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# The role of coenzyme Q10 against myopathy induced by simvastatin in adult male albino rats

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## ABSTRACT

**Background:** Simvastatin (SIM) is one of the statin category that is used to lessen cholesterol. One of the most common side effects of SIM is myopathy. Coenzyme Q10 (CoQ10) is an antioxidant and biochemical cofactor produced naturally by the mitochondria of nearly all body cells especially in organs with high energy demand as muscles.
**Aim:** This study targeted to evaluate the role of CoQ10 to improve the myopathy effect of SIM.
**Material and Methods:** This study included 70 adult male albino rats divided into 4 groups; each subgroup was composed of ten rats, and received the drug diluted in distilled water via a gastric tube; Control group: received a daily dosage of common food and water. Myopathy group: Included two subgroups; SIM I: received 10 mg/kg/day of SIM for 4 weeks and SIM II; received 10mg/kg/day of SIM for 12 weeks. Treated group; subdivided in to two subgroups; SIMI+CoQ10; administered 10 mg/kg/day of SIM with10mg/kg/day of CoQ10 for 4 weeks and SIMII+CoQ10; received 10mg/kg/day of SIM and 10mg/kg/day of CoQ10 for 12 weeks. Recovery group; include two subgroups; RI; received 10mg/kg /day of SIM for 4 weeks, followed by another 4weeks of stopping drug administration, RII; received 10mg/kg/day of SIM for 12 weeks, followed by another 12 weeks stop of drug administration. At the end of the experiment, the body and muscle weights were measured, Blood samples were taken from retro venous plexus for biochemical analysis and muscular specimens of gastrocnemius muscle were dissected for microscopic studies.
**Results:** The myopathy group showed a significant decrease in the body and muscle weights with elevation in the level of CK with muscle fiber degeneration and inflammatory cells infiltration especially in groups of SIM II than SIM I. Compared with control group, there was a significant increase in area fraction of caspase3 positive reaction. In contrast the treated groups showed a significant increase in body and muscle weight with decrease in CK level, with upturn in architecture of the muscle tissue, as there was a significant decrease in area fraction of caspase reaction more than the withdrawal group.
**Conclusion:** Degenerative changes that induced by SIM can be improved by CoQ10 administration.

**KEYWORDS**: CoQ10, myopathy, SIM, CK, caspase.

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## INTRODUCTION

Skeletal muscle is the most common type of muscle in vertebrates out of the three types found in the body. It is voluntarily manipulated, unlike cardiac and smooth muscle. It is striated, and has an individual appearance due to its long, thin, multinucleated fibres with fine red and white lines frequently cross [1]

Myopathy is a disease that affect the structure and function of the skeletal muscles [2]. Acquired myopathy has many different causes, including metabolic, endocrine, and induced by certain drugs as statins. Simvastatin (SIM) is one of statins and is used to diminish the levels of blood cholesterol through inhibition of HMG CoA reductase [3], so the use of statin has increased as a result. One of the side effects of SIM is myopathy [4], which is characterized by muscle discomfort and weakness [5].

Coenzyme $Q_{10}$ ($CoQ_{10}$) is essential for development and protection of cells. It is an antioxidant and biochemical cofactor produced naturally by the mitochondria of nearly all body cells especially in organs with high energy demand as heart and muscles, its levels have been found to be lower in people who taking statins. However, the amount of $CoQ_{10}$ in the food sources is insufficient to significantly increase the bodies' levels of the nutrient, so the exogenous $CoQ_{10}$ may be able to lessen side effects that some drugs may occasionally produce [6].

## MATERIAL AND METHODS

### Experimental Animals

This experiment was carried out at Faculty of medicine, Minia University, Egypt. Before any animal handling was carried out, the ethical committee at Minia University was obtained (Approval No.499/2022 ). Seventy adult male albino rats were used. They were 7 to 8 weeks old and weighing between 150-200 gm. They were purchased from the laboratory animal unit at Minia university. The animals were accommodated in hygienic well ventilated plastic cages with regular light and dark cycles. Before the trial began, the animals were allowed to familiarize for aweek and were provided with usual admission to food and water.

**Chemicals compounds**
SIM was obtained from Merck Co., Egypt in the form of (Zocor 10mg). $CoQ_{10}$ were purchased from Pharma City Co., Egypt in the form of capsules(25mg). Commercially available colorimetric assay kits for Creatine kinase isoenzyme (CK-MM) were bought from Biomed Co., Egypt.

**Experimental design**
After the acclimatization period, rats were haphazardly divided into 4 groups :
Control group (C): 10 rats received a daily dosage of distilled water that was equal to the dose given to the other groups.
Myopathy group: it includes two subgroups
A-(SIMI): 10 rats received 10 mg/kg/day of SIM diluted in distilled water via a gastric tube for 4 weeks [7].
B-(SIMII): 10 rats received 10mg/kg/day of SIM diluted in distilled water via gastric tube for a duration of 12 weeks .
Treated groups: it includes two subgroups
A-(SIMI+$coQ_{10}$):10 rats administered 10mg/kg/day of SIM along with10mg/kg/day of $coQ_{10}$ [8] which was dissolved in distilled water via a gastric tube, for 4 weeks.
B-(SIMII+$coQ_{10}$): 10 rats received 10mg/kg /day of SIM and 10mg/kg /day of $coQ_{10}$, diluted in distilled water, via a gastric tube for 12 weeks.
Withdrawal group: it includes two subgroups
A-(RI): 10 rats administered 10mg/kg /day of SIM via a stomach tube dissolved in distilled water for 4 weeks, after which the drug was stopped for a another 4 weeks.
B-(RII): 10 rats administered 10mg/kg /day of SIM diluted in distilled water via gastric tube for 12 weeks, followed by another 12 weeks stopping of drug administration.

At the end of the study for each group, rat's weights were recorded, blood samples were drawn from retro venous plexus, then subjected for centrifugation process for biochemical analysis. Later rats were decapitated using halothane. Specimens of gastrocnemius were rapidly removed , recorded weights for each and carefully dissected for tissue preparation. Muscle samples were rinsed in normal saline was then some quickly fixed in 10% formalin solution for 48 hours and the other fixed in glutaraldehyde solution. Following this, the samples were processed to create paraffin slices for the histological and immunohistochemical and ultrastructure examination.

## METHODS USED FOR THE EXPERIMENT

**I-Biochemical Analysis:**
Measurement of rat creatine kinase isoenzyme (CK-MM) activity [9]

**II-Histological study**:
Specimens of rat's gastrocnemius muscle were collected then fixed in 10% formaline saline, dehydrated in ascending grades of ethyl alcohol, cleared in xylene, impregnated in soft paraffin followed by hard paraffin, and sectioned in 5-µm-thickness. Sections were stained with Hematoxylin and Eosin [10] for general structure of the skeletal muscle.

