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High-Fat Diet Induced Perturbation in Physiological Parameters in Females Albino Rat

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Abstract

A high-fat diet (HFD) is characterized by an excessive intake of dietary fats, while often being deficient in essential nutrients and fiber. Studies in animal models have consistently demonstrated that high-fat diets can lead to significant elevation of weight gain, body organs and biochemical parameters. The present research aimed to clarify the adverse physiological consequences of HFD on female rats. The present study was performed on 12 female rats that were divided into equal groups. Group I fed normal basal diet and group II fed HFD for 12 months. The body weight and gain, relative organs weight as well as abdominal fat mass were recorded. Hematological parameters, lipid profile, liver and kidney functions and heart fatty acid binding protein (H-FABP) were determined. Also, histopathology for liver, kidney and heart were performed. Electrocardiography (ECG) was performed. The body weight, weight gain, relative organs weight and abdominal fat mass were significantly increased in group II than group I. Hematological parameters, lipid profile, liver and kidney functions, H-FABP and ECG as well as histopathology were deteriorated in group II than group I. The findings revealed that prolonged consumption of a high-fat diet resulted in significant physiological perturbations. Understanding the intricate interactions between high-fat diets, body weight, body organs and biochemical parameters is essential for devising effective prevention and treatment strategies for obesity and related metabolic disorders.

KEYWORDS
ECG, Female Albino rats, High-fat diet, Obesity

INTRODUCTION

Obesity has been emerged as a significant global health issue and a prominent risk factor for various disorders. It is linked to increased morbidity and mortality, and is associated with a wide range of medical conditions. Obesity is characterized by the accumulation of excessive body fat and is primarily attributed to an energy imbalance, particularly when consuming diets high in fat (Lian *et al*., 2020).

A positive correlation exists between daily lipid intake and both body weight and fat accumulation (Rodrigues *et al*., 2012). When animals are exposed to a high-fat diet (HFD), it frequently leads to the development of obesity. The composition of fats appears to play a significant role in this process, as saturated fats (such as palmitic acid) have a more harmful effect compared to unsaturated fats (Lutz and Woods, 2012).

As per the World Health Organization, obesity has become a global epidemic, with its prevalence nearly tripling between 1975 and 2016. In 2015, an estimated 1.9 billion adults worldwide were considered overweight, accounting for 39% of the global population. Individuals with obesity face an increased risk of various diseases, including hypertension, dyslipidemia, insulin resistance (IR), glucose intolerance, type 2 diabetes, coronary heart disease, arthritis, sleep apnea, and certain types of cancer. Consequently, obesity has a detrimental impact on life expectancy in the modern world. It not only affects physical and mental health but also has significant economic consequences (Mika *et al*., 2022).

Furthermore, the development of obesity and disturbed lipid metabolism due to a high-fat diet (HFD) is linked to the accumulation of fat in the liver, leading to nonalcoholic fatty liver disease (NAFLD) and potential hepatic failure. This condition results in increased serum activities of ALT and AST enzymes (Altunkaynak, 2005). In addition, obesity is characterized by persistent low-level inflammation, which triggers adipose tissue to release various adipokines and pro-inflammatory factors (Jin and Zhang, 2020).

Long-term feeding on HFD in rats for 4 weeks and its effect on their relative organs' weights have been previously studied. They found that after 4 weeks of feeding, liver weight of rats fed on HFD was significantly higher than of rats fed on normal diet (Piña-Zentella *et al*., 2016). Furthermore, the high-fat diet also impacts the erythrogram and leukogram, leading to changes in their counts, which can either decrease or increase depending on the duration of HFD feeding (Egbung *et al*., 2009). The lipid profile is also affected by the high-fat diet, resulting in an elevation of serum total cholesterol (TC), triglycerides (TGs), and low-density lipoprotein cholesterol (LDL-C), along with a significant reduction in high-density lipoprotein cholesterol (HDL-C) levels in the rats fed on the HFD (Ghasi *et al*., 2000).

