

Effect of Exercise Training on Metabolic Homeostasis and Some Hepatic and Cardiovascular Functions in a Rat Model of High Fat Diet Induced Obesity

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Abstract

Background: Obesity is associated with many chronic disorders such as type-2 diabetes mellitus, essential hypertension and Non-Alcoholic Fatty Liver Disease (NAFLD). Physical exercise has been shown to have positive effects in the prevention and attenuation of many of the obesity-related disorders, however; the mechanisms have not been fully elucidated.

Objective: The present study was designed to examine the effect of moderate intensity exercise training on existing cardio metabolic and hepatic complications linked to obesity including dyslipidemia, insulin resistance, hypertension and NAFLD.

Material and Methods: This study was conducted on 3 groups of adult male albino rats: Group-I: Normal diet fed group Group-II: High Fat Diet (HFD) induced obesity group in which obesity was induced by HFD for 12 weeks and Group-III: HFD induced obesity group fed on HFD for 12 weeks followed by moderate intensity swimming exercise training for 8 weeks. In all groups, BMI, Abdominal Circumference (AC), systolic, diastolic and mean arterial blood pressures, heart rate, serum glucose, insulin and HOMA-IR, serum Total Cholesterol (TC), Triglyceride (TG), Very Low-density Lipoprotein Cholesterol (VLDL-c), Low-Density Lipoprotein Cholesterol (LDL-c), High-Density Lipoprotein Cholesterol (HDL-c) and Atherogenic Index (AI), serum adiponectin, leptin, irisin, Tumor Necrosis Factor alpha (TNF- α), Interleukin-6 (IL-6), Malondialdehyde (MDA), Superoxide dismutase (SOD), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), Lactate Dehydrogenase (LDH) and albumin were measured and histopathological examinations for hepatic tissues were also done.

Results: The present study revealed that HFD significantly increased BMI, AC, systolic, diastolic and mean arterial blood pressures, heart rate, serum glucose, insulin, HOMA-IR, TC, TG, LDL-c, VLDL-c, AI, ALT, AST, ALP, LDH, TNF- α , IL-6, MDA and leptin levels, however, there were significant decreases in serum HDL-c, SOD, albumin, adiponectin and

irisin levels. NASH and cirrhosis were also observed in HFD-induced obesity group. Conversely, chronic moderate intensity swimming exercise training significantly reversed these manifestations even in absence of caloric restriction.

Conclusion: Moderate exercise training seems to be an effective strategy to reverse almost all risk factors of cardiovascular diseases and NAFLD associated with metabolic syndrome.

Key Words: Obesity – NAFLD – Hypertension – Exercise.

Introduction

OBESITY is a serious public health problem that is greatly correlated with many diseases including type-2 diabetes mellitus, essential hypertension, Non-Alcoholic Fatty Liver Disease (NAFLD) and atherosclerotic heart problems which are produced through metabolic syndrome risks (insulin-resistance, dyslipidemia and hypertension) [1,2].

Moreover, adipose tissue is not only the primary site for excess lipid storage but it also has an endocrine function as it synthesizes a number of biologically active substances (adipocytokines) that regulate the body metabolism [3]. Disturbance of these adipocytokine pathways in obesity plays a major role in development of many obesity-related sequelae [4].

Another important predisposing factor for many obesity-related disorders is the low-grade inflammation of the enlarged fatty tissue and its release of many inflammatory cytokines as tumor necrosis factor- α (TNF- α) and Interleukin-6 (IL-6) that have a negative impact on several non-adipose tissues [5].

Both high-fat diet and declines of physical activity are the major causes for development of

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obesity [6]. Increasing physical activity has become a useful non-pharmacological treatment approach to control obesity, reverse existing cardiovascular diseases and prevent or attenuate hepatic steatosis, however, these data do not identify the physiological or cellular mechanisms that elicit this improvement [2,7].

Noteworthy, many studies have reported that exercise training can affect adipocytokines circulating levels and its expression in adipocytes that may be one of the mechanisms by which exercise improves the metabolic homeostasis, however, the effect of exercise on adipocytokines levels depends on exercise type and magnitude; thus, the results revealed by distinct studies can't be standardized [8].

The present study was designed to determine the effects of moderate intensity swimming exercise training on cardiovascular, metabolic and hepatic changes produced by HFD induced obesity and to demonstrate some underlying mechanisms.

Material and Methods

This study was conducted in Faculty of Medicine, Zagazig University in the period from January to November 2017 and involved thirty healthy adult male albino rats of local strain weighing 151-190gm obtained from Faculty of Veterinary Medicine Animal House. Rats were kept under hygienic conditions in steel wire cages (5/cage) at room temperature, maintained on a natural light/dark cycle with free access to water and adapted to the new environment for one week before the experiment going on. All experimental procedures were approved by the Institutional Research Board and Ethics Committee of Faculty of Medicine, Zagazig University.

Rats were randomly assigned to three equal groups: Group (I): Normal diet fed (control) group; rats were fed on normal chow diet (5% of diet calories derived from fat, 18% from proteins and 77% from carbohydrates; 3.3kcal/g) for 12 weeks [9], Group (II): A high fat diet induced obesity group; rats were fed on high fat diet (58% of diet calories derived from fat, 18% from protein and 24% from carbohydrates; 5.6kcal/g) for 12 weeks [9] (diets were obtained from Faculty of Agriculture, Zagazig University), and Group (III): A high fat diet induced obesity followed by exercise training group; rats were fed a high fat diet chow for 12 weeks then subjected to a moderate intensity swimming exercise training protocol for 8 weeks.

