Effect of Curcumin on the Cardiovascular System of Obese Albino Rats

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Abstract: Background: cardiovascular diseases (CVD), principally ischemic heart disease and stroke, remain the leading cause of mortality worldwide and a major contributor to disability and rising healthcare costs. In 2010 alone, CVD was a primary cause of 15.6 million global deaths. Obesity is one of the major causes for incidence of cardiovascular disease. Abundant evidence shows that obesity is associated with structural and functional changes in the heart in both humans and animal models. A ten kg higher body weight is associated with a 3.0 mm Hg higher systolic and 2.3 mm Hg higher diastolic blood pressure. These increases translate into an estimated 12% increased risk rate for CHD and 24% increased risk rate for stroke. This increase in blood pressure is greatest when the obesity is of abdominal distribution. **Aim of the Work:** is to evaluate the hypolipidemic effect of curcumin extract (50 mg/kg/day) on the cardiovascular changes induced by obesity in albino rats that treated by intra-peritoneal injection of Triton WR 1339 (250 mg/kg) to induce obesity because it induces hyperlipidemia higher than cholesterol and oil supplemented diets. **Materials and Methods:** this study was performed using 80 male albino rats of Wistar strain, initially weighing 120 ± 5 grams and 5 weeks old. Rats were obtained from the National Institute for vaccine and anti-serum "VACSERA", Cairo, Egypt. They were housed in stainless steel cages measuring 120 X 60 X 60 cm (10 rats / cage) at a well-ventilated animal house at the Faculty of Veterinary Medicine, Alexandria University, Egypt. Rats were permitted adequate standard diet and given water ad libitum for one week of adaptation period prior to the experimental work. Care and use of the animals were conducted under supervision of the Animal Care Committee of the Alexandria University, Egypt. This study was carried out at the Faculty of Veterinary Medicine, Alexandria University. The experiment lasted for eight weeks. A total of 80 male albino rats (each rat was about 120 ± 5 gram) were allocated in eight cages (10 rats/cage) and divided into four groups (20 rats per each group). **Results:** our study was focused on the therapeutic effect of the curcumin which has gained an increased interest in recent years as a potential treatment for obesity-related comorbidities. In the present study, 60 rats (120±5g and 5 weeks old) treatment with triton for duration of 4 weeks was designed to exhibit obesity features in rats characterized by an increase in the body weight gain, incidence of hyperlipidemia, cardiac and aortic remodling. During period of triron WR 1339 injection rats were calm, easy to handle without injuries or deaths. Appetite was increased in obese group more than in control group, this indicated by increased amount of food needed for each group (about 20 grams/ rat/ day for obese group and 14 grrams/ rat/ day for control group). Obesity group increased in weight by (up to 70 grams per week) while control group showed lower rate of weight gain (about 30 grams per week). **Conclusion:** the obtained results revealed that, rats treated with triton WR 1339 for duration of 4 weeks tended to exhibit obesity features characterized by an increase in the body weight gain, elevated serum lipid level and features cardiovascular remodeling. Where, curcumin treatment of the obese rats showed a significant reduction in the body weight, improvement in cardiovascular remodeling and improvement in serum lipid profile and atherogenic indices.

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Keywords: Curcumin, Cardiovascular System, Obese Albino Rats

1. Introduction

Cardiovascular diseases (CVD), principally ischemic heart disease and stroke, remain the leading cause of mortality worldwide and a major contributor to disability and rising healthcare costs. In 2010 alone, CVD was a primary cause of 15.6 million global deaths [(1)].

Obesity is one of the major causes for incidence of cardiovascular disease [(2)]. Abundant evidence shows that obesity is associated with structural and functional changes in the heart in both humans and animal models [(3)].

A ten kg higher body weight is associated with a 3.0 mm Hg higher systolic and 2.3 mm Hg higher diastolic blood pressure. These increases translate into an estimated 12% increased risk rate for CHD and 24% increased risk rate for stroke. This increase in blood pressure is greatest when the obesity is of abdominal distribution [(4)].

Mechanisms contributing to structural and functional changes in the heart due to obesity could

include altered cardiac metabolism, mitochondrial dysfunction, oxidative stress, impaired insulin signaling, inflammation, pressure/volume overload, sleep apnea, neuro-humoral activation, cardiac fibrosis and apoptosis [5].