**III-Immunohistochemical study**: using the anti caspase-3 antibody [11] (AB clonal, Egypt), it is a mouse poly clonal antibody for detection of apoptosis expressed in cytoplasm of degenerated skeletal muscles.

**IV- Transmission electron microscopy for ultrastructure sections [12]**.

**V- Morphometric study:** The morphometric evaluation was performed for all groups.

**Morphometric Analysis of Muscle Fiber Degeneration**.
Morphometric assessment of muscle fiber degeneration was conducted using Fiji Image J software. High-resolution photomicro-graphs were captured from H&E-stained muscle sections at standardized magnifications. Degenerated muscle fibers were identified based on histological features such as cytoplasmic fragmentation, loss of striation, and infiltration of inflammatory cells.

**Caspase3 immunopositivity:** Image J software was used to measure area fraction in a standard measuring frame using a magnification X400 by light microscopy transferred to the monitored screen. Regardless of the staining intensity, areas with positively immunostained tissues were used for evaluation.

**VI- Statistical analysis:**
Graph pad prism was used to assess the quantitative data (version 7.01 for windows) Graph Pad Software, San Diego, Californea, USA. For the parameters of each group the mean and standard deviation (SD) were determined. The biochemical parameters were analyzed using the One Way Anova test followed by the Tukey-kramar post hoc for multiple comparisons between the

groups. The student T- test was used to determine if the significant difference between each pair of groups. Statistics were deemed significant when p value of less than 0.05 .

## RESULTS

**I-Biochemical results**

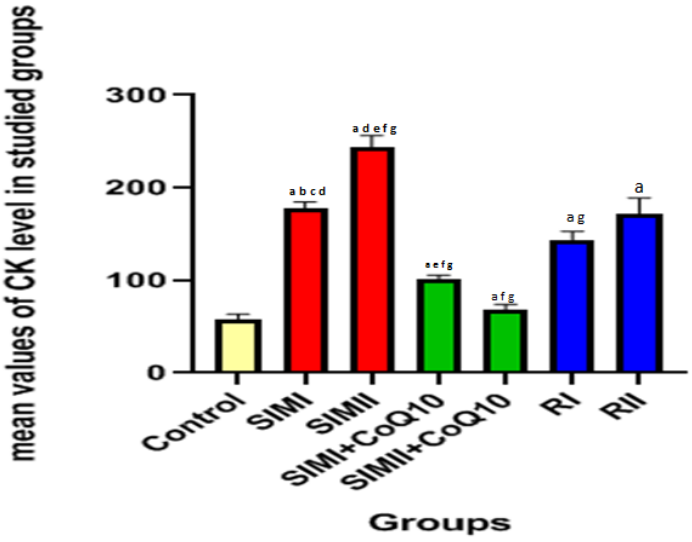
Statistical analysis of CK level among groups showed that, the myopathy and withdrawal groups showed a significant increase compared to the control group. While treated groups showed a significant decrease compared to the myopathy and withdrawal groups .

When CK levels were evaluated statistically between groups, it was discovered that myopathy group mean values were significantly higher than of those control groups($p<0.001$).The treated groups had a significant increase of mean values compared to the control groups and a significant decrease compared to the myopathy groups (both $P<0.05$).In comparison to the control group, the treated groups, myopathy groups and Withdrawal groups displaced a substantial rise and a significant decrease respectively ($P <0.0001$). Comparing the treated groups there was a significant difference between one and three months groups ($P<0.0001$)**(Table1, bar chart 1**).

**Table( 1): The Mean values of CK in studied groups(IU/l)**

| Groups | Mean± SEM | P value* |
|---|---|---|
| **Control** | **58.05±1.700** | |
| **SIMI** | **177.7±.2.194** | $<0.0001^{a\,b\,c\,d\,e\,f*}$ $0.8055^{g*}$ |
| **SIMII** | **243.5±3.988** | $<0.0001^{a\,d\,e\,f\,g*}$ |
| **SIM1+CoQ10** | **101.5±1.348** | $<0.0001^{a\,e\,f\,g*}$ |
| **SIMII+CoQ10** | **68.27±1.837** | $<0.0001^{f\,g*}$ $0.2389^{a*}$ |
| **RI** | **144.0±2.821** | $<0.0001^{a\,g*}$ |
| **RII** | **171.6±5.443** | $<0.0001^{a*}$ |

***p value<0.05 is significant.**




**Bar chart (1): The mean values of CK studied groups(IU/l).**

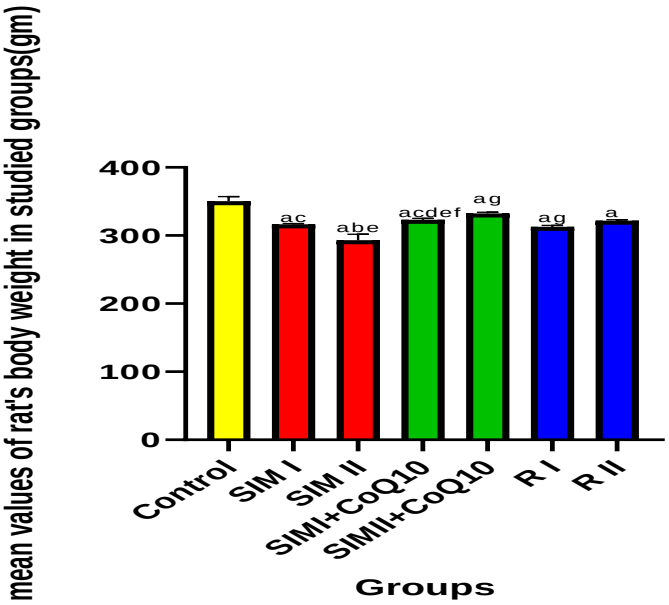
**II-Body and muscle weight assessment:**

By comparing the body weight between studied groups, it was found non-significant difference in between groups regarding the initial body weight($P>0.05$).On the other hand there was a significant difference in between groups regarding the final body weight, muscle weight and percentage of change in weight($p<0.01$).As the final body and muscle weight were significant higher among treated groups specially SIMII+$CoQ_{10}$. The myopathy groups and withdrawal groups showed a significant decrease in body and muscle weight compared to control group. The reduction in body and muscle weight was more than other groups in SIMII group that had simvastatin for 12 weeks **(Tables 2,3,bar charts 2,3).**

**Table (2) :The mean values of rat body weight in studied groups.**

| Groups | Mean± SEM | P value* |
|---|---|---|
| Control | 350.7±2.074 | |
| SIMI | 316.4± 0.3549 | <0.0001[a*] |
| SIMII | 293.5±2.788 | <0.0001[a b c d *]<br>0.0074[e*] |
| SIMI+CoQ10 | 323.2±0.702 | <0.0001[a b c d f*] |
| SIMII+CoQ10 | 332.4±0.7026 | <0.0001[a]<br>0.0201[g*] |
| RI | 312.8±0.6305 | <0.0001[a*]<br>0.0017[g*] |
| RII | 321.7±0.3959 | <0.0001[a*] |