Exercise training protocol: The rats in the training group were confined to a swimming exercise performed one hour per day, six days per week for eight weeks in a cylindrical tank of 80cm high, and 120cm diameter and filled with heated water 50cm deep at (30-32°C) preceded by pre-training period done on three weeks (swimming exercise performed for only 15 minutes in the first week, the second week continued only 30 minutes, and the third week performed 45 minutes, then duration was increased gradually until the rats became able to do exercise training for one hour per day). Upon completion of exercise, rats were dried by a towel and returned to their cages. The animal groups that were not trained were subjected to stand in a 120cm diameter plastic tank filled until 5cm height with water at 30-32°C) [10,11]. No deaths occurred in any group.

• Anthropometric measures:

Measurement of body weight: By using a digital balance (Germany) at the start and the end of experiment.

Measurement of rat length: Nose to anus length was measured according to [12].

Calculation of Body Mass Index [BMI]: BMI= body weight (gm)/length (cm)². The cutoff value of obesity is BMI >0.68gm/cm² [12].

Measurement of Abdominal Circumference (AC): A plastic tape was used to measure the abdominal circumference at the largest zone of the rat's abdomen [13].

• Measurement of systolic, diastolic and Mean Arterial Blood Pressure (MABP) and Heart Rate (HR):

Measured by non-invasive blood pressure monitor (NIBP; 250 system, BioPAC system, INC.) as described by Abubakar et al., [14].

$$\text{MABP} = \frac{\text{Diastolic} + (\text{systolic} - \text{diastolic})}{3}$$

• Sample collection:

Retro-orbital venous plexus blood samples were obtained 48h after the last training to avoid immediate effects of exercise and food was removed from the animal cages the night before [15]. Serum was obtained by allowing the blood samples to clot then centrifuged at 3000rpm for 20 minutes and kept at (-20°C) and used to measure the levels of glucose, insulin and HOMA-IR, Total Cholesterol (TC), Triglyceride (TG), Very Low-Density Lipoprotein Cholesterol (VLDL-c), Low-Density Lipoprotein Cholesterol (LDL-c), High-Density

Lipoprotein Cholesterol (HDL-c) and atherogenic index, serum leptin, adiponectin, irisin, Tumor Necrosis Factor Alpha (TNF- α), Interleukin-6 (IL-6), Malondialdehyde (MDA), Superoxide Dismutase (SOD), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), Lactate Dehydrogenase (LDH) and albumin. Livers were also excised and processed for histopathological studies.

• *Biochemical analysis:*

Measurement of serum glucose and insulin:

Serum glucose was estimated as described by Tietz [16] using specific glucose kit (Bioscience, Egypt) and analyzed by spectrophotometers device (URIT-8 10, China).

Insulin was measured as described by Temple et al., [17] using specific insulin kit (BioSource Belgium) and analyzed by spectrophotometers device.

Calculation of Homeostasis model assessment of insulin resistance (HOMA-IR): Was calculated according to the following formula:

$$\text{HOMA-IR} = \frac{\text{Insulin (}\mu\text{U/mL)} \times \text{glucose (mg/dL)}}{405} \quad [18]$$

Measurement of serum lipids profile:

TC and TG were measured by enzymatic colorimetric method described by Tietz [16] using specific cholesterol and triglycerides kits (Spinreact Spain) and analyzed by spectrophotometers device. HDL-c was measured by precipitating reagent method described by Tietz [16] using HDL-c precipitating reagent kit (Spinreact, Spain) and analyzed by spectrophotometers device. LDL-c and VLDL-c were measured by using Friedewald et al., [19] formula.

$$\text{LDLc} = \text{TC} - \text{HDLc} - \left(\frac{\text{TG}}{5}\right) \quad \text{VLDLc} = \frac{\text{TG}}{5}$$

Calculation of Atherogenic Index (AI) : Was calculated from the following formula:

$$\text{AI} = \text{Log (triglycerides/HDL-c)} \quad [20]$$

Measurement of serum Leptin: Was measured as described by Considine et al., [21], using commercial ELISA kit, (Catalog Number RAB0005, provided by Sigma-Aldrich Co).

Measurement of serum TNF- α level: Was measured as described by Fernando et al., [22], using commercial ELISA kit, (Catalog Number RAB0480, provided by Sigma-Aldrich Co).

Measurement of serum IL-6 level: Was measured as described by Engvall and Perlmann [23], using IL-6 ELISA Kit (Catalog Number RAB0306 provided by Sigma-Aldrich Co).

Measurement of serum adiponectin level: Was measured as described by Kishore and Reid [24] using commercial ELISA kit, (Catalog Number RAB0005, provided by Sigma-Aldrich Co).

Measurement of serum irisin level: Was measured as described by Yang et al., [25] using irisin ELISA kit (EK-067-16; Phoenix Pharmaceuticals, Burlingame, CA).

Measurement of serum MDA level: Was measured as described by Satoh [26], using Biodiagnostic kit (Biodiagnostic company, Dokki, Giza, Egypt).

Measurement of serum SOD activity: Was measured as described by Nishikimi et al., [27], using kit provided by (Biodiagnostic company, Dokki, Giza, Egypt).

Measurement of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels: Were measured according to Rec [28], using rat ALT & AST ELISA kits, (Catalog Number: 2011-11-0595, Shanghai Sunred Biological Technology, China).

Measurement of serum Alkaline Phosphatase level: Was measured as described by Belfield and Goldberg [29], using commercial kit (Catalog Number 15-1711 provided by Sigma-Aldrich Co). Measurement of serum lactate dehydrogenase (LDH): Was measured according to Kachmar and Moss [30], using commercial kit (Catalog Number 279 001, provided by Egyptian Company for Biotechnology).