Nowadays, there is increased interest for using natural dietary products to manage obesity and related health problems due to their safety, efficacy and cost [6].

One of these compounds is curcumin which is derived from the rhizomatous herb, turmeric (curcuma longa). Curcumin has been shown to exhibit antioxidant, anti-inflammatory, antiviral and antibacterial activities [8]. Curcumin also protect against atherosclerosis and platelet aggregation [7].

Aim of the Work

The aim of this study is to evaluate the hypolipidemic effect of curcumin extract (50 mg/kg/day) on the cardiovascular changes induced by obesity in albino rats that treated by intra-peritoneal injection of Triton WR 1339 (250 mg/kg) to induce obesity because it induces hyperlipidemia higher than cholesterol and oil supplemented diets.

2. Material and Methods

This study was performed using 80 male albino rats of Wistar strain, initially weighing 120 ± 5 grams and 5 weeks old. Rats were obtained from the National Institute for vaccine and anti-serum "VACSERA", Cairo, Egypt. They were housed in stainless steel cages measuring 120 X 60 X 60 cm (10 rats / cage) at a well-ventilated animal house at the Faculty of Veterinary Medicine, Alexandria University, Egypt. Rats were permitted adequate standard diet and given water ad libitum for one week of adaptation period prior to the experimental work. Care and use of the animals were conducted under supervision of the Animal Care Committee of the Alexandria University, Egypt.

This study was carried out at the Faculty of Veterinary Medicine, Alexandria University. The experiment lasted for eight weeks. A total of 80 male albino rats (each rat was about 120 ± 5 gram) were allocated in eight cages (10 rats/cage) and divided into four groups (20 rats per each group) as the followings: ***group I (Control group):*** 20 rats will be fed normal laboratory diet for 4 weeks then sacrificed, ***group II (Obese group):*** 20 rats will be treated by intra-peritoneal injection of Triton 250 mg/kg to induce obesity and fed normal laboratory diet for 4 weeks then sacrificed, ***group III (treated group):*** 20 rats similar to the second group but treated with curcumin orally by orogastric tube of 50 mg/kg/day for another 4 weeks then sacrificed, ***group IV (Recovery group):*** 20 rats similar to the second group but left for another 4 weeks (for spontaneous recovery) then sacrificed.

After 4 weeks from the beginning of the experiment as well after overnight fasting, blood samples were drawn from the retro-orbital plexus of veins of the rats, of the control and obese groups and from the treated and recovery groups after 8 weeks, under diethyl ether anesthesia before sacrificing by decapitation. Blood samples were collected without anticoagulant in clean and dry Wassermann tubes and left in slope position to clot at room temperature. The tubes were centrifuged at 3000 rpm for 5 minutes and the non hemolysed serum was carefully separated and transferred into clean dry epindorffs which kept frozen at -20 ^{0}C until used for biochemical analysis.

Serum levels of total cholesterol (TC) and Triacylglycerol (TG) were measured by commercial kits (Vitro Scient Company Egypt). Serum high density lipoprotein cholesterol level (HDL-c) was measured by commercial kit (Spectrum Company Egypt). Low density lipoprotein cholesterol (LDL-c) and very low density lipoprotein cholesterol (vLDL-c) were calculated. Rats of all groups were eviscerated after decapitated under di-ethyl ether anesthesia, heart and aorta were removed and washed by normal saline to remove the blood and then fixed in 10% formol saline.

LV transverse sections of ten animals from each group were fixed in 10% buffered formalin and embedded in paraffin. Thin sections of 1 µm were cut from the tissue block and stained with hematoxylin and eosin, and with the collagen-specific stain Mallory's tri-chrome and Masson's tri-chrome stain.

The myocyte perimeter was determined for at least 100 myocytes per hematoxylin and eosin-stained slide. The myocyte perimeter measurements were obtained from digitized images (40× magnification lens) collected using a video camera attached to a Leica microscope (Leica Mikroskopie & Systems GmbH, Germany) and computerized image analysis software, optimus program (version 6.21.19, Media Cybernetics, 1998). Myocyte perimeter was measured using a digitizing pad, and the selected cells were cut transversely with the nucleus clearly identified in the centre of the myocyte.

Total area of interstitial collagen fibers was determined for the entire Masson's trichrome-stained cardiac section using an automatic image analyzer (Optimus program). The components of the cardiac tissue were identified according to colour level as follows: blue for collagen fibres; red for myocytes; and white for interstitial space. The Total area of interstitial collagen fibers was calculated in average, 35 microscopic fields were analyzed using a 20× lens.