Therefore, our study aimed to explore the impact of a high-fat diet (HFD) on various aspects, including body weight and relative organ weights, hematological parameters, serum biochemical parameters and electrocardiography as well as histo-

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pathological studies.

MATERIALS AND METHODS

Animals and diet

Twelve female Albino rats were obtained and housed at the Animal House, Faculty of Science, Suez Canal University, Egypt. The rats were divided into two groups, with six rats in each group, and three rats were kept together in a single cage. They were allowed to acclimate to their surroundings for two weeks under normal room temperature and natural daylight conditions. During this period, they were provided with a standard basal diet and access to water to maintain a reasonable weight. The research protocol was approved by the Institutional Animal Ethics Committee of Suez Canal University (Protocol No. IS/BT/PHD10-11/001). Both control and HFD were formulated according to Kilany *et al*. (2020).

Study design

The experimental rats were divided into two groups as follows:
Group I: received control diet during the whole experimental period (12 months).
Group II: received HFD all over the experimental period (12 months).
Both experimental diets were offered *ad libitum*.

Feed consumption and body weight

The rats' initial and final body weights were recorded. The weight gain was calculated for each rat at the end of experiment. Additionally, the amount of feed consumed by each rat was also recorded during the study.

Blood and samples collection

Two retro-orbital blood samples were taken from rats that had fasted overnight under effect of tetrahydrofuran (THF) inhalation anesthesia. The first blood sample was collected in a tube containing the di-potassium salt of ethylene diamine tetraacetate (EDTA) for evaluating hematological parameters. The second blood sample was collected in a plain tube to obtain serum for biochemical analysis. After the blood collection, the rats were euthanized using an overdose of THF. The liver, heart, spleen, uterus, abdominal fat, and kidney were weighed, and their relative weights in relation to the body weight of the rats were calculated.

Hematological analysis

Hematological parameters were determined using established and standardized techniques through improved Neubauer hemocytometer. The percentage for each type of white cells was calculated according to Vázquez *et al*. (2007).

Biochemical parameters

Serum level of TC, TGs, LDL-C, VLDL-C, and HDL-C were determined by Spinreact, Spain kits according to the described method of Fossati and Prencipe (1982). Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities were assayed according to the methods of Center (2007). Serum creatinine and blood urea nitrogen (BUN) levels were determined according to Henry *et al*. (1974) and Reiss *et al*. (1965). All these parameters were assayed using Stanbio, Texas, USA commercial kits.

Heart-fatty acid binding protein (H-FABP) assay

The ELISA technique was employed to estimate the serum concentrations of H-FABP (Heart Fatty Acid Binding Protein) obtained from GenWay Biotech, Inc., USA. The procedures were conducted following the guidelines provided in the manufacturer's enclosed pamphlet.

Electrocardiography ECG monitoring

The rats were anesthetized using THF inhalation until they reached a state of full anesthesia. Once anesthetized, they were positioned in a supine (lying on their back) position for electrocardiogram (ECG) monitoring. Lead 2 ECG was recorded for each rat to study specific ECG parameters, including the analysis of the PR interval, ST segment changes, and ventricular rate. Subsequently, the average measurement of each parameter was calculated for every group under study.

Histopathological examination

Formalin fixed liver, kidney and Heart were subjected to routine histopathological procedures according to Selvan *et al*. (2008).The obtained slides were examined using a light microscope.

Statistical analysis

The data from the present study were subjected to statistical analysis using student's T-test to compare the different tested groups. The data were analyzed using SPS version 16 for Windows. Results were considered statistically significant at a probability level of 0.05 ($P \leq 0.05$).

RESULTS

Body weight and relative organs weights

The body weight of high fat diet group showed significant ($P \leq 0.05$) increase than normal diet group. Also, there was a significant increase in relative abdominal fat, relative liver, kidney and heart weights in high fat diet group as compared to normal diet group. The relative weight values of spleen and uterus was non-significantly ($P>0.05$) changed between experimental groups (Table 1).