***p value<0.05 is significant.**



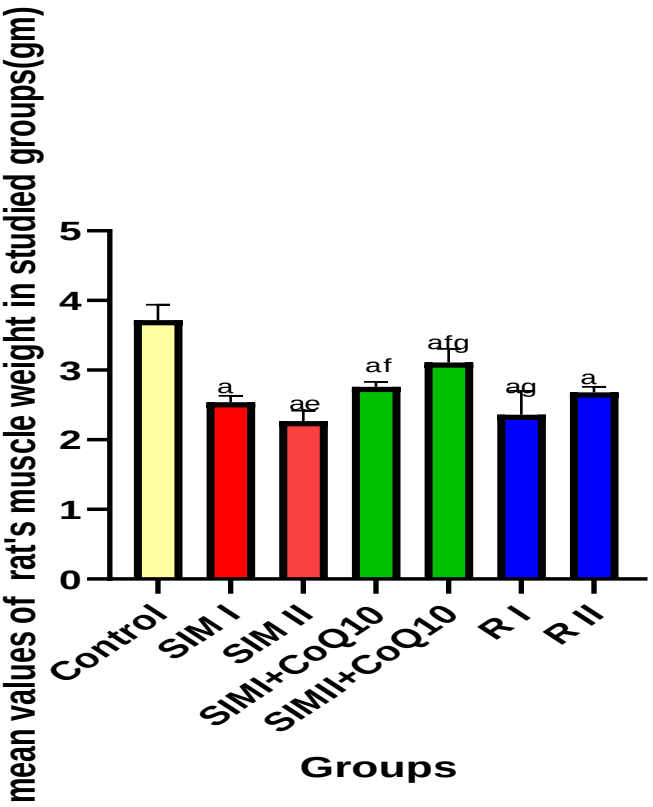

**Bar chart(2):The mean values of rat's body weight in studied groups.**

**Table(3) : The mean values of rat muscle weight in studied groups.**

| Groups | Mean± SEM | P value* |
|---|---|---|
| Control | 3.720±0.06960 | |
| SIMI | 2.539±0.02961 | <0.0001[a] |
| SIMII | 2.270±0.02267 | <0.0001[a e*] |
| SIMI+CoQ10 | 2.760±0.02211 | <0.0001[a f*] |
| SIMII+CoQ10 | 3.109±0.03695 | <0.0001[a f*] |

| | | |
|---|---|---|
| | | **$0.0201^{g*}$** |
| **RI** | **2.360±0.1087** | **$<0.0001^{a*}$**<br>**$0.0017^{g*}$** |
| **RII** | **2.680±0.0249** | **$<0.0001^{a*}$** |

***p value<0.05 is significant.**




**Bar chart(3): The mean values of rat's muscle weight in studied groups.**

**Histological results**

**In TS of Hematoxylin and Eosin staining,** the skeletal muscle fibers of the control group, had acidophilic sarcoplasm with marginal located nuclei and polygonal appearances. The perimysium is a sheath made of connective tissue enveloped each muscle bundle. Endomysium surrounded every muscle fiber (Figure1 A ).

SIM I group, showed dilated perimysium, several muscle fibers lost their polygonal form and became rounder, some fibers were atrophied and others were splitted, nerve trunk with inflammatory cells and congested blood vessel and instead of appearing to be in the periphery, their nuclei were rounded in the center ( Figure 1B). In group SIM II, The fiber size was not uniform, a large percentage of them seemed lacked clear boundaries. Several expanded fibers displayed split appearances, while others displayed cytoplasmic fragmentation with abnormal central myonuclei with congested blood vessels and inflammatory infiltration (Figure 1C) .

The group of SIMI + $CoQ_{10}$ showed; peripherally arranged of internal nuclei with preserved of endomysium and slightly dilated perimysium, restoration of striation and polygonal appearance of many muscle fibers and limited splitting of muscle fibers, (Figure 1D).

The group SIMII+ $CoQ_{10}$, showed marked decreased splitting of muscle fiber, renovation of polygonal shape in the majority of myofiberes, peripherally arranged of internal nuclei with preserved of endomysium and nearly normal perimysium, less congested blood vessels in between and marked decrease in the inflammatory infiltration (Figures 1E).

RI group showed still presence of splitting of muscle fiber, restoration of polygonal shape of some muscle, peripherally arranged of flat internal nuclei, slightly decreased of inflammatory infiltration (Figure 1F).

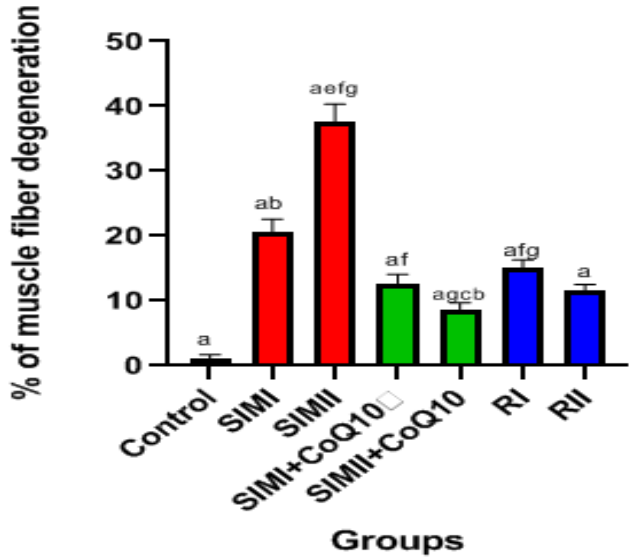
RII group showed decreased splitting of muscle fiber, restoration of polygonal shape in most muscle fibers, peripherally arranged

of flat internal nuclei with intact endomysium and perimysium, decreased of inflammatory infiltration (Figure 1G).

**Table (4) The mean values of muscle fiber degeneration among studiedgroups.**

| Groups | Mean± SEM | P value* |
|---|---|---|
| **Control** | **1.2±0.5** | |
| **SIMI** | **20.5±2.1** | $<0.0001^{a*}$ |
| **SIMII** | **37.6±2.7** | $<0.0001^{aefg*}$ |
| **SIMI+CoQ10** | **12.7±1.4** | $<0.003^{af*}$ |
| **SIMII+CoQ10** | **8.7±1** | $<0.62^{agcb}$ |
| **RI** | **15±1.3** | $<0.015^{afg*}$ |
| **RII** | **11.6±0.9** | $<0.009^{a*}$ |

***p value<0.05 is significant.**




**Bar chart(4): The mean values of muscle fiber degeneration amongstudied groups.**

Sections in (Figure 2A) containing skeletal muscle tissue were generated for the negative control as it showed no obvious immunoliablity for anticaspase3 in cytoplasm For activated caspase 3.

