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A physiological characterization of the high-fat diet on the induction of obesity in adult male Swiss mice

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ABSTRACT

The global prevalence of obesity and overweight is increasing, with an estimated 750 million obese and 1.8 billion overweight adults worldwide. In light of this growing health concern, this paper aimed to examine the effects of a high-fat diet (HFD) on obesity using mice as an animal model. Adult male Swiss mice, aged 12-15 weeks and weighing between 27 and 31 g, were used in this study. The mice were divided into two groups: a treatment group that was fed HFD for six weeks, and a control group maintained on a normal feeding regimen for rodents. The mice were weighed on a weekly basis throughout the duration of the study. After six weeks, the mice were put under anaesthesia and blood samples were drawn directly from their hearts for testing purposes. It was discovered that the HFD group had a greater increase in body weight (61%) compared to the control group (46%). Additionally, the abdominal fat mass in the HFD group was twice as high as that of the control group ($p < 0.005$). Staining techniques revealed that the HFD mice accumulated significantly more abdominal fat relative to total body fat than the control group. Biochemical analysis of the blood samples showed that only triglyceride (TG) levels were appreciably augmented in the HFD group in contrast to the control group ($p < 0.05$). Other factors examined, including cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), did not show significant differences between the two groups. In conclusion, this study demonstrated that a six-week HFD induced early stages of obesity development in adult male Swiss mice. These data offer valuable insights into the effects of dietary interventions on obesity and may have implications for future research and treatment strategies.

Keywords: High-fat diet, Obesity, Coronary heart disease, Biochemical analysis.
Article type: Research Article.

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INTRODUCTION

Obesity refers to the excessive accumulation of adipose tissue in specific body regions. The issue stems from an imbalance between caloric consumption and utilization (Torres-Carot *et al.* 2022; Cavaliere *et al.* 2023) Torres-Carot *et al.* 2022). While fat tissue was previously regarded as a passive storage depot, contemporary understanding acknowledges its active and dynamic role within the body. Adipose tissue has an essential function in managing body weight and energy balance through the secretion of a diverse array of bioactive molecules with significant potential (Steele & Finucane 2023). Obesity is widely recognized as a significant contributing factor to the development of chronic illnesses like certain forms of cancer, type 2 diabetes, hypertension, and coronary heart disease. The impact of obesity in childhood has grown over time. It causes both immediate and long-lasting damage. Compared to children of normal weight, obese children have higher blood pressure, insulin levels and unhealthy cholesterol profiles (Rakhra *et al.* 2020; Upadhya & Kitzman 2020; Humaidan Al-Moussawi 2022). While acknowledging the limitations of body mass index (BMI) as a precise measurement, it remains the widely adopted tool for assessing weight status. BMI provides a rough estimation of adiposity and determines overweight and obesity taking a person's weight in kilograms and dividing that by the square of their height in meters (Mohajan & Mohajan 2023). The World Health Organization (WHO) employs the BMI to categorize individuals based on their weight status. According to the WHO classification, a BMI below 18.5 kg m^{-2} is defined as undernutrition, while a BMI ranging from 18.5 to 24.9 kg m^{-2} is considered within the normal weight range. BMI values between 25 and 29.9 kg m^{-2} indicate overweight, while a BMI of 30 kg m^{-2} or higher signifies obesity. Extreme obesity is defined as a BMI equal to or exceeding 40 kg m^{-2} (Neto *et al.* 2023). In 2022, the WHO reported that over 2.55 billion adults worldwide were afflicted with excess weight or obesity. Among this staggering figure, approximately 1.8 billion individuals were classified as overweight, while approximately 750 million fell into the obese category (Fig. 1; Horta *et al.* 2023).

Fig. 1. The worldwide BMI for both women and men: The age-standardized global BMI values for (a) women and (b) men were derived from data obtained from the WHO in 2022.

While genetic factors do play a role in regulating body weight, size, composition, and metabolic responses to food intake in both humans and animals, the rapid increase in obesity worldwide cannot be solely attributed to genetics (Bertoncini-Silva *et al.* 2023). Instead, it is believed that the impact of environmental factors, such as diet, varies among individuals due to differences in genetic susceptibility. Dietary fat consumption has frequently been implicated as a causative factor in the rise of body fat accumulation (Kumar *et al.* 2021). Studies involving human subjects have demonstrated that the consumption of high-fat diets (HFDs), comprising approximately 30% of total energy intake from fat, can readily contribute to the development of obesity (Maurer *et al.* 2021; Qi & Wang 2023; Wang *et al.* 2023). Epidemiological investigations conducted in various countries, including China, Canada, and the USA, have observed a positive correlation between the increased fat intake and the prevalence of obesity. Consequently, there has been a global initiative to reduce fat consumption in the human diet (Wang *et al.* 2016, 2020; Nardocci *et al.* 2021). Research indicates that infants born to mothers with a pre-pregnancy BMI exceeding

32, classified as obese, face a 2.1-3.7 times higher risk of perinatal mortality compared to infants born to mothers with a BMI below 25 (Tambalis *et al.* 2020). Consequently, the presence of obesity as a chronic condition emphasizes the necessity for effective treatment strategies. Timely recognition and effective resolution of obstacles to treatment can lead to resource conservation and enhance the likelihood of sustained success, thereby safeguarding patients from the psychological and physical repercussions associated with weight fluctuations. To advance our understanding of obesity and evaluate potential drug combinations for treating obese individuals, it is imperative to employ laboratory models that exhibit obesity. Small laboratory animals such as mice, rats, and rabbits are commonly utilized for this purpose. However, genetic manipulation of these animal models to induce obesity presents its own challenges and complexities. Alternatively, employing larger animal models and implementing diverse feeding regimens can be costly. Hence, the current investigation aimed to propose an uncomplicated approach for inducing obesity. To evaluate the effect of obesity on metabolic organs such as the liver and kidneys, as well as the reproductive organ (testis), a cross-sectional histological study was performed.

