≤2 fields), 2+ (3–6 fields), and 3+ (≥60% of examined myocardium showing fibrosis).

RESULTS

Microscopic examination revealed histopathological changes across the experimental groups. In Group II, all 10 rats (100%) exhibited fragmented nuclei, whereas Group IV exhibited 7 rats (70%). No nuclear fragmentation was observed in Groups I and III. Altered branching patterns of cardiomyocytes were noted in all rats of Group II (100%) and in 3 rats (30%) of Group IV, while Groups I and III maintained normal morphology.

Inflammatory infiltrates were present in all Group II rats (100%) and in 2 rats (20%) of Group IV. Scattered calcification was observed in all Group II rats (100%), graded as score 3. In Group IV, 4 rats (40%) showed calcification in two fields (score 1), while 6 rats (60%) exhibited more extensive calcification (score 2).

Fibrosis was prominent in Group II, with all 10 rats (100%) displaying fibrosis across all examined fields, graded as score 3. In Group IV, 6 rats (60%) showed fibrosis in two fields (score 1), and the remaining 4 rats (40%) had fibrosis in 3 to 6 fields (score 2). No fibrosis was observed in Groups I and III.

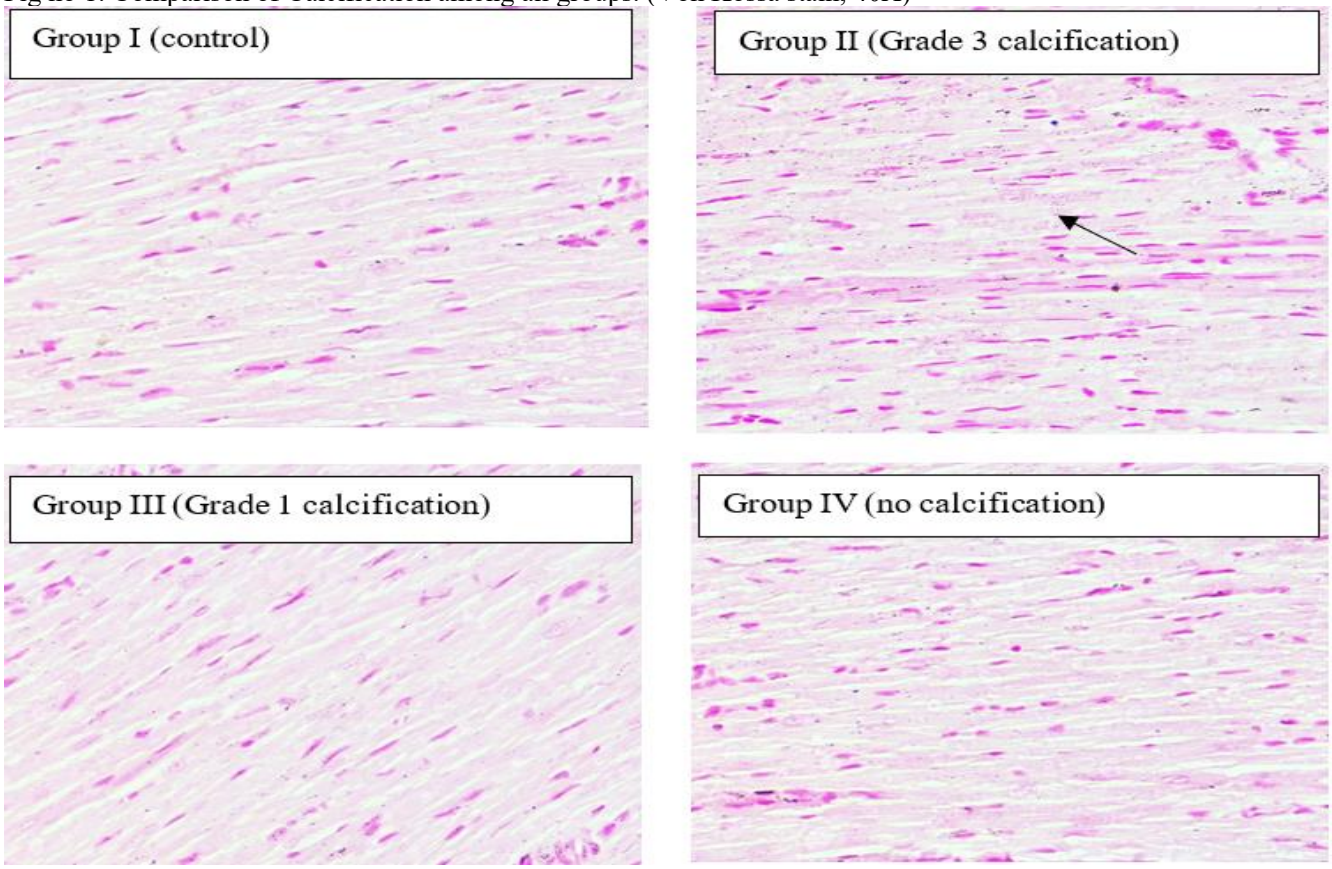
Table no.1: Comparison of branching patterns among groups.