Measurement of serum albumin: Was estimated by using the bromocresol green according to the method described by Stoskopf [31].

• *Tissue sampling and histopathological examination:*

Immediately after collecting blood samples, rats were killed by decapitation after light ether anesthesia. The abdominal cavities of the rats were opened to remove the livers. All removed livers were fixed in 10% buffered formalin solution for duration of 48-60 hour. After this, tissue samples were processed through ethyle alcohol and xylene series, and embedded in paraffine blocks. Liver specimens were sectioned (5 μ m thick), then stained with hematoxylin and eosin [32]. The slides were

examined under a light microscope by an expert pathologist in a blinded fashion.

• *Statistical analysis:*

Results were presented as mean \pm SD and analyzed using Version 18 SPSS program (SPSS Inc. Chicago, IL, USA). One way analysis of variance (ANOVA) was used followed by student-Least Significant Differences (LSD) test to compare statistical differences between groups. Pearson's test was done to detect correlations between parameters. *p*-value less than 0.05 was considered to be significant.

Results

The present study showed that HFD (Group II) significantly increased body weight, BMI, AC, serum glucose, insulin and HOMA-IR, serum total cholesterol, triglyceride, LDL-c, VLDL-c and atherogenic index, serum leptin, TNF- α , IL-6, MDA, ALT, AST, ALP, LDH. It also significantly increased systolic, diastolic and mean arterial blood pressures and heart rate ($p < 0.001$) with significant

positive correlations versus BMI, but, it significantly decreased serum albumin, HDL-c, adiponectin, SOD and irisin levels ($p < 0.001$) with significant negative correlations versus BMI when compared to control group (Group I) (Tables 1-4).

Whereas, chronic moderate exercise training (Group III) significantly decreased body weight, BMI, AC, serum glucose ($p < 0.001$), insulin ($p < 0.01$) and HOMA-IR, serum total cholesterol, triglyceride, LDL-c, VLDL-c, and atherogenic index, serum leptin, TNF- α , IL-6, MDA, ALT, AST, ALP, LDH ($p < 0.001$) and it also significantly decreased systolic, diastolic and mean arterial blood pressures and heart rate ($p < 0.001$), but it significantly increased serum albumin, adiponectin, SOD ($p < 0.001$), HDL-c and irisin levels ($p < 0.01$) when compared to HFD-induced obesity group (Group II) (Tables 1-4).

Moreover, histopathological examination in the present study revealed development of NASH and fibrosis in the HFD fed rats (Group II) Figs. (2,3) that were improved by exercise training (Group III) Fig. (4).

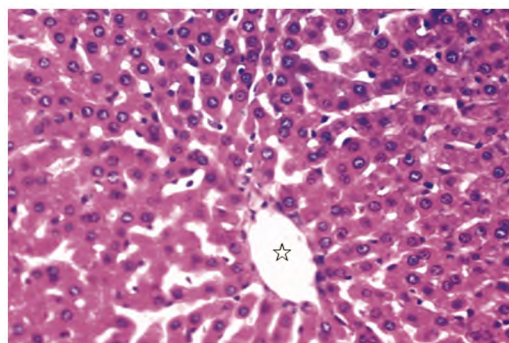


Fig. (1): Photomicrograph of normal liver tissue of control group showing normal sized central vein surrounded by normal rows and cords of normal hepatocytes (H & E X400).

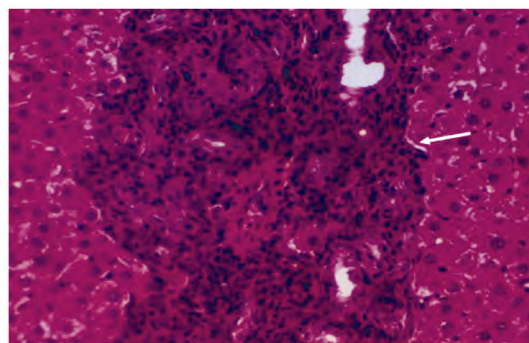


Fig. (2): Photomicrograph of liver tissue of high fat diet fed rat showing heavy aggregations of chronic inflammatory cells and dense fibrosis surrounded by hepatocytes. This indicates NASH with fibrosis (H & E X400).

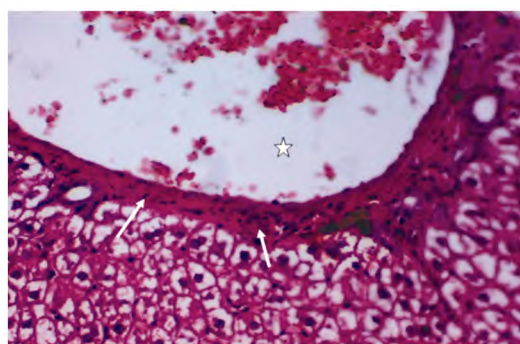


Fig. (3): Photomicrograph of liver tissue of high fat diet fed rat showing dilated congested central vein surrounded by dense fibrosis and aggregates of chronic inflammatory cells. This indicates NASH (H & E X400).

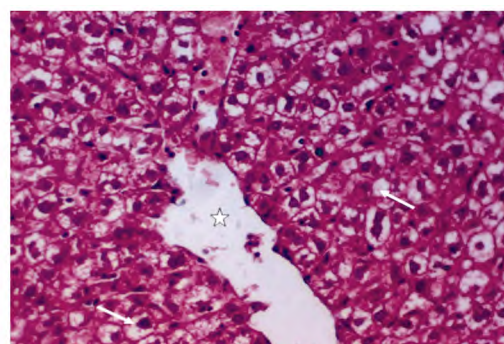


Fig. (4): Photomicrograph of liver tissue of high fat diet fed followed by exercise training rat showing mildly dilated congested central vein surrounded by mild fatty change of the hepatocytes. This indicates improvement of NASH (H & E X400).