Hematological parameters evaluation

The RBCs count, total WBCs, Hb and EOS % were non-significantly ($P> 0.05$) changed between experimental groups. The percentage of MON, BAS, NEU and HCT of high fat diet group exhibited a significant elevation ($P \leq 0.05$) than normal diet group. The percentage of LYM showed significant decline in HFD group than control one (Table 2).

Serum biochemical analysis

High fat diet induced a significant ($P \leq 0.05$) elevation of the levels of TC, LDL, TGs and VLDL-C in high fat diet group than

normal diet group. HDL-C level significantly (P ≤0.05) declined in high fat diet group than normal diet group. As shown in Table 3.

The high fat diet for 12 months induced elevation of liver enzymes (Table 4). Whereas ALT and AST of high fat diet group exhibited significant (P≤ 0.05) increase than normal diet group.

The level of creatinine, urea and BUN of high fat diet group exhibited significant (P≤ 0.05) increase than normal diet group. However the level of uric acid showed non-significant (P>0.05) change between experimental groups (Table 4).

Fatty acid binding protein (FABP)

High fat diet for 12 months induced a significant (P≤ 0.05) elevation of FABP than normal diet group, (Table 4).

Electrocardiography ECG monitoring

There was a significant (P≤0.05) increase in heart rate and ST segment elevation of high fat diet group than normal diet group. The values of PR interval were non-significant (P> 0.05) between two groups (Table 5 and Fig. 1).

Histopathological findings

Histopathological examination of liver showed that the normal diet group was showing normal architecture, (CV) central vein, (H) polyhedral hepatocytes with centrally located nuclei arranged in cords radiating from central vein and in between cords there are hepatic sinosoids. All of the livers of the rats from high fat diet group were showing hepatocytes with unstained cytoplasm and little vacuoles (white arrow), mononuclear cell infiltration (star) with mild fibrous connective tissue formation in between the cords (black arrow) as shown at Fig. (2).

Histopathological examination of the kidney showed that the normal diet group was showing normal architecture, (g) glomerulus which is a tuft of capillary, (rt) renal tubules, vessels in the interstitium. The kidneys of the high fat diet group revealed multiple renal tubular degeneration (white arrow), cystic dilatation

Table 1. Effect of high fat diet on body weight and relative organs weight of female albino rats (Means±SE).

Parameters / Group	ND	HFD	*p* value
Body weight	139.611±8.641^{b}	262.811±11.891^{a}	0.00
Abdominal fat relative weight	3.891±0.731^{b}	5.531±1.121^{a}	0.05
Liver	5.608±0.141^{b}	3.103±0.541^{a}	0.00
Left Kidney	0.394±0.071^{a}	0.404±0.329^{a}	0.01
Right kidney	0.461±0.041 ^{b}	1.171±0.061 ^{a}	0.00
Spleen	0.348±0.081^{a}	0.228±0.013^{a}	0.03
Uterus	0.711±0.024^{a}	0.651±0.025 ^{a}	0.08
Heart	0.741±0.011^{b}	0.862±0.032^{a}	0.02

Within the same row, means with different superscripts are significantly differed at (P ≤ 0.05).

Table 2. Effect of high fat diet on erythrogram and leukogram of female albino rats (Means±SE).

Parameters / Group	ND	HFD	*p* value
RBCs (10^{6}/µL)	5.381±0.17^{a}	4.658±0.59^{a}	0.14
Hb (g/dl)	12.931±0.6^{a}	14.571±0.5^{a}	0.06
HCT (%)	0.067±0.15^{a}	0.121±0.19^{b}	0.00
WBCs (10^{3}/µL)	6.181±0.57^{a}	6.751±0.11^{a}	0.19
LYM (10^{3}/µL)	4.231±0.38^{b}	2.041±0.37^{a}	0.01
MON (10^{3}/µL)	0.067±0.00^{b}	0.121±0.01^{a}	0.00
NEU (10^{3}/µL)	1.511±0.27^{a}	3.151±0.29^{b}	0.01
EOS (10^{3}/µL)	0.501±0.07^{a}	0.391±0.06^{a}	0.09
BAS (10^{3}/µL)	0.051±0.01^{a}	0.081±0.00^{b}	0.02

Within the same row, means with different superscripts are significantly differed at (P ≤ 0.05).
Red Blood Cells count (RBCs), Hemoglobin concentration (Hb), Hematocrit value (HCT), White Blood Cells count (WBCs), Lymphocytes (LYM), Monocytes (MON), Neutrophile (NEU), Eosinophile (EOS) and Basophile (BAS).