For ultra-structural studies, small fragments of the left ventricle muscle from three rats of each group were fixed in 2.5% glutraldehyde for 1 h to 2 h, followed by post-fixation in 1% osmium tetroxide in

0.1 M phosphate buffer for 2 h. After dehydration in a graded ethanol series, the fragments were embedded in epoxy resin. Ultra-thin sections were double-stained with uranyl acetate and lead citrate, and examined using a Jem.1010 Transmition electron microscope (Germany).

After measuring of the following parameters: 1) Total area of collagen fibers in myocardium, perimeter of myocardial cell, thickness of tunica intema aorta and number of aortic medial smooth muscle number, 2) Body weight, 3) Serum lipid profile. Using Excel 2010, Statistical analysis was done by one way analysis of variance (ANOVA). Means and standard error were also calculated.

3. Results

a- Body weight

Table 1 and Figure 1 show the influence of obesity on the body weight of the animals in different groups. Rats in the obesity group showed significant increase in the body weight compared to the control group. Although, the recovery and treated group showed significant reduction in the body weight, the reduction was more in treated group than the recovery one.

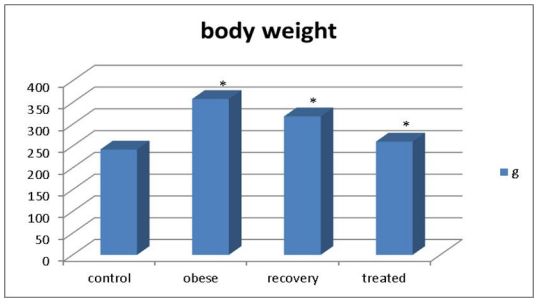

Figure (1): histogram shows comparison of body weight in various groups.
* Significantly different when compared to control group (obese vs control) and (recoveryand treated vs obese).

Table (1): Shows a comparison between results of body weight in various groups.

Groups	Body weight (grams)
Control	242 ± 04.37 [c]
Obesity	358 ± 10.70 [a]
Recovery	318 ± 08.15 [b]
Treated	260 ± 05.81 [c]

Means with different superscript differ significantly (P<0.05).

b- Biochemical results,

The results observed in table (2) and figure (2 A) cleared that; the serum level of lipid profile (apart from serum level of HDL-c) showed a significant increase in obesity group when compared to control group. On the other side it showed a significant reduction in both treated group and recovery group when compared to obesity group, however, the reduction was more in treated group than recovery group.

As regard to the serum level of HDL-c, the results observed in table (2) and figure (2) showed a significant reduction in obesity group when compared to control group. On the other side it showed a significant increase in both treated group and recovery group when compared to obesity group, however, the increase is more in treated group than recovery group. In general, the serum level of high density lipoprotein cholesterol "HDL-c" still lower in all experimental groups when compared to the control group.

Table (3) and figure (2 B) show atherosclerotic indices in different groups. CRI, AC and AIP showed significant increase in obesity group compared to the control one. While, in spite of significant improvement in both recovery and treated group compared to obesity group, the improvement was more in treated group than the recovery one.

Table (2); shows Comparison of serum lipids profile in various groups.

Groups	Total cholesterol (mg/dl)	Tri-glycerides (mg/dl)	vLDL-c (mg/dl)	LDL-c (mg/dl)	HDL-c (mg/dl)
Group I (Control)	056.40± 03.25 [c]	056.06± 04.61 [c]	011.30± 00.92 [c]	008.26± 02.46 [c]	036.90± 01.61 [a]
Group II (Obesity)	258.00± 12.30 [a]	275.00± 12.10 [a]	055.10± 02.41 [a]	185.00± 14.30 [a]	017.80± 00.36 [b]
Group III (Recovery)	166.00± 05.25 [b]	131.00± 14.60 [b]	026.20± 02.92 [b]	107.00± 06.58 [b]	033.60± 02.08 [a]
Group IV (Treated)	074.70± 04.30 [c]	085.30± 03.67 [c]	017.10± 00.73 [c]	022.30± 03.94 [c]	035.30± 01.12 [a]

Means with different superscript differ significantly (P<0.05).

c- Histological result

Light microscopic study of LV myocardium of control group revealed normal morphological aspects that included normal branched cardiac muscle fibers with normal pale nucleus and normal interstitium with scanty amount of collagen fibers. While myocardium obtained from rats in obesity group revealed significant increase in the interstitial collagen fibers and significant increase in the cardiac cell perimeter.