Table (1): Body weights, final BMI and AC of all studied groups.

Parameters	Groups	Group I	Group II	Group III
<i>Initial body weight (gm):</i>	$\bar{X} \pm SD$	172.4±8.54	166.2±7.31	169±4.94
	<i>p</i> -value of LSD		NS ^a	NS ^b
<i>Final body weight (gm):</i>	$\bar{X} \pm SD$	265±8.273	418.5±12.695	342.1±12.749
	<i>p</i> -value of LSD		<i>p</i> <0.001 ^a	<i>p</i> <0.001 ^{a,b}
<i>Final BMI (gm/cm²):</i>	$\bar{X} \pm SD$	0.54±0.72	0.77±0.06	0.69±0.08
	<i>p</i> -value of LSD		<i>p</i> <0.001 ^a	<i>p</i> <0.001 ^a , <i>p</i> <0.05 ^b
<i>AC (cm):</i>	$\bar{X} \pm SD$	15.1±1.19	21.9±2.07	18.2±1.03
	<i>p</i> -value of LSD		<i>p</i> <0.001 ^a	<i>p</i> <0.001 ^{a,b}
	<i>r</i> with BMI		<i>r</i> =0.934, <i>p</i> <0.001	

a : Versus group-1.

b : Versus group-2.

NS: Non-Significant (*p*>0.05).

Table (2): Serum glucose, insulin, HOMA-IR, serum cholesterol, triglyceride, HDL-c, LDL-c, VLDL-c and atherogenic index of all studied groups.

Parameters	Groups	Group I	Group II	Group III
<i>Serum glucose (mg/dl):</i>	$\bar{X} \pm SD$	84.5±10.31	231.6±21.57	10.63±10.63
	<i>p</i> -value of LSD		<i>p</i> <0.001 ^a	<i>p</i> <0.001 ^{a,b}
	<i>r</i> with BMI		<i>r</i> =0.894, <i>p</i> <0.001	
<i>Serum insulin (µU/ml):</i>	$\bar{X} \pm SD$	20.499±3.38	42.79±7.11	33.949±5.45
	<i>p</i> -value of LSD		<i>p</i> <0.001 ^a	<i>p</i> <0.001 ^a , <i>p</i> <0.01 ^b
	<i>r</i> with BMI		<i>r</i> =0.944, <i>p</i> <0.001	
<i>HOMA-IR:</i>	$\bar{X} \pm SD$	4.285±0.96	24.679±5.74	10.983±2.51
	<i>p</i> -value of LSD		<i>p</i> <0.001 ^a	<i>p</i> <0.001 ^{a,b}
	<i>r</i> with BMI		<i>r</i> =0.973, <i>p</i> <0.001	
<i>Serum cholesterol (mg/dl):</i>	$\bar{X} \pm SD$	71.78±11.53	181.72±19.58	98.08±6.78
	<i>p</i> -value of LSD		<i>p</i> <0.001 ^a	<i>p</i> <0.001 ^{a,b}
	<i>r</i> with BMI		<i>r</i> =0.98, <i>p</i> <0.001	
<i>Serum triglyceride (mg/dl):</i>	$\bar{X} \pm SD$	70.703±14.32	142.462±33.92	101.045±8.61
	<i>p</i> -value of LSD		<i>p</i> <0.001 ^a	<i>p</i> <0.001 ^{a,b}
	<i>r</i> with BMI		<i>r</i> =0.889, <i>p</i> <0.01	
<i>Serum HDL-c (mg/dl):</i>	$\bar{X} \pm SD$	41.8±7.15	19.12±3.17	35.35±5.77
	<i>p</i> -value of LSD		<i>p</i> <0.001 ^a	<i>p</i> <0.05 ^a , <i>p</i> <0.01 ^b
	<i>r</i> with BMI		<i>r</i> =-0.951, <i>p</i> <0.001	
<i>Serum LDL-c (mg/dl):</i>	$\bar{X} \pm SD$	15.84±3.13	134.11±19.58	42.51±6.003
	<i>p</i> -value of LSD		<i>p</i> <0.001 ^a	<i>p</i> <0.001 ^{a,b}
	<i>r</i> with BMI		<i>r</i> =0.907, <i>p</i> <0.001	
<i>Serum VLDL-c (mg/dl):</i>	$\bar{X} \pm SD$	14.14±2.865	28.49±6.7859	20.2±1.722
	<i>p</i> -value of LSD		<i>p</i> <0.001 ^a	<i>p</i> <0.01 ^a , <i>p</i> <0.001 ^b
	<i>r</i> with BMI		<i>r</i> =0.889, <i>p</i> <0.01	
<i>Atherogenic index:</i>	$\bar{X} \pm SD$	0.226±0.044	0.867±0.137	0.46±0.087
	<i>p</i> -value of LSD		<i>p</i> <0.001 ^a	<i>p</i> <0.001 ^{a,b}
	<i>r</i> with BMI		<i>r</i> =0.943, <i>p</i> <0.001	

Table (3): Serum leptin, adiponectin, irisin, TNF- α , IL-6, MDA and SOD of all studied groups.