It was evident that SIMI group had rounded muscle fibers, cytoplasm had a high level of antibody for activated caspase 3, some immunopositive muscle fibers broke, and some nuclei and fibers had positive staining ,as seen in Figure (2B).

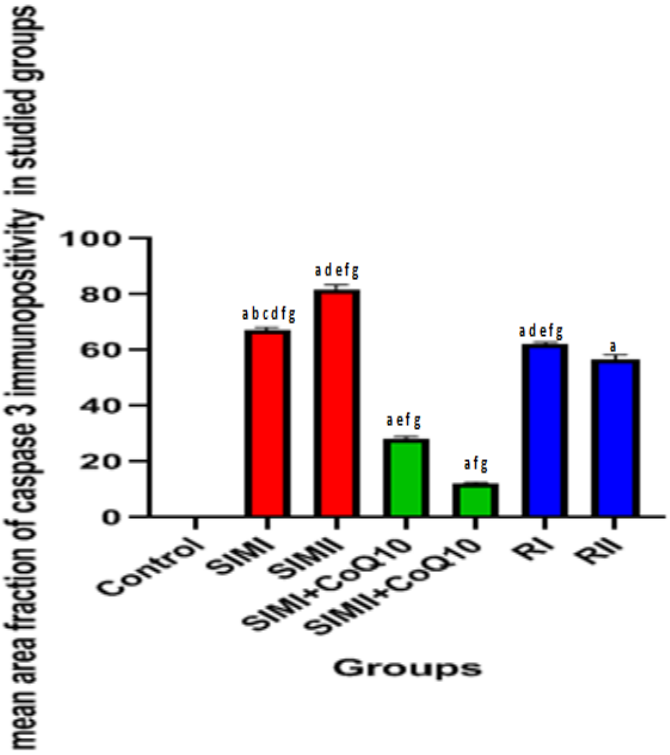
Positive nuclear and cytoplasmic expression was seen in the majority of muscle fibers in SIMII group(Figure 2C). Muscle fibers with negative immunoreactivity were rare. Figure (2D) of SIMI+ $CoQ_{10}$ showed decrease positive immunoreactivity in some of the cytoplasm of the muscle fibers but still at the periphery, while Figure(2E) of SIMII+ $CoQ_{10}$ demonstrates negative immunoreactivity of the majority of the cytoplasm of the muscle fibers and their peripheral nuclei with preserved architecture of the muscle fiber of the treated groups respectively as the control group. Figure(2F) showed mild decrease in positive immunoreactivity in the cytoplasm of some of muscle fibers of RI group and increased in other fibers to give patchy appearance. Figure(2G) showed moderate decrease in positive immunoreactivity in the cytoplasm of all of muscle fibers of RII group. They demonstrates negative immunoreactivity of peripheral flat nuclei.

**Table (5): The Mean area fraction of caspase 3 immunopositivity in studied groups.**

| Groups | Mean± SEM | P value* |
|---|---|---|
| **Control** | **0.2360± 0.02320** | |
| **SIMI** | **67.33± 0.8941** | $<0.0001^{a\,b\,c\,d\,e\,g*}$ $0.0452^{f*}$ |
| **SIMII** | **81.50± 2.040** | $<0.0001^{a\,d\,e\,f\,g*}$ |
| **SIMI+CoQ10** | **28.26 ± 0.8425** | $<0.0001^{a\,e\,f\,g*}$ |
| **SIMII+CoQ10** | **12.06 ± 0.5639** | $<0.0001^{a\,f\,g*}$ |

| | | |
|---|---|---|
| **RI** | **62.00± 0.8422** | $<0.0001^{a\ b\ c\ d\ e\ f*}$ $0.0369^{g*}$ |
| **RII** | **56.55 ± 1.928** | $<0.0001^{a*}$ |

***p value<0.05 is significant.**




**Bar chart (5): The mean area fraction of caspase 3 immunopositivity studied groups.**

In the ultrastructure results, The section of the control group displayed a peripheral oval euchromatic nucleus with indentation of the nuclear envelope and regular arrangement of myofibrils forming sarcomere with alternative dark and light bands bisected by Z lines. Mitochondria present at the periphery of the fibers, There is multiple glycogen granules arranged in between the myofibrils as in Figure (3A) .

SIMI group of showed wide spaces between myofibrils, mitochondria with destroyed cristae and the nucleus with peripheral chromatin condensation as in Figure (3B).

SIMII group observed vaculations with increased intermyofibrillar space and localized areas of myofibrillar loss and swollen mitochondria are observed and the heterochromatic, oval nucleus with disruption of the nuclear membrane as in Figure (3C).

SIMI+$CoQ_{10}$ group viewed intact myofibirils, oval to spindle shape nucleus beneath nuclear membrane, mitochondria lies between myofibrils with preserved cristae. There is multiple glycogen granules arranged at side of the nucleus as in Figure (3D). SIMII+$CoQ_{10}$ group displayed intact myofibirils, oval nucleus beneath regular nuclear membrane, normal mitochondria between myofibrils with preserved cristae similar to control as in Figure (3E). R1, R3 groups showing intact myofibirils, oval nucleus beneath regular nuclear membrane and intact endomysium as in Figures (3F,G).