On the other hand recovery group showed non-significant improvement in total area of interstitial collagen fibers and significant improvement in cardiac

cell perimeter. While the treated group showed significant improvement in total area of interstitial collagen fibers and cardiac cell perimeter Table (4) and figure (3A & B and 5A).

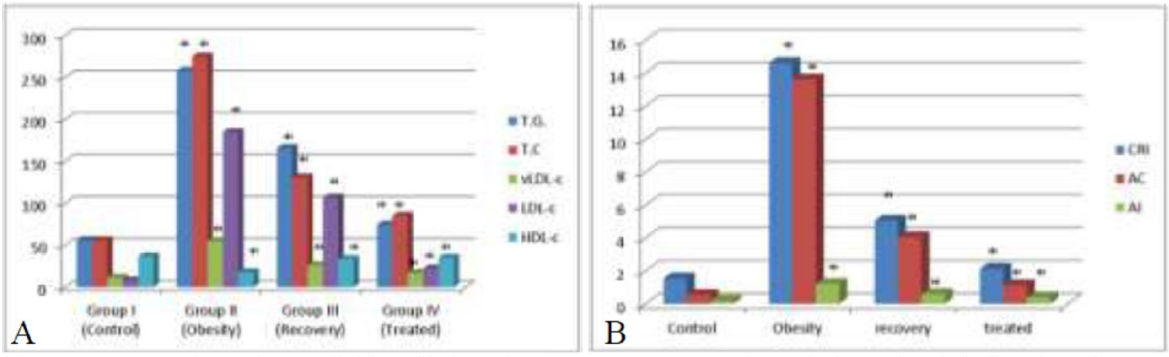

Figure (2): "A" comparison of serum lipid profile in various groups. "B" comparison of atherosclerotic indices in various groups
* Significantly different when compared to other group (obese vs control) and (recovery and treated vs obese).

Table (3): Shows comparison of Castelli's risk index, atherogenic coefficient and atherogenic indices in various groups.

Groups	Castelli's risk index (CRI)	Atherogenic Coefficient (AC)	Atherogenic index of plasma (AIP)
	TC / HDLc	(TC - HDLc) / HDLc	log (TG / HDLc)
Control	01.53 ± 0.03 [c]	00.53 ± 0.03 [c]	00.18 ± 0.05 [d]
Obesity	14.60 ± 0.79 [a]	13.60 ± 0.79 [a]	01.19 ± 0.02 [a]
Recovery	05.03 ± 0.34 [b]	04.03 ± 0.34 [b]	00.58 ± 0.05 [b]
Treated	02.12 ± 0.14 [c]	01.12 ± 0.14 [c]	00.38 ± 0.02 [c]

Means with different superscript differ significantly (P<0.05).

In the case of aortic histological study, aorta from the control rats revealed normal thin endothelium with smooth surface, regular tunica media elastic lamina with normal smooth muscle in-between. Where those of the obesity group, showed significant increase in tunica intima and number of the tunica media vascular smooth muscle.

When the recovery group revealed non-significant improvement in intimal thickness or number of vascular smooth muscle, the treated one revealed significant improvement in both intimal thickness and number of vascular smooth muscle table (5) and figure (4A & B and 5B).

Electron microscopic study of the ultra-structure of the LV myocardium of the control group revealed normal morphological aspects that included fibers containing sarcoplasm filled with myofibrils, well-defined sarcomeres, mitochondria with lamellar cristae, plasma membranes with straight undulating aspects and nuclei with loose chromatin (Figure 4). Electron microscopy revealed marked ultra-structural abnormalities in cardio-myocytes from obesity group, changes in mitochondria, absence and/or disorganization of myofilaments, dilated sarcoplasmic reticulum vesicles and the presence of large amounts of lipid droplets between the myofibrils (Figure 6A).