Table 3. Effect of high fat diet on Serum biochemical parameters of female albino rats (Means±SE).

Parameters / Group	GD	HFD	*p* value
TC (mg/dl)	81.671±1.201^{a}	106.671±1.251^{b}	0.01
HDL-C (mg/dl)	71.001±8.541^{a}	42.331±2.731^{b}	0.01
LDL-C (mg/dl)	19.671±4.671^{a}	23.001±5.511^{b}	0.01
TG (mg/dl)	62.331±4.631^{a}	98.001±12.101^{b}	0.01
VLDL-C (mg/dl)	12.471±0.931^{a}	19.601±2.421^{b}	0.01

Within the same row, means with different superscripts are significantly differed (P ≤ 0.05).
Total Cholesterol (TC), Triglyceride (TG), Low density lipoprotein (LDL-C), Very low-density lipoprotein (VLDL-C) and High-density lipoprotein (HDL-C).

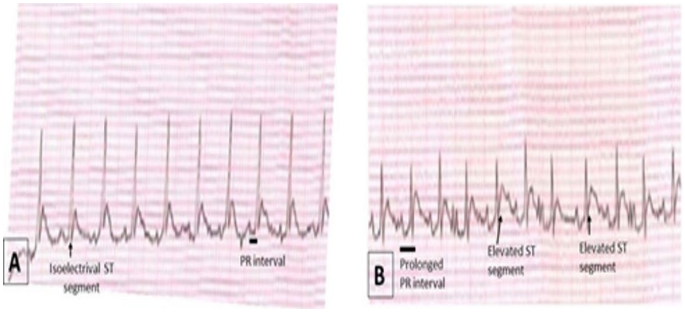

Fig. 1. Electrocardiograph (ECG) of normal diet group (A) revealed normal PR interval and isoelectrical ST segment. High fat diet (HFD) group (B) revealed elevated ST segment with prolonged PR interval.

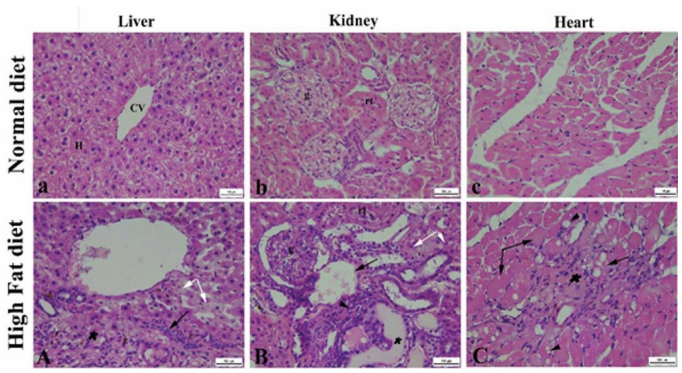

Fig. 2. Histopathological examination is showing liver, kidney, and heart tissues from normal diet group and high fat diet (HFD) group (H&E sections higher magnification X400).

(star), dilatation in glomerular capillaries and other blood vessels congestion (black arrow), mononuclear inflammatory cells infiltrations and collagen replacement (arrowhead). glomeruli (g), renal tubule (rt) (Fig. 2).

Histopathological examination of the heart showed normal architecture, individual branched and striated cardiac myocytes with highly acidophilic sarcoplasm and centrally located vesicular nucleus. Narrow spaces of endomysium were seen among myocytes. The Heart of high fat diet group revealed inflammatory cells infiltration and numerous fibroblasts (flat dense nuclei) were observed in intercellular spaces (star), in addition multi focal hyaline degeneration (loss of sarcoplasmic striation become homogenous structureless with pyknotic nuclei (black arrow) and some vacuoles formation (arrow head) (Fig. 2).