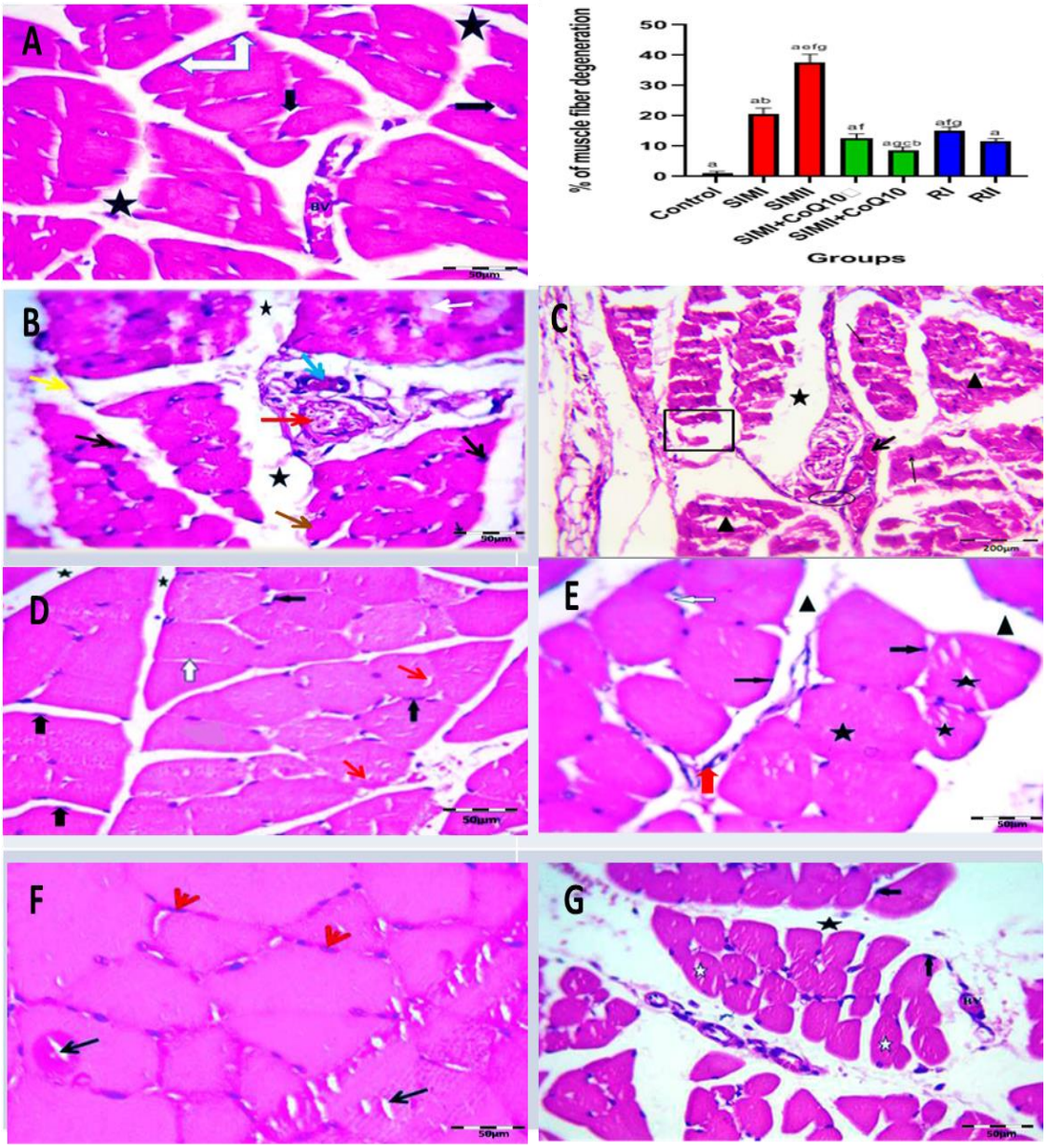



Figure 1: Representative photomicrographs of TS section in rat's skeletal muscle tissue from (A)control group's rat show displaying polygonally muscle fibers with acidophilic cytoplasm and nuclei lie peripherally (head of arrow). The endomysium (arrow). The perimysium between the muscle bundles(star) and blood vessels (BV).(B) SIMI group showing dilated perimysium(star) and damage of some muscle fibers(white arrow), some muscle fibers have rounded nuclei(black arrow), shrinkage of some myofiber (brown arrow),collagen fibers (yellow arrow),nerve trunk with inflammatory cells (red arrow) and congested blood vessel(blue arrow). (C)SIMII group demonstrating fragmentation of cytoplasm (head arrow). See how some muscle fibers have abnormal, central myonuclei(thin arrow arrow), degeneration of some myofibers (square), with inflammatory cells, (circles) congested blood vessels(thick arrow) and widening of C.T (star). (D)SIMI + CoQ10 group showing decreased splitting of some muscle fiber (red arrow), peripherally arranged of internal nuclei ( black arrow) with preserved of endomysium (white arrow)and perimysium (star). (E) photomicrograph of rat's skeletal muscle TS of SIMII+CoQ10 group showing restoration of polygonal shape of most muscle fibers, decreased splitting of muscle fiber (star), peripherally arranged of internal nuclei (black arrow), with intact of endomysium (white arrow) and slightly normal perimysium(head of arrow), decrease in inflammatory cells(red arrow). (F) RI group showing restoration of polygonal shape of some muscle fibers, splitting of some muscle fiber (black arrow), peripherally arranged of internal nuclei ( red arrow). (G) RII group showing decreased splitting of muscle fiber(white star), peripherally arranged of internal nuclei(black arrow) with preserved of endomysium and perimysium (black star), see blood vessels in between (BV) (H&EX 400, scale bar 50µm) with bar chart of the mean values of muscle fiber degeneration among studied groups