Parameters	Groups	Group I	Group II	Group III
<i>Serum leptin (ng/ml):</i>	$\bar{X} \pm SD$ <i>p</i> -value of LSD <i>r</i> with BMI	3.15 \pm 0.53	9.86 \pm 0.70 <i>p</i> <0.001 ^a <i>r</i> =0.963, <i>p</i> <0.001	6.6 \pm 1.4 <i>p</i> <0.001 ^{a,b}
<i>Serum adiponectin (ng/dl):</i>	$\bar{X} \pm SD$ <i>p</i> -value of LSD <i>r</i> with BMI	7.32 \pm 1.11	3.511 \pm 0.74 <i>p</i> <0.001 ^a <i>r</i> =-0.928, <i>p</i> <0.001	5.51 \pm 0.61 <i>p</i> <0.001 ^{a,b}
<i>Serum irisin(ng/ml):</i>	$\bar{X} \pm SD$ <i>p</i> -value of LSD <i>r</i> with BMI	17.28 \pm 1.83	8.19 \pm 0.84 <i>p</i> <0.001 ^a <i>r</i> =-0.961, <i>p</i> <0.001	12.17 \pm 1.15 <i>p</i> <0.001 ^a , <i>p</i> <0.01 ^b
<i>Serum TNF-α (pg/ml) :</i>	$\bar{X} \pm SD$ <i>p</i> -value of LSD <i>r</i> with BMI	47.17 \pm 3.77	63.16 \pm 1.94 <i>p</i> <0.001 ^a <i>r</i> =0.905, <i>p</i> <0.001	54.23 \pm 2.06 <i>p</i> <0.001 ^{a,b}
<i>Serum IL-6 (pg/ml):</i>	$\bar{X} \pm SD$ <i>p</i> -value of LSD <i>r</i> with BMI	9.57 \pm 1.636	23.66 \pm 3.691 <i>p</i> <0.001 ^a <i>r</i> =0.9, <i>p</i> <0.001	15.5 \pm 2.427 <i>p</i> <0.001 ^{a,b}
<i>Serum MDA (nmol/ml):</i>	$\bar{X} \pm SD$ <i>p</i> -value of LSD <i>r</i> with BMI	40.2 \pm 5.28	66.01 \pm 8.43 <i>p</i> <0.001 ^a <i>r</i> =0.931, <i>p</i> <0.001	52.18 \pm 5.15 <i>p</i> <0.001 ^{a,b}
<i>Serum SOD (U/L):</i>	$\bar{X} \pm SD$ <i>p</i> -value of LSD <i>r</i> with BMI	52.99 \pm 4.34	33.95 \pm 5.45 <i>p</i> <0.001 ^a <i>r</i> =-0.906, <i>p</i> <0.001	44.09 \pm 4.45 <i>p</i> <0.001 ^{a,b}

Table (4): Systolic, diastolic and mean arterial blood pressures, heart rate and serum ALT, AST, ALP, LDH and albumin of all studied groups.

Parameters	Groups	Group I	Group II	Group III
<i>Systolic blood pressure (mmHg):</i>	$\bar{X} \pm SD$ <i>p</i> -value of LSD <i>r</i> with BMI	127.1 \pm 1.792	169 \pm 4.163 <i>p</i> <0.001 ^a <i>r</i> =0.904, <i>p</i> <0.001	144.1 \pm 3.479 <i>p</i> <0.001 ^{a,b}
<i>Diastolic blood pressure (mmHg):</i>	$\bar{X} \pm SD$ <i>p</i> -value of LSD <i>r</i> with BMI	88.2 \pm 3.824	125.42 \pm 6.893 <i>p</i> <0.001 ^a <i>r</i> =0.933, <i>p</i> <0.001	103.8 \pm 4.91 <i>p</i> <0.001 ^{a,b}
<i>MABP (mmHg):</i>	$\bar{X} \pm SD$ <i>p</i> -value of LSD <i>r</i> with BMI	101.233 \pm 2.39	139.95 \pm 5.82 <i>p</i> <0.001 ^a <i>r</i> =0.955, <i>p</i> <0.001	117.233 \pm 3.55 <i>p</i> <0.001 ^{a,b}
<i>Heart rate (beat/min):</i>	$\bar{X} \pm SD$ <i>p</i> -value of LSD <i>r</i> with BMI	321.5 \pm 12.38	532.5 \pm 14.13 <i>p</i> <0.001 ^a <i>r</i> =0.946, <i>p</i> <0.001	402.8 \pm 12.06 <i>p</i> <0.001 ^{a,b}
<i>Serum ALT (mg/dl):</i>	$\bar{X} \pm SD$ <i>p</i> -value of LSD <i>r</i> with BMI	44.93 \pm 8.25	137.2 \pm 9.33 <i>p</i> <0.001 ^a <i>r</i> =0.991, <i>p</i> <0.001	89.9 \pm 7.12 <i>p</i> <0.001 ^{a,b}
<i>Serum AST (mg/dl):</i>	$\bar{X} \pm SD$ <i>p</i> -value of LSD <i>r</i> with BMI	133.9 \pm 12.56	190.8 \pm 13.91 <i>p</i> <0.001 ^a <i>r</i> =0.835, <i>p</i> <0.05	160.7 \pm 17.83 <i>p</i> <0.001 ^{a,b}
<i>Serum ALP (U/L):</i>	$\bar{X} \pm SD$ <i>p</i> -value of LSD <i>r</i> with BMI	67.07 \pm 4.015	101.1 \pm 8.283 <i>p</i> <0.001 ^a <i>r</i> =0.933, <i>p</i> <0.001	83.6 \pm 3.930 <i>p</i> <0.001 ^{a,b}
<i>Serum LDH (U/L) :</i>	$\bar{X} \pm SD$ <i>p</i> -value of LSD <i>r</i> with BMI	258.22 \pm 4.976	571.4 \pm 7.09 <i>p</i> <0.001 ^a <i>r</i> =0.9, <i>p</i> <0.001	440.84 \pm 6.927 <i>p</i> <0.001 ^{a,b}
<i>Serum albumin (g/dl):</i>	$\bar{X} \pm SD$ <i>p</i> -value of LSD <i>r</i> with BMI	4.2 \pm 0.25	1.852 \pm 0.51 <i>p</i> <0.001 ^a <i>r</i> =-0.928, <i>p</i> <0.001	2.938 \pm 0.53 <i>p</i> <0.001 ^{a,b}