DISCUSSION

Obesity is abnormal or excessive fat accumulation triggered by disproportion in energy intake and expenditure, obesity have an increased risk of many diseases, including hypertension, dyslipidemia, insulin resistance (IR), glucose intolerance, type 2 diabetes, coronary heart disease, arthritis, sleep apnea, and some cancers. As a result, obesity reduces life expectancy in the modern world. Obesity not only impairs physical and mental health but also has many economic consequences (Mika *et al*., 2022). Therefore, the present study investigated the effect of high fat diet on some physiological parameters of female albino rats.

In current study, Feeding of HFD significantly elevated body weights of experimental animals. These results were in agreement. The obesity promoting effect to body weight was being attributed to the promotion of adipogenesis inside the body that was clear in current study. The increment of dietary fat (58% calories fat) could cause insulin resistance in rats over a short period of time (Srinivasan *et al*., 2004). Relative organs mass showed statistically different values between groups that were in harmony with Kostrycki *et al*. (2019). The possible attribution is that higher energy intake in HFD group caused promotion of weight gain consequent to the increased fat mass (Santos *et al*., 2019). Moreover, the increment relative organ weights may be due to that HFD induced low grade of inflammatory reaction as well as accumulation of fat droplets specially in liver (Ma *et al*., 2021).

For the hematological parameters, the current results showed that there were non-significant differences between RBCs count, total WBCs, Hb and EOS %. These results coincided with Kostrycki *et al*. (2019) who reported that no significant differences between HFD group and normal diet group in RBCs count, total WBCs, Hb and EOS %. The percentage of MON, LYM, BAS, NEU and HCT of high fat diet group exhibited a significant elevation than normal diet group these were in agreement with Tanaka *et al*. (1998). Neutrophilia in obese rats may be because obesity can induce glucocorticoids production which plays a role in bone marrow granulopoiesis. They enhance the mobilization of neutrophils from the bone marrow and also causes prolongation of

Table 4. Effect of high fat diet on liver enzymes, kidney function and heart-fatty acid binding protein (H-FABP) of female albino rats (Means±SE).

Parameters / Group	ND	HFD	*p* value
ALT (IU/L)	44.001±6.811[a]	60.671±8.011[b]	0.03
AST IU/L	146.331±19.341[a]	225.331±12.781[b]	0.01
Serum creatinine (mg/dI)	0.371±0.031[a]	0.611±0.061[b]	0.00
Urea (mg/dI)	47.671±2.331[a]	59.671±2.961[b]	0.00
Uric acid (mg/dI)	2.101±0.361[a]	2.931±0.591[a]	0.12
BUN (U/L)	22.331±0.881[a]	28.001±1.531[b]	0.00
H-FABP (ng/ml)	0.173±0.003[a]	0.349±0.931[b]	0.04

Within the same row, means with different superscripts are highly significantly differ (P ≤ 0.05). Serum Aspartate aminotransferase (AST), Serum Alanine transaminase test (ALT), Blood Urea Nitrogen (BUN) and Heart-Fatty acid binding protein (H-FABP).

Table 5. Effect of high fat diet on ECG of female albino rats (Means±SE).

Parameters / Group	ND	HFD	*p* value
PR interval	110.971±11.35[a]	114.721±8.381[a]	0.17
Heart Rate	138.921±2.691[a]	169.861±5.531[b]	0.00
ST Elevation	0.011±0.054[a]	0.161±0.068[b]	0.02

Within the same row, means with different superscripts are highly significantly differ (P ≤ 0.05).

their intravascular half-life (Rusten *et al*., 1994; Suwa *et al*., 2000). Lymphocytopenia in obese rats is a common finding during the systemic inflammatory response due to reduction of T-cells in peripheral blood, spleen, and thymus (Núñez *et al*., 2011).