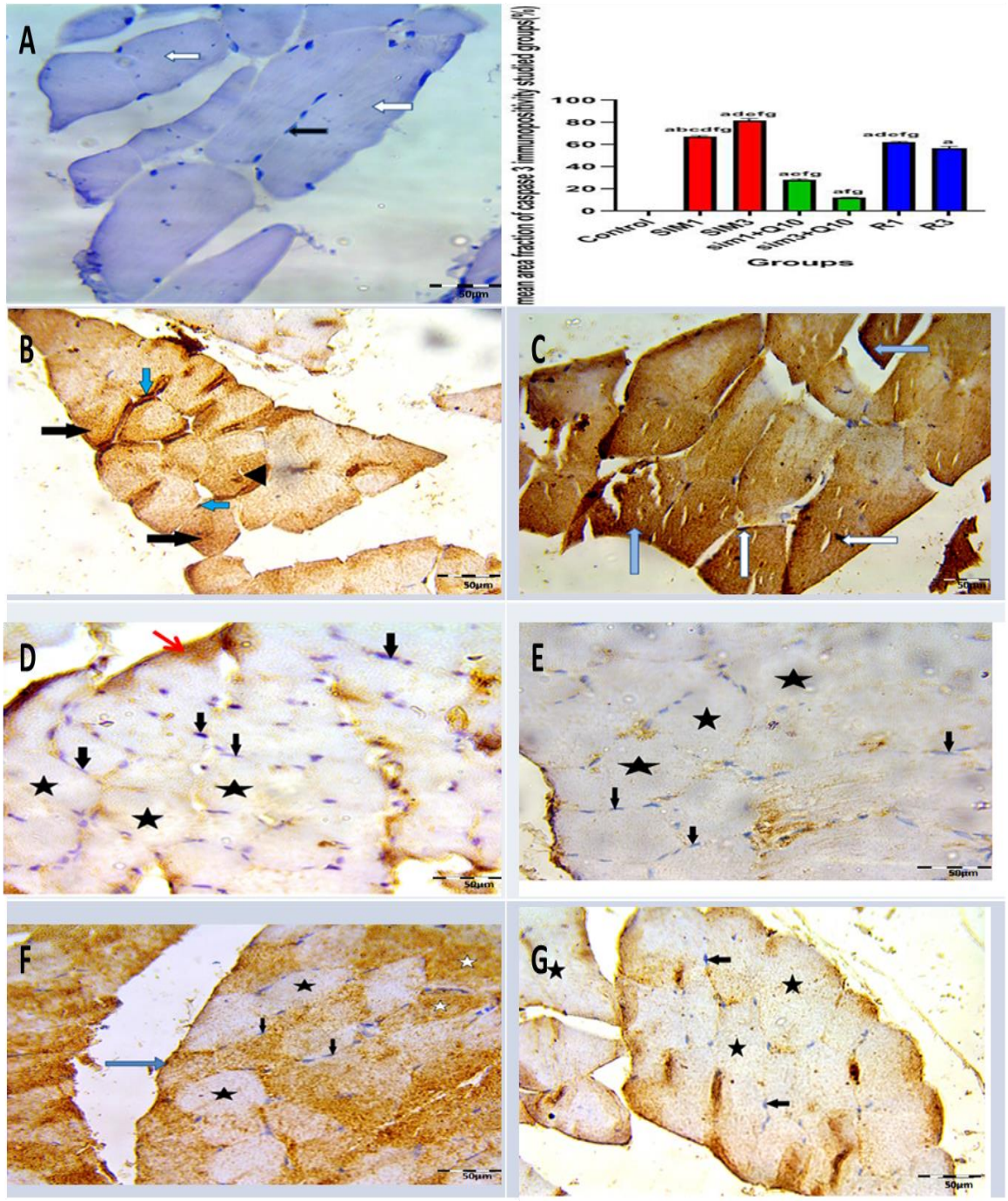



Figure 2: Representative photomicrographs of TS section in rat's skeletal muscle tissue from (A) control group immunolabelled for activated caspase 3, revealing negative immunoreactivity in the muscle fibers(white arrow), and negative immunoreactivity in the nuclei(black arrow).(B) SIMI group immunolabelled for activated caspase 3, (black arrow) indicates that certain rounded muscle fibers have mild positive immunoreactivity in their cytoplasm and (arrow head), some nuclei have positive immunoreactivity (bluearrow). (C) SIMII group immunolabelled for activated caspase 3, (blue arrow) indicates that tissue exhibits positive immunoreactivity in the cytoplasm of the majority of muscle fibers, with positive immunoreactivity at the nuclei (white arrow). (D) SIMI+ CoQ10 group immunolabelled for activated caspase 3, (star) shows negative immunoreactivity in the cytoplasm of most of muscle fibers but still positive at peripheral (red arrow). (Black arrow) demonstrates negative immunoreactivity of peripheral flat nuclei. (E) SIMII+ CoQ10 group immunolabelled for activated caspase 3, (star) shows negative immunoreactivity in the cytoplasm of all of muscle fibers and nuclei as control group(Black arrow) demonstrates negative immunoreactivity of peripheral flat nuclei .(F) RI group immunolabelled for activated caspase 3 , (black star) shows mild decrease positive immunoreactivity in the cytoplasm of some of muscle fibers and (white star) shows increase in immunoreactivity in the cytoplasm of other of muscle fibers to give patchy appearance.(Black arrow) demonstrates negative immunoreactivity of some peripheral nuclei, and positive immunoreactivity of some peripheral nuclei (blue arrow). (G) RII group immunolabelled for activated caspase 3, (star) shows moderate decrease positive immunoreactivity in the cytoplasm of majority of muscle fibers. (Black arrow) demonstrates negative immunoreactivity of peripheral nuclei (immunohistochemistry for activated caspase3 x400, scale bar 50µm).bar chart of the mean area fraction of caspase 3 immunopositivity studied groups.