Discussion

Obesity is a predisposing factor for many disorders including type-2 diabetes, essential hypertension and Nonalcoholic Fatty Liver Disease (NAFLD). However, the mechanisms that link obesity with high blood pressure and NAFLD have not been fully elucidated [33]. NAFLD constitutes spectra of liver diseases ranging from lipid accumulation in liver (steatosis) to necrotic inflammation (nonalcoholic steatohepatitis; NASH) with or without hepatic fibrosis/cirrhosis [34]. NAFLD can be improved through weight reduction and exercise without medical therapy; however, the mechanism of improvement remains unknown even though many studies have been conducted to address this issue [35].

The present study was designed to examine the effect of moderate intensity exercise on existing cardio metabolic and hepatic complications linked to obesity including hyperlipidemia, insulin resistance, hypertension and NAFLD.

In the present study, we observed a significant increase in final body weight and BMI in high fat diet fed group of rats, which indicates the occurrence of an overall obesity. In addition, these HFD fed rats showed a significant increase in Abdominal Circumference (AC) which indicate the occurrence of visceral (=abdominal or central) obesity. These findings are in accordance with those of many researchers [33,36].

Furthermore, in this model of obesity, we found many of the characteristics of Metabolic Syndrome (MS) as dyslipidemia, hyperglycemia, hyperinsulinemia, insulin resistance, type 2 diabetes mellitus, hyperleptinemia, hypertension, NAFLD, and a significant increase in AI. All these criteria of MS were greatly reversed by chronic moderate intensity exercise training even in the absence of caloric restriction.

Our findings are in agreement with those of Jun et al., [37] and Touati et al., [38] who revealed that exercise ameliorated all the manifestations of Metabolic Syndrome (MS) without shifting to a normal caloric diet.

Our research results also showed that HFD induced obesity in rats produced significant increases in systolic, diastolic and mean arterial blood pressures. These findings are in consistence with the study of Aubin et al., [39] who reported that a short period of high fat diet intake might increase the number Ca²⁺ channels or change their regulations which increase the transmembrane

Ca²⁺ influx that lead to blood pressure elevation. Furthermore, the changes in hemodynamic parameters (BP↑ & HR↑) observed in the present study in HFD-induced obesity group may be partially attributed to activation of sympathetic-renin-angiotensin system, dyslipidemia, increased oxidative stress and pro-inflammatory cytokines and diminished endogenous NO production [10,33].

Moreover, liver injury is evidenced in HFD fed rats in this study by the histopathological changes in hepatic tissue as indicated by fatty infiltration with the presence of foci of mixed inflammatory cell infiltration and fibrosis that may indicate the development of NASH and cirrhosis. These histopathological changes were associated with significant increases in serum levels of ALT, AST, ALP and LDH with significant positive correlations versus BMI, and with significant decreases in serum levels of albumin with significant negative correlations versus BMI. These findings are in accordance with the findings of Gutierrez and Romero [40]. Elevated ALT and AST circulating levels indicates a significant hepatic injury [41].

Increased caloric consumption over caloric expenditure is the most common cause of NAFLD in developed countries [42]. Regional triglycerides accumulation and fatty acid transport is changed in NAFLD obese patients. Lipoprotein lipase activity is decreased in fatty tissue while increased with increase in fatty acid transport proteins expressions in hepatic tissue in obese patients [43].

Insulin Resistance (IR) as indicated by the significant increase in serum glucose and insulin levels together with HOMA-IR increase in that study, in HFD fed group, may promote hypertension and NAFLD occurrence.

Insulin can be considered as both inflammatory and anti-inflammatory, in normal conditions insulin stimulates endothelial NO production to exert a vasorelaxant and anti-inflammatory effect. However, hyperinsulinemia in IR may activate mitogen-activated protein kinase pathway leading to vasoconstriction, inflammation and sodium and water retention that enhance blood pressure elevation [44].

IR and hyperinsulinemia also play an important role in NALFD development. Hyperinsulinemia and elevated blood glucose and fatty acids reduce β -oxidation and promote hepatic fatty acids and triglycerides uptake & de novo lipid synthesis [45].

In addition, we found that HFD for a period of 12 weeks also produced a significant increase in

the serum TC, TG, LDL-c and VLDL-c levels together with a significant decrease in serum HDL-c levels in HFD-induced obesity in rats. These findings are supported by the work of Touati et al., [38]. A significant increase in Atherogenic Index (AI) has also been demonstrated in our study in HFD fed group. As a consequence of increased hepatic triglycerides, the liver produces an atherogenic lipid profile that adversely affects the cardiovascular functions [46].

Increased hepatic fatty acids oxidation and macrophage activation with increased secretion of proatherogenic substances as TNF- α , IL-6 and oxidized LDL have also been argued as possible mechanisms for atherosclerosis acceleration and cardiovascular disease development in NAFLD subjects [47]. It has also been shown that NASH patients have increased atherosclerosis when compared with simple steatosis ones therefore; NAFLD appears to be an early predisposing factor for atherosclerosis [48].