Current results demonstrated a significant elevation in lipid profile of HFD rats than control ones causing dyslipidemia. These results were in accordance with Jain *et al*. (2010). Meanwhile, they noticed a significant reduction of HDL-C in the rats fed on HFD diet comparing with control group. This is mainly attributed to the excessive dietary fat that resulted in a lipid disorder (Karr, 2017). This is mainly attributed to the elevated non-esterified fatty acids (NEFA, or free fatty acids) resulted from their excessive spillover due to HFD (Karpe *et al*., 2011). Increased levels of NEFA can adversely affect insulin signaling, decrease muscle uptake of glucose, amplify TGs synthesis and induce gluconeogenesis in the liver (Mlinar *et al*., 2007). The liver creates cholesterol to help digestion of food and synthesize hormones (Stewart *et al*., 2020). In our experiment rats fed HFD for 12 months which leads liver to make as much cholesterol as rats need, the cholesterol in foods they eat is extra.

Our results declared that induction of obesity via HFD significantly elevated AST and ALT than normal diet group. These were in accordance with Piña-Zentella *et al*. (2016). This result is harmony with inducing obesity and abnormal lipid metabolism via the continuous effect of fat-rich feeding. The former events are associated with inflammation that occurred due to HFD and causes hepatocyte damage leading to hepatic failure causing a boost in AST and ALT level in the serum (Kameshwaran *et al*., 2013). Elevated liver enzymes due to increase malondialdehyde (MDA) during obesity, which is an indicator for extensive lipid peroxidation (Mozos *et al*., 2017). MDA plays a substantial role in oxidative stress and may disrupt the integrity of hepatic cell membranes, which causes leakage of their enzymes into blood (Yefsah-Idres *et al*., 2016).

Hight fat diet administration produced significant increment in creatinine, BUN and urea than normal diet group, this data was in accordance to Metwally *et al*. (2017). Such increase has prevalence and implications for the risk of kidney damage and chronic kidney disease (CKD) (Blüher, 2010). Excess lipid accumulation may lead to lipotoxicity and may be the major driver of organ dysfunction such as kidney injury (Declèves and Sharma, 2015). However, our results showed non-significant effect of uric acid between groups this was agreement with Arunwan Udomkasemsab (2019). Elevated kidney functions due to increase MDA level during obesity may disrupt the integrity of renal cell membrane which causes leakage of their enzymes into blood (Yefsah-Idres *et al*., 2016).

Current study showed a significant elevation of H-FABP biomarker for myocardial injury this was in agreement with Shearer *et al*. (2005) and Zhang *et al*. (2018). The induction of obesity via HFD is a predisposing factor for the dysfunction of blood vessel endothelial cells as well as cardiac injury (Hadi *et al*., 2005). This result can be considered early prediction for obesity induced myocardial injury, especially in groups where H-FABP directly correlated (Hasić *et al*., 2011). Increasing NEFA in obese subjects potentially increased oxidative stress and promoted inflammatory cytokines output (IL-6, IL-1b and TNF-α), these cytokines could cause electrophysiological remodeling in cardiac muscle (Alí *et al*., 2019).

This study showed a significant increase in heart rate and ST segment elevation of high fat diet group than normal diet group, this data was in accordance to Verwaerde *et al*. (2015). This result was harmony with the increase in fat mass, TC, LDL-C, H-FABP that were associated with impairment in cardio electrophysiology. The perturbation in ventricular muscles was reflected on the depolarization-repolarization segment (ST) causing significant elevation of such segment a rise in heart rate and ST segment.

CONCLUSION

The excessive consumption of HFD can have negative consequences for overall health. Induction obesity via HFD is associated with many metabolic abnormalities like dyslipidemia which may affect body organ's function such as hepatic, renal cell membranes and endothelial blood vessel's function changes. Also, hematological disorders are existed. Balancing the types and quantities of fats in our diet, along with adopting a healthy overall eating pattern and lifestyle, are crucial for maintaining optimal health.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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