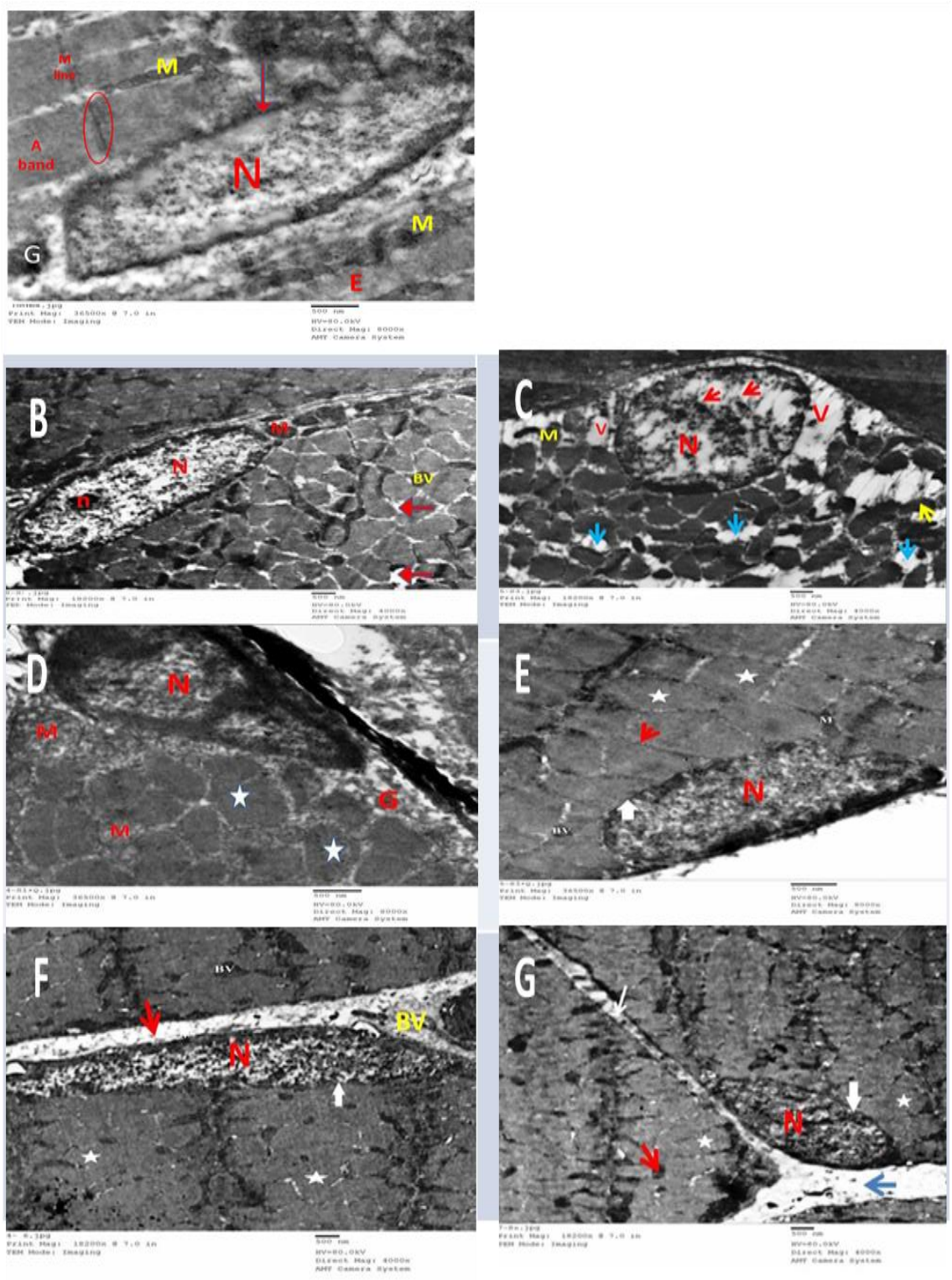



Figure 3: Representative photomicrographs of Ultrastructure section in rat's skeletal muscle tissue from (A) control group showing myofibrils forming (A band), H band(oval shape) with (M line). Note a peripheral oval euchromatic nucleus(N) beneath the sarcolemma(red arrow) below the endomysium(E). Mitochondria (M) present at the periphery of the fibers. There is multiple glycogen granules (G) arranged near to the nucleus(TEM; X 8,000).(B) SIMI group showing wide spaces between myofibrils (Red arrow), congested blood vessels (BV) and mitochondria with destroyed cristae (M). Note the nucleus (N) with prominent nucleolus(n)( TEM;X4,000).(C) SIMII group showing vaculations(V)with increased inter myofibrillar space (Blue arrow) and localized areas of myofibrillar atrophy (yellow arrow). Note the rounded heterochromatic nucleus (N) with disruption of the chromatin( red arrow) and swollen mitochondria(M)(TEM; X4000). (D) SIMI+ CoQ10 group showing intact myofibirils (star), oval to spindle shape nucleus (N) beneath nuclear membrane. Insets of mitochondria between myofibrils (M) with preserved cristae. There is multiple glycogen granules (G) arranged at side of the nucleus(TEM;X8,000). (E)SIMII+CoQ10 group showing intact myofibirils (star), oval nucleus (N) beneath regular nuclear membrane(arrow). Intact blood vessel inbetween

myofibrils(BV), mitochondria between myofibrils (M) with preserved cristae and normal intermyofibrillar spaces(red arrow) similar to control(TEM; X 8,000).(F) RI group showing intact myofibirils (star), oval nucleus (N) beneath regular nuclear membrane (white arrow)and nearly intact endomysium (red arrow) with less congested blood vessel(BV)( TEM; X 4,000). (G) RII group showing intact myofibirils (star) with nearly normal blood vessels in between(red arrow), oval nucleus (N) beneath regular nuclear membrane (thick white arrow), intact endomysium (thin white arrow) and perimysium(blue arrow) (TEM; X 4,000).

## DISCUSSION

Myopathy refers to a group of muscle disorders characterized by muscle weakness due to structural or metabolic dysfunction. It can be caused by, inflammatory conditions, metabolic imbalances, or drug induced effects such as statin associated myopathy. Symptoms vary but often include progressive weakness, muscle pain, and fatigue [13].

SIM is a statin medication widely suggested to lower low-density lipoprotein (LDL) cholesterol, thereby reducing the risk of cardiovascular diseases. However, its use has been associated with muscle related adverse effects, collectively known as statin-associated muscle symptoms [14].

CoQ10 is a naturally occurring compound that plays a crucial role in cellular energy production and functions as a potent antioxidant. It is essential for the synthesis of adenosine triphosphate (ATP), the primary energy currency of cells, and helps protect cells from oxidative damage [15] .

The primary objective of this research was to evaluate the possible protective effect of CoQ10 for induced myopathy by SIM. This study looked at the body and muscle weight changes before and at the end of the study. When compared to the control group, it showed a statistically significant decrease in the mean values in myopathy group (SIMI, SIMII)and withdrawal group (RI, RII). This allied with the findings of [16] as it was reported that the muscle weight to body weight ratio was significantly reduced in SIM treated animals. This weight loss might result from damage of the muscle fibers with subsequent protein degradation, denaturation or the use of the stored fat in the muscle as an energy source.

This results conflict with [17] who reported that SIM decrease leptin hormone that is responsible for sense of fullness and this leads to marked increase in body weight.

Treated group (SIMI+CoQ10, SIMII+CoQ10) showed marked increase in the mean value of body and muscle weight compared to myopathy group. This was in aligned to [18] who reported that CoQ10 is crucial for efficiently transferring electrons within the mitochondrial oxidative respiratory chain and producing ATP.

This disagree with [19] who stated that CoQ10 supplementation has not been shown to significantly impact body weight or muscle mass. This lack of effect may be due to CoQ10 's primary role in energy metabolism and oxidative stress reduction, rather than directly influencing muscle hypertrophy or adipose tissue accumulation. Additionally, research indicates that while CoQ10 may enhance exercise performance and reduce muscle fatigue, it does not lead to increases in muscle mass.

The withdrawal group (RI, RII) showed improvement in body and muscle weight, this agree with [20] who reported that statins can influence metabolism, potentially increasing appetite and caloric intake. After discontinuation, these effects might persist for a while, contributing to weight gain and the muscle function may improve, leading to increased physical activity and muscle mass, which could reflect as weight gain on the scale.

The current study also looked at serum levels of CK, a biochemical marker for muscle injury and a helper in the synthesis of energy in skeletal muscle [21].

When compared to the control group, it showed a statistically significant rise in the mean values in groups SIMI, SIMII, RI and RII. This aligned with the findings of [22] who provided an explanation for this discovery, stating that statins lead to sarcolemma degradation, which causes CK to leak out of the muscle cytosol, reducing the muscle's capacity to produce ATP and weakening the stability of contractile filaments.

According to [23] who informed that supra-physiologic levels of CoQ10 maintain the function of injured mitochondria and rectify probable tissue CoQ10 deficiencies, which explains why treated group exhibited a considerable decrease in serum CK compared to myopathy group.

In the current study, by using haematoxylin and eosin(H&E) staining, the control group exhibited to be polygonal appearance with acidophilic sarcoplasm in TS. It had elongated, vesicular nuclei that peripherally were sited immediately below the sarcolemma, this in agree with [24].

According to the myopathy group; SIMI group described segmental muscle fiber degeneration, losing their striations, some muscle fibers split and central rounded nucleus. SIMII showed wavy appearance of all muscle fibers, fragmentation of the sarcoplasm, congested blood vessels, with marked inflammatory cellular infiltration and disfigured of muscle spindle. These findings were confirmed by [25] who stated that the lack of oxygen and metabolite exchange to the larger and hypertrophied fibers may have caused the muscle fibers to split, moving their nuclei to the center of the fibers.

On the other hand [26] who found no significant independent associations between statin use and adverse muscle outcomes. the authors concluded that the observed muscle related adverse phenotypes in statin users might be attributed to age rather than the medication itself.