While the ultra-structure study of aorta from each group revealed that, control group showed continuous endothelium with smooth surface, intact elastic lamina with narrow sub-endothelial space and regular elastic lamellae with normal smooth muscle in between. On the other hand obesity showed increased thickness of the endothelium with hook-like cytoplasmic extension in to the lumen, rupture of internal elastic lamina and sub endothelial extension of smooth muscle. After treatment, recovery group still has thickening of endothelium, rupture of internal elastic lamina and sub endothelial extension of smooth muscle, while the treated group showed marked improvement and regain its normal structure and arrangement (figure 6B).

Table (4): Comparison of collagen area and cardio-myocyte perimeter in various groups.

Groups	Collagen area (μm^2)	Cardio-myocyte Perimeter (µm)
Control	01177 ± 00569 [b]	080.0 ± 2.82 [c]
Obesity	46173 ± 11380 [a]	138.0 ± 6.21 [a]
Recovery	33969 ± 09458 [a]	121.0 ± 3.47 [b]
Treated	03590 ± 00720 [b]	089.9 ± 3.17 [c]

Means with different superscript differ significantly (P<0.05).

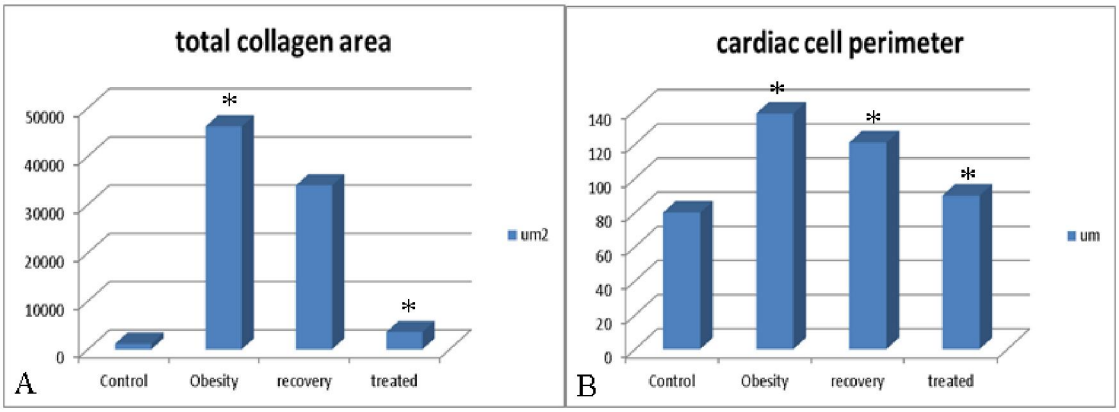

Figure (3): "A" comparison of total collagen area in various groups. "B" comparison of cardiac cell perimeter in various groups
* Significantly different when compared to other group (obese vs control) and (recovery and treated vs obese).

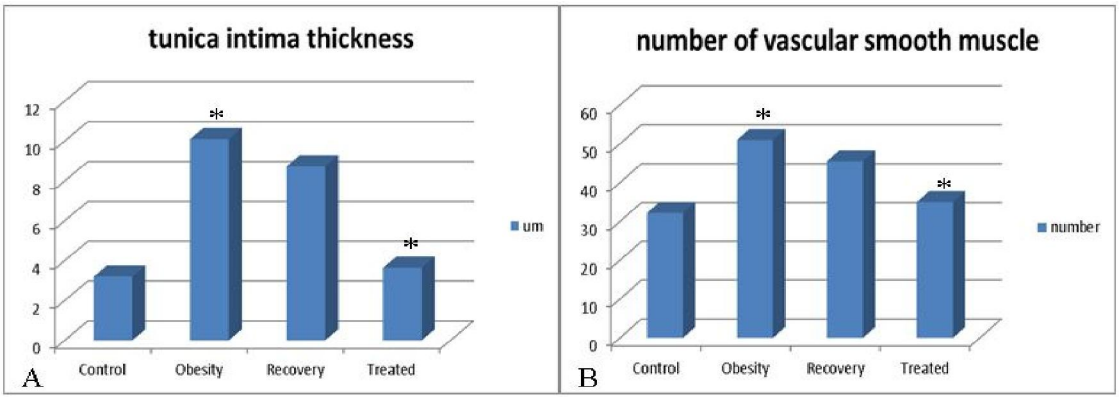

Figure (4): "A" comparison of intimal thickness in various groups. "B" comparison of the number of vascular smooth muscle of the tunica media in various groups
* Significantly different when compared to other group (obese vs control) and (recovery and treated vs obese).