Other important detectable parameter in our model is the presence of Oxidative Stress (OS), which was evidenced by the significant increase in serum level of MDA indicating lipid peroxidation associated with the significant decrease in serum SOD level in HFD-fed rats. OS activate hepatic stellate cells that form collagen and increase the inflammatory response, leading to apoptosis and fibrogenic effect in NASH [49]. Human studies also support the role of OS in the pathogenesis of hypertension, especially in obesity. Increased superoxide over no production together with sympathetic nervous system stimulation by OS reduces vasodilation and plays a key role in development of obesity related hypertension [50].

Our results also revealed that HFD induced obesity resulted in significant changes in various adipocytokines. There were significant increases in serum TNF α , IL-6 and leptin levels with significant positive correlations versus BMI but there were significant decreases in serum adiponectin and irisin levels with significant negative correlations versus BMI in the HFD fed group. This is in agreement with previous studies [51,52]. However, at variance of our results, Stengel et al., [53] reported higher circulating irisin levels in obese subjects that positively correlated with body weight and BMI. But, Sanchis-Gomar et al., [54] didn't find any correlation between circulating irisin levels and BMI.

Hepatic fat accumulation activates the inhibitor of nuclear factor kappa-B kinase in hepatic cells

that activates nuclear factor-kappa-B and promotes the expression of proinflammatory cytokines including TNF- α and IL-6 that enhance hepatic injury and atherosclerosis [55].

Leptin also plays an important role in NASH pathogenesis in obese individuals [56]. Leptin levels are enhanced by IL-1 and TNF- α and help to maintain inflammation and down regulate preproinsulin gene transcription and insulin secretion in obesity [57]. Hyperleptinemia also elevates the sympathetic drive via the corticotropin-releasing factor and a condition of partial or selective leptin resistance seems to exist whereas the sympathoexcitatory effects are maintained leading to hypertension and tachycardia [58].

On the other hand, it was reported that circulating adiponectin level was reduced in obese individuals [59]. Adiponectin could help in the treatment of liver diseases through its insulin-sensitizing and anti-inflammatory effects [60]. Likewise, plasma irisin level is also decreased in NAFLD obese individuals and may protect against liver steatosis through modulating the peroxisome proliferator-activated receptor alpha signaling pathway [61]. Moreover, Lu et al., [62] found that irisin inhibits high glucose induced endothelial cell apoptosis and vascular inflammation.

Noteworthy, our experimental findings showed that exercise even without reduction of caloric intake is associated with decrease of HFD-induced visceral obesity. This is in agreement with those from clinical studies [63].

In the present study and in another study [38], exercise training and/or diverting from a HFD to a control diet ameliorated lipid profiles and decreased the Atherogenic Index (AI). Touati et al., [38] also observed that the AI decreased in the exercise-trained rats more than the modified diet subjected ones.

Exercise training could suppress de novo lipogenesis through suppression of hepatic sterol regulatory element-binding protein-1c. It also increased the expression and phosphorylation of hepatic 5' AMP-activated protein kinase and thereby the training-induced β -oxidation of fatty acids to be a potent non-pharmacological method that act against HFD-induced NAFLD and its complications [35].

Our study also revealed a significant improvement of insulin resistance indicated by the significant decrease in serum glucose and insulin levels together with decreased HOMA-IR in HFD-fed group subjected to exercise training. Regular phys-

ical activity improves insulin function and glucose tolerance in obese patients with IR [64].

Moreover, the present study demonstrated that obese rats subjected to moderate intensity exercise training were associated with significant decreases in systolic, diastolic and MABP. These results are in accordance with those of Touati et al., [38] who showed that diet modification and/or regular exercise training resulted in a significant reduction of arterial blood pressure and even prevention of hypertension in obese rats that is more effective in trained obese rats than in sedentary obese ones with modified diet and reported that both exercise and diet modification improve endothelial dysfunction by increasing expression and activity of endothelial NOS and reduction of OS.

The exercise training beneficial effects on HFD-induced fatty liver were also demonstrated in our study by the significantly decreased serum ALT, AST, ALP and LDH and the improvement in liver histopathology. Many studies have also reported reductions in hepatic lipid content in NAFLD patients after exercise training intervention programs that did not decrease weight which suggest that exercise per se can reverse hepatic steatosis [65,66].

Exercise training also significantly decreased the serum levels of TNF α , IL-6 and leptin but significantly increased the serum levels of adiponectin and irisin in the HFD fed group subjected to exercise training. Exercise training especially that which is associated with reduced fat mass corrects the dysfunction in adipokine and cytokine expression and the degree of improvement vary with the type and magnitude of exercise [67]. Moreover, exercise stimulates the expression of fibronectin type-III domain containing protein 5, which is cleaved and secreted as irisin [68]. Irisin increases energy expenditure and may help in control of certain diseases associated with IR such as NAFLD [69].

Exercise also controls the release and activity of TNF- α & IL-6 that helps in the protective effects of physical activity as their strict balance is important for metabolic homeostasis [70]. Decreased renin-angiotensin and sympathetic nervous systems activities were also reported with regular exercise training leading to lowering of HR and BP [15].

In summary, the data from this study demonstrated that HFD-induced obesity is associated with insulin resistance, dyslipidemia, altered adipocytokines production, decreased antioxidant levels, hemodynamic changes, fatty liver disease

(steatohepatitis) and hepatic dysfunction. In addition, moderate exercise training seems to be an effective method to improve almost all factors of cardiovascular diseases and NAFLD risks associated with metabolic syndrome. Thus, exercise training may be recommended either alone or with drug therapy for treatment of HFD-induced obesity associated complications.