Parameters	Group I	Group II	Group III	Group IV	p-value#
Altered Branching pattern of cardiomyocytes	0 (0.0%)	10 (100.0%)	0 (0.0%)	3 (30.0%)	< 0.001*
Fragmented nucleus	10 (100.0%)	0 (0.0%)	10 (100.0%)	7 (70.0%)	

Table no.2: Comparison of number of fields of calcification and fibrosis among groups

Variables	Group I	Group II	Group III	Group IV	p-value#
Number of Fields of Calcification	0.0 ± 0.0	5.6 ± 1.3	0.0 ± 0.0	3.1 ± 1.0	< 0.001*
Number of Fields of Fibrosis	0.0 ± 0.0	7.6 ± 0.8	0.0 ± 0.0	3.3 ± 0.9	< 0.001*

Fig no 1: Comparison of Calcification among all groups. (Von Kossa stain, 40X)



DISCUSSION

The toxic effects of Vitamin D_3 are known worldwide and they produce cardiotoxicity in both animals and human beings. Vitamin D_3 toxicity leading to cardiac tissue damage ultimately impeding the proper functioning of cardiomyocytes. Coenzyme Q_{10} a vital constituent of electron transport chain, source of synthesis of energy and exhibits antioxidant & anti-inflammatory properties, regresses the production of ROS & suppresses membrane lipid peroxidation & maintains normal architecture of cardiomyocyte[11]. This study was conducted to know the cardioprotective effects of coenzyme Q_{10} on cardiomyocyte on Vitamin D_3 induced cardiotoxicity.

The branching pattern of cardiomyocytes was studied and categorized into altered and non-altered among all the groups. The branching pattern of myocardial cells of Group I & III rats showed 10(100%) and group IV 7(70%) rats showed non altered pattern whereas Group II 10(100%) and Group IV 3(30%) revealed altered branching patterns. Elshama said et al. (2016) also showed comparable results in the study, VDT leads to altered branching patten of myocardial cells.[12] The nuclear status of myocardial cells of Group I & III 10(100%) and group IV 7(70%) showed

unfragmented nucleus whereas group II 10(100%) and group IV 3(30%) animals showed fragmented nucleus**.** Elshama said et al. (2016) also stated vitamin D_3 toxicity leading to cardiotoxicity and ultimately resulted in fragmentation of nucleus of myocardial cells.[12]

In Group I and III 0(0%) & group IV 8(80%) rats showed no inflammatory infiltrates, while 10(100%) rats in Group II & 2(20%) rats of Group IV had inflammatory infiltrate

The replacement of myocardial cells by connective tissue leading to fibrosis and damage to myocardium with calcification were shown among groups. All 10(100%) rats of group II showed fibrosis in all fields and graded as score 3 and in group IV 6(60%) rats showed 2 fields of fibrosis and graded as score 1 and 4(40%) showed 3 to 6 fields of fibrosis and graded as score 2. All rats 10(100%) of group I & III showed no field of fibrosis and graded as score 0.

All 10(100%) rats of group II showed scattered calcification in all fields and graded as score 3 and in group IV 4(40%) rats showed 2 fields of calcification and graded as score 1 and 6(60%) showed score 2 with 3 fields of calcification. All rats 10(100%) of group I & III showed no field of calcification and graded as score 0. Chavhan sambhaji et al. (2011) also showed similar results of VDT leading to calcification & fibrosis and damaging the myocardial cells. Kimura Tohru et al. (2021) also observed results in replacement of myocardial cells with connective tissue i.e. fibrosis and calcium deposition in myocardial tissue.

CONCLUSION

The study revealed that Coenzyme Q_{10} has strong cardioprotective effects on vitamin D_3 induced cardiotoxicity. Combined use of Coenzyme Q_{10} and Vitamin D_3 prevented myocardial tissue injury and ultimately maintaining proper functioning of cardiac tissue. It is therefore recommended that synergetic use of Coenzyme Q_{10} with Vitamin D_3 prophylactically and in management of Vitamin D_3 induced cardiotoxicity by physician.

ETHICAL APPROVAL

Ethical approval of article was granted by the Institutional Review Board of King Edward Medical University vide reference No 475/RC/EMU dated 13 November, 2023.

AUTHOR'S CONTRIBUTIONS

AF: Manuscript writing, data collection & analysis
FS: Conceived & designed, proof reading, final approval
SK: Conceived & designed, interpretation, proof reading
AR: Manuscript writing, data analysis
AH, SH: Data analysis & interpretation, critical review
All Authors: Approval of the final version of the manuscript to be published

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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