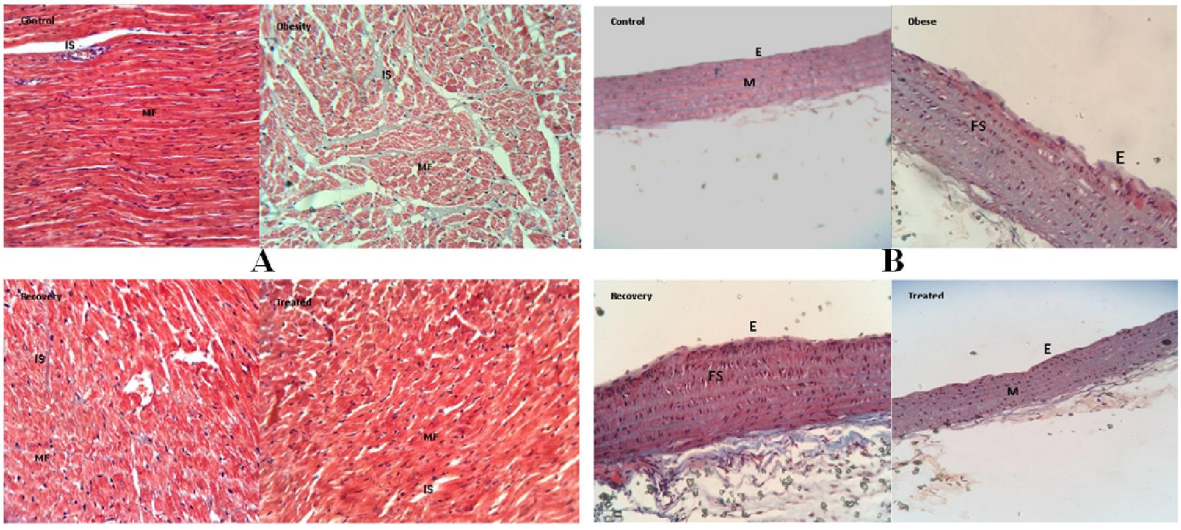

Figure (5): "A" LV micrographs stained with Masson's tri-chrome (400x), control and treated groups myocardium show normal myofibril "MF" and normal interstitium "IS" with scanty amount of interstitial collagen fibers. While obese one shows disorganization of myofibril "MF" and sever interstitial collagen deposition.
"B" aortic micrographs stained with Masson's tri-chrome (400x), control group and treated one show continuous endothelium with smooth surface "E" regular elastic lamellae with normal smooth muscle in between "M" while obesity and recovery groups show increased thickness of endothelium "E" and presence of fatty streaks between smooth muscle in the media "FS".

Table (5): Comparison of intimal thickness and number of vascular smooth muscle in various groups.

Groups	Intimal thickness (µm)	Vascular smooth muscle cells (number)
Control	03.20 ± 0.12 [b]	32.2 ± 4.53 [c]
Obesity	10.10 ± 0.94 [a]	51.0 ± 4.42 [a]
Recovery	08.73 ± 0.44 [a]	45.5 ± 2.72 [ab]
Treated	03.64 ± 0.16 [b]	35.0 ± 2.95 [bc]

Means with different superscript differ significantly (P<0.05).