According to treated group, it demonstrated that using CoQ10 had a protective effect against myotoxicty caused by simvastatin. The results showed that the muscle fibers' striations had returned, that their splitting had been limited, and that the internal nuclei of the satellite cells and fibroblasts were arranged peripherally with the endomysium and perimysium preserved to be nearly similar to control group especially in SIMII + CoQ10. This was in line with studies by [15] who reported that CoQ10 supported cellular bioenergetics by acting as a cofactor of mitochondrial respiratory complexes, as it had antioxidant properties that function as a radical scavenger and collectively assist the cellular antioxidant network. It had a role in regulating gene expression, mitochondrial function, and signaling, which had a significant effects for the aging process and cell death.

This contradicts with [27] who conveyed that CoQ10 supplements do not help patients who have previously experienced statin-associated muscle complaints continue on statin therapy or lessen the level of plasma CK. Considering that during the trial, CK was substantially below clinical values of clinical concern and did not vary between groups or after withdrawal of statin.

Withdrawal group demonstrated slightly return of muscle fibers to their polygonal shape, a reduction in muscle fiber splitting, peripherally arranged internal nuclei, and intact endomysium and perimysium. This was toned with [20] findings, which showed that during medication withdrawal, meaningful increases in muscle function occurred concurrently with a reduction in the intensity of subjective symptoms.

disagreed,[28] as it was noted that stopping using statins had a significantly increased chance of developing myopathy as opposed to continuous taking the drug. This could be the consequence of some cases developing a persistent myopathy even after stopping the statin use, or it could be the result of stopping the medication too soon after beginning statin therapy and not having early myopathy symptoms documented in their medical records before they stopped taking the statin.

The expression of activated caspase-3 in control group was extremely low, while there was a significant increase in area fraction of activated caspase-3 expression in simvastatin group as an early measure of apoptosis that was in accordance with [27].

The expression of activated caspase-3 in SIMI showed moderate increased expression of activated caspase-3 and SIMII groups showed very marked increased expression of activated caspase-3 in mainly comparison to the control group, confirmed by area fraction of activated caspase-3. This was consistent with research by [29] , who reported that simvastatin cause oxidative stress that can activate several apoptotic signaling pathways, including the activation of the mitochondrial outer membrane permeabilization pathway, which releases pro-apoptotic factors like cytochrome c into the cytoplasm. This can trigger the activation of caspases and lead to cell death. disagreed [30] with these results as SIM, has known anti-inflammatory effects that may help reduce the likelihood of apoptosis. Statins lower the levels of pro-inflammatory cytokines such as TNF-α and IL-6, which are typically involved in inducing apoptosis and added that variants in certain genes can affect statin metabolism and influence the severity of side effects.

According to the treated groups, it demonstrated decrease in the expression of activated caspase-3, confirmed by the area fraction of activated caspase-3. This was in a line with [31] as it explained the role of CoQ10 in maintaining mitochondrial health by improving the efficiency of ATP production and stabilizing the mitochondrial membrane. CoQ10 is a potent antioxidant that helps neutralize reactive oxygen species (ROS), which are highly reactive molecules that can cause oxidative stress. Oxidative stress occurs when there is an imbalance between the production of ROS and the body's ability to neutralize them with antioxidants. Excessive ROS can damage cellular components, including lipids, proteins, and DNA, leading to cellular dysfunction and eventually apoptosis. opposed [32]with these findings as he reported that in conditions where the apoptotic signal is strong enough, such as during prolonged stress or in certain diseases, CoQ10 might not inhibit caspase activation sufficiently to prevent apoptosis, in cases of extreme oxidative stress, the production of ROS can exceed the antioxidant capacity of CoQ10, leading to significant cellular damage and induction of mitochondrial dysfunction, which is a key trigger for apoptosis. According to Withdrawal group showed mild to moderate decrease in the expression of activated caspase-3, confirmed by the area fraction of activated caspase-3, this was in a line with [33] who suggested a reversal of mitochondrial dysfunction and a decrease in apoptosis and inflammatory responses in muscle cells. differed and suggested [32] that in cases where mitochondrial impairment is severe, apoptosis may continue despite the restoration of CoQ10 levels and the withdrawal of statins. This can occur because oxidative stress and mitochondrial permeability transition, which lead to apoptosis.

The ultrastructure of the control group showed regular arrangement of myofibrils forming with A band, H bands with M lines and a peripheral oval euchromatic nucleus with regular of the nuclear envelope. Mitochondria present at the periphery of the fibers with multiple glycogen granules, these finding was approved by [34].

The ultrastructure study of the myopathy group revealed the presence of vacuoles, disfigured mitochondria, heterochromatic nuclei, prominent nucleolus, decondesation of the chromatin as a sign of apoptosis, interstitial oedema appear in vaculations, with increased in intermyofibrillar space due to myofibrillar disruption mainly in SIM3. These findings supported those of [35, 36] who observed that rats were treated with simvastatin developed enlarged mitochondria and an accumulation of vacuoles.differed [37]with these finding as he reviewed that statin treatment has no significant effect on mitochondrial

morphology or function.

In the treated group indicated a clear improvement in many places, oval euchromatic nucleus with regular nuclear membrane, preserve cristae of the mitochondria, disappearance of vacuoles and normal intermyofibrillar space. 38approved with these finding and revealed that CoQ10 helps maintain mitochondrial cristae structure, preventing mitochondrial swelling and dysfunction. CoQ10 also, stabilizes muscle cell membranes, particularly the sarcolemma and organelle membranes. CoQ10 Protects myofibrils and mitochondrial membranes from oxidative stress-induced degradation.

varied [38] with these findings as he reported that while CoQ10 plays a crucial role in muscle cell bioenergetics and antioxidant defense, its supplementation does not universally restore normal muscle ultrastructure. Factors such as limited bioavailability, the irreversible nature of certain muscle damages, the complicated muscle disorders, and inconsistent clinical outcomes contribute to its variable efficacy.

According to the Withdrawal group showed slightly return of ultrastructure of muscle and this was in a line with [39] who reported that discontinuation of statin leads to decrease of SAMS along time with normalization of mitochondrial density in muscle fibers.disagreed [40] with these findings as In certain cases, muscle damage may persist even after statin withdrawal. This persistence could be due to underlying conditions or the severity of the initial muscle injury. For instance, some cases might develop statin-associated autoimmune necrotizing myopathy, a rare condition that can continue to cause muscle weakness even after stopping statins.

## CONCLUSION

The previously mentioned data indicate that CoQ10 has a role in improvement of damaged muscle tissue through its anti-oxidative effects, ultimately improving the histological structure of the muscle tissue. By improving the level of CK, this may offer a strategy for protecting and treating SIM induced myopathy and its associated complications, but CoQ10 supplementation should be considered as part of a broader, as the discontinuation of SIM has a good role in the recovery of the muscle along the time.

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