Further studies are required, especially in humans, to determine the preferred type and magnitude of exercise that will be more effective.

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تأثير التدريب الرياضى على التوازن الأيضى وبعض وظائف الكبد والقلب والأوعية الدموية فى نموذج للسمنة المحدثه بالغذاء الدهنى فى الجرذان

خلفية البحث: ترتبط السمنة مع العديد من الإضطرابات المزمنة مثل داء السكرى من النمط الثانى وإضطراب أيض الدهون وإرتفاع ضغط الدم الأساسى وحدوث أمراض القلب والأوعية الدموية وكذلك حدوث مرض الكبد الدهنى غير الكحولى. ولقد لوحظ أن حالات السمنة المحدثه بالغذاء الدهنى يصحبها تغييرات فى مستوى الأديبوكينات التى تفرز من الأنسجة الدهنية فى الدم. هذا وقد أظهرت العديد من الدراسات أن ممارسة التدريب الرياضى يمكن أن يكون له آثار إيجابية فى الوقاية من وعلاج مضاعفات مرض السمنة ولكن نتائج هذه الدراسات لم تحدد بوضوح الآليات التى تؤدي إلى هذا التحسن.

الهدف من البحث: صممت هذه الدراسة لفحص تأثير التدريب الرياضى المعتدل الشدة على الإبتزان الأيضى وبعض وظائف القلب والأوعية الدموية ووظائف الكبد فى نموذج للسمنة المحدثه تجريبيا بإستخدام غذاء عالى الدهن فى الجرذان.

مواد وطرق البحث: أجريت هذه الدراسة على عدد ثلاثين من ذكور الجرذان البيضاء البالغة التى يتراوح وزنها من 151-190 جرام والتى تم تقسيمها عشوائيا إلى ثلاث مجموعات متساوية. المجموعة الأولى تم تغذيتها على الغذاء الطبيعى لمدة 12 أسبوعا، والمجموعة الثانية وهى مجموعة السمنة المحدثه بتغذية الجرذان على غذاء عالى الدهن لمدة 12 أسبوعا والمجموعة الثالثة وهى مجموعة السمنة المحدثه بإتباع نظام غذائى عالى الدهن لمدة 12 أسبوعا ثم تلى ذلك تعرض الجرذان لبرنامج من التدريب الرياضى معتدل الشدة عن طريق السباحة لمدة 8 أسابيع مع الإستمرار فى الغذاء عالى الدهن. فى نهاية فترة التجربة تم قياس وزن وطول ومحيط البطن النهائى للجسم وحساب مؤشر كتلة الجسم وضغط الدم الشريانى الإنقباضى والإنبساطى ومتوسط ضغط الدم ومعدل ضربات القلب فى كل المجموعات. كما تم قياس مستوى الجلوكوز والأنسولين مع حساب مقاومة الأنسولين ومستوى الكوليسترول الكلى والدهون الثلاثية والبروتين الدهنى عالى الكثافة والبروتين الدهنى منخفض الكثافة والبروتين الدهنى منخفض الكثافة جدا مع حساب مؤشر تصلب الشرايين ومستوى الليبتين والأديبونكتين والأيريزين وعامل نخر الورم ألفا وأنترليوكين-6 والمالون داي ألدهيد والسوبر أوكسيد ديسميوتيز والالانين أمينوترانسفيريز وأسبارتيت أمينوترانسفيريز واللاكتيت ديهيدروجينيز والكالين فوسفاتيز والألبومين فى مصل الدم. وقد تم أيضا عزل الكبد وتحضير أنسجته للدراسة الميكروسكوبية.

النتائج: أدت السمنة المحدثه بالغذاء عالى الدهن إلى زيادة ذات دلالة إحصائية فى كل من وزن الجسم النهائى ومحيط البطن ومؤشر كتلة الجسم وضغط الدم الإنقباضى والإنبساطى ومتوسط ضغط الدم ومعدل ضربات القلب ومستويات الجلوكوز والأنسولين فى مصل الدم ومقاومة الأنسولين ومستويات الكوليسترول الكلى والدهون الثلاثية والبروتين الدهنى منخفض الكثافة والبروتين الدهنى منخفض الكثافة جدا ومؤشر تصلب الشرايين ومستويات الليبتين وعامل نخر الورم ألفا وأنترليوكين-6 والمالون داي ألدهيد ومستويات الالانين أمينوترانسفيريز وأسبارتيت أمينوترانسفيريز واللاكتيت ديهيدروجينيز والكالين فوسفاتيز مع وجود نقص ذى دلالة إحصائية فى مستويات البروتين الدهنى عالى الكثافة والألبومين ومستويات الأديبونكتين والأيريزين والسوبر أوكسيد ديسميوتيز. كما أظهر الفحص المجهزى حدوث إتهاب كبد دهنى غير كحولى مع تليف بالكبد فى مجموعة السمنة المحدثه بالغذاء عالى الدهن. هذا وقد أظهرت نتائج المجموعة الثالثة التى تم تعرضها للتدريب الرياضى وجود تحسنا ملحوظا فى جميع المعاملات المذكورة أعلاه عند مقارنتها بالمجموعة الثانية.

الإستنتاج: ممارسة التدريب الرياضى معتدل الشدة عن طريق السباحة له فوائد عظيمة فى التغلب على السمنة وما يصاحبها من إضطراب فى الإبتزان الأيضى المعروف بإسم متلازمة الإضطراب الأيضى وتقليل عوامل الخطورة على القلب والأوعية الدموية ومرض الكبد الدهنى غير الكحولى.