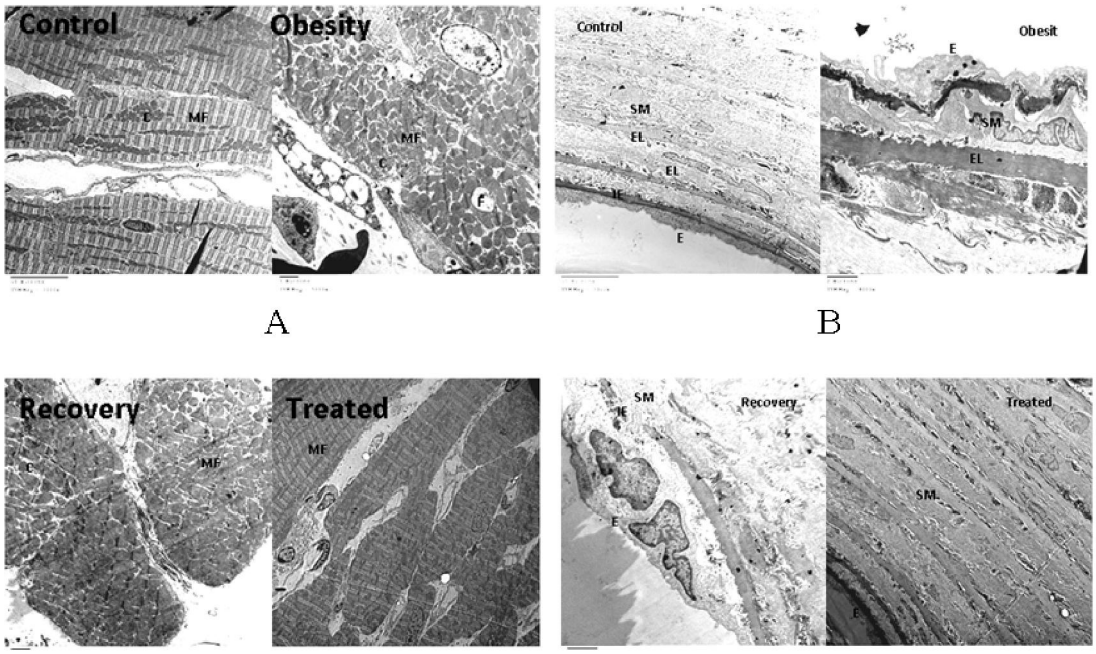

Figure (6): "A" LV ultra-structure, control and treated groups myocardium show normal myofibril "MF" and normal mitochondria "c", while obese one shows disorganization of myofibril "MF", abnormal mitochondria "C" and large intracellular fat globule "F". Recovery group shows disorganized myofibril "MF".
"B" ultra-structure of aorta, control group and treated one show continuous endothelium with smooth surface "E", intact elastic lamina "IE" with narrow sub-endothelial space, regular elastic lamellae "EL" with normal smooth muscle in between "SM" while obesity and recovery groups show rupture of internal elastic lamina (IE) and sub endothelial extension of smooth muscle "SM".

4. Discussion

Obesity refers to abnormal or excessive fat accumulation with an increase in the body weight. Changes in dietary pattern, such as increased consumption of high fat diet are considered a primary cause of this problem [(9)]. Obesity is strongly associated with structural and functional changes in the heart in both humans and animal models [(3)]. Hyperlipidemia-induced inflammation and oxidative stress are crucial factors in obesity-induced cardiac remodeling and dysfunction [(10)]. Cardiac consequences of obesity include cardiac remodeling such as cardiac hypertrophy, cardiac fibrosis, cardiac apoptosis and subclinical impairment of left ventricular (LV) systolic and diastolic function [(11)].

Atherosclerotic indices reflect the true relationship between protective and atherogenic lipoprotein and is associated with the size of pre- and anti- atherogenic lipoprotein particle [(12)]. ***Cai et al.*** [(13)] reported that the atherosclerotic indices are significant and independent predictors for CVD risk and might be better than traditional lipid parameters.

All of the currently available anti-lipidemic therapies have their own inherent shortcomings and disadvantages. Therefore, natural treatments have been investigated as potential therapies for lowering blood lipid levels [(14)]. Curcumin supplementation lowers plasma triglycerides and cholesterol concentrations by reducing the expressions of lipogenic genes [(15)].

Our study was focused on the therapeutic effect of the curcumin which has gained an increased interest in recent years as a potential treatment for obesity-related comorbidities. In the present study, 60 rats (120±5g and 5 weeks old) treatment with triton for duration of 4 weeks was designed to exhibit obesity features in rats characterized by an increase in the body weight gain and incidence of hyperlipidemia.

After curcumin treatment we found, significant reduction in body weight in treated group compared to the obesity group. This result is agreed with ***Maithilikarpagaselvi et al.*** [16] report, who studied the effect of curcumin on hyperlipidemia and hepatic fat accumulation in high-fructose-fed male rat. These observations about body weight loss without caloric restriction are interesting and are probably due to inhibition of lipid metabolic pathways, detected in this study by improved lipid profile after curcumin treatment, with subsequent decrease in the size of adipose tissue in the body.

The same explanation is suggested by ***Ejaz et al.*** [17], who reported significant weight reduction in obese C57/BL mice after curcumin treatment and he proposed that it was through inhibition of lipid metabolic pathways regulated by Adenosine monophosphate-activated protein kinase (AMPK) and key transcription proteins involved in adipogenesis which cause an increase in basal metabolism, energy expenditure, and weight loss.

Also weight reduction caused by curcumin treatment may be due to decrease fat absorption from gastrointestinal tract as observed in this study by increased amount of fat in rats excreta detected by greasy excreta of the treated group compared to the excreta of recovery group. This explanation is agreed with ***Ghosh et al.*** [18] and ***Funamoto et al.*** [19].

While the recovery group showed significant improvmen in the serum lipid profile, this improvement was lower than those of the treated group.

Calculation of atherosclerotic indices of the serum lipids levels in our study revealed significant increase of, atherogenic index (AI), atherogenic coefficient (AC) and Castelli's risk index (CRI) in obesity group compared to those of the control group. This elevation in atherosclerotic indices explain the presence of histological changes in the heart and aorta based on serum lipid profile as reported by, ***Amato et al.*** [20], who found the same result of elevated atherosclerotic indices in obesity.

After curcumin treatment we detected significant improvement in all in AI, AC, and CRI. This result also is agreed with ***Amato et al.*** [20].

Also recovery group revealed significant improvement in in all atherosclerotic parameter compared to the obesity group but the improvement detected in the treated group was greater than those in the recovery group.

Morphological analysis of myocardial histology in our study revealed a significant increase in the total area of the collagen fibers in the myocardium and a significant increase in the size of myocardial cell in obesity group compared to those of the control group, this result is nearly similar to those of ***Qian et al.*** [21].

However this result is disagree with ***Carroll et al.*** [22] who report that there was non-significant increase in the total area of the collagen fibers in the myocardium or in the size of the myocardial cell in Sprague-Dawley rats fed high fat diet for 12 week. However it was verified in another study on obese rats feed HFD done by ***Yunpeng et al.*** [23] that obesity causes accumulation of collagen fibers in the cardiac interstitium and increase in the cardiac cell size, and that is similar to our finding in this study.

Treated group in our study showed marked improvement in the changes induced by obesity in cardiac muscle ultra-structure include, improvement of myofibril arrangement, returning of mitochondria to normal shape, structure and number, and absence of cytoplasmic lipid droplet inclusion. Also we detected a significant improvement in both total collagen area and myocardial cell perimeter in treated group while in recovery group there was significant improvement in cardiac cell perimeter and in significant decrease in the total collagen area compared to obesity group. These results are agreed with ***Qian et al.*** [21].

The possible mechanism of this improvement is probably through reduction of serum TC and TG and increasing serum level of HDL-c which in turn prevent fat deposition in myocardial cell.

In our study we detected histological changes in obesity group including, aortic intima and aortic media including significant proliferation of smooth muscle cells (SMC), lipid droplet in the cytoplasm of SMC, proliferation of fiber between SMC, lipid droplet in the basal membrane of aorta, significant intimal thickening compared to control group, these findings is constant with ***Feng et al.*** [24].

Initial intimal thickening abnormality composed of very little extra celluar matrix, few SMCs but foam cell macrophage are not present in these thickening. In our study we detecting presence of extracellular deposition of lipid between VSMCs without presence of foam cell and this result is nearly similar to the findings of ***Yutaka et al.*** [25] who proposed that infiltration of the wall by lipid and/or apo-lipoprotein is proceed foam cell infiltration, and explained this by deposition of lipids from serum in the interstitium.

The VSMCs proliferation probably due to increase in the serum cholesterol as observed in the results this study, this explanation is agreed with ***Yutaka et al.*** [25] who reported that the cause of

VSMCs in their study was the high level of serum cholesterol.

Conclusion

The obtained results revealed that, rats treated with triton WR 1339 for duration of 4 weeks tended to exhibit obesity features characterized by an increase in the body weight gain, elevated serum lipid level and features cardiovascular remodeling. Where, curcumin treatment of the obese rats showed a significant reduction in the body weight, improvement in cardiovascular remodeling and improvement in serum lipid profile and atherogenic indices. Recovery group showed significant improvement in the body weight, serum lipid profile and atherogenic indices, it also showed insignificant improvement in the cardiac total collagen area and significant improvement in the cardiac cell perimeter. Finally this group showed insignificant improvement in vascular smooth muscle proliferation and thickness of the tunica intema of the aorta. These results suggest that, curcumin supplementations may have some benefits on CVS in patients suffering from obesity.

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