MATERIAL AND METHODS

A total of 20 healthy adult Swiss male mice (12-15 weeks old; weighing 27-31 g) were obtained from the Department of Anatomy and Cellular Biology, College of Medicine, University of Baghdad, Iraq, for the experiment. The mice were accommodated in plastic cages and allowed to acclimate for three weeks in laboratory conditions, including a relative humidity of 35%-45%, a 12-hour light/dark cycle, and a room temperature maintained at 27 ± 2°C. They had ad libitum access to commercial pellets and tap water. All procedures involving animal subjects adhered to the ethical guidelines approved by the local Ethics Committee of the University of Baghdad. Following the completion of the third week, the mice were weighed and subsequently divided into two subgroups: a control group of 10 mice and a treatment group of another 10 mice. Throughout the study duration, the control group was provided unrestricted access to standard rodent food, whereas the treatment group was given HFD. The mice were weighed on a weekly basis. For six weeks, the treatment group had free access to HFD consisting of the following ingredients: 20 g standard rodent chow, 15 g roasted peanuts, 15 g milk chocolate, and 10 g sesame crackers. These components were scaled up by a factor of ten and mixed well. Additionally, 25 g roasted sesame seeds were added to the mixture. The mixture was then moistened with water and formed into pellets resembling regular rodent chow, which were then dried in air. One portion of the HFD contained 510 g of the specified components, with an energy value of 6308 kilojoules. The treatment group also consumed cream biscuits, which had an energy value of 2641 kilojoules per 200 g. Both groups could eat as much as they wanted from their respective diets throughout the study period. The body weight of the mice in both the control and treatment groups was measured weekly, and the average percentage alteration in body weight for each group after six weeks was calculated using the following formula:

$$\text{(Final body weight - Base body weight) / Base body weight} \times 100 \quad \textbf{(1)}$$

After fasting for 12 hours, mice were lightly anesthetized with diethyl ether [$(C_2H_5)_2O$] and cardiac blood samples were obtained and maintained at typical indoor temperatures. The serum was isolated by spinning the samples at 2500 rpm for 8 min using a commercial kit (Cayman Chemical, Ann Arbor, Mich) to measure cholesterol, LDL-C, HDL-C, and TG levels. The animals were then dissected and liver, kidney, and testis tissues were removed and fixed in Bouin's solution. The tissues were then processed, paraffin-embedded, and sliced into 8-micron sections with a microtome. Haematoxylin and eosin (H & E) staining was performed on the sections for histological examination. Moreover, the weight of abdominal fat was recorded for both groups of mice. For quantitative analysis, histomorphometric parameters were evaluated in 20 random fields of view in the liver and kidney sections of both groups. In the liver sections, the number and diameter of hepatocytes, the diameter of portal vein, and the frequency of binucleate and multinucleate cells were measured. In the kidney sections, the number and diameter of glomeruli and the diameter of collecting ducts were assessed. In the testis sections, spermatogonia stem cells A and B, primary spermatocytes, Leydig cells, and Sertoli cells were counted using the same method. To detect fat droplets accumulation, liver tissue was cut into 14-micron slices with a freezing microtome after fixation in 10% formalin. The slices were mounted on albumin-glued slides and stained with solvent black 3 ($C_{29}H_{24}N_6$) for further analysis. The mean values were compared using t-test with SPSS version 23.0 and a p-value of less than 0.05 was considered statistically significant.

RESULTS

The body weight of the treatment group exhibited a noticeable increase starting from the first week of the experiment ($p < 0.01$; Table 1). Notably, when compared to the body weight of the control group, the treatment group experienced a significant and remarkable increase in body weight during the initial week.

Table 1. A comparative analysis of weight (g) in control and treatment groups over six weeks

Weight (g)	1st week	2nd week	3rd week	4th week	5th week	6th week
Control	27 ± 1.13	29 ± 1.02	31 ± 1.87	31 ± 1.06	32 ± 1.47	35 ± 0.79
Treatment	30 ± 1.62**	37 ± 0.38***	40 ± 1.28***	41 ± 1.37***	43 ± 1.61***	44 ± 0.43***

Note: The statistical significance levels for the observed results are indicated by ** ($p < 0.01$) and *** ($p < 0.001$) respectively.

Biochemical analyses were conducted to compare the levels of cholesterol, LDL-C, HDL-C, and TG between the control and treatment groups following a six-week period (Table 2).

Table 2. A comparative analysis of weight gain (%) in control and treatment groups over six weeks.

Weight gain (%)	1st week	2nd week	3rd week	4th week	5th week	6th week
Control	0 ± 4.51	23 ± 2.06	23 ± 2.78	34 ± 3.65	37 ± 1.93	47 ± 3.85
Treatment	0 ± 7.63	24 ± 3.18	37 ± 5.63	45 ± 5.12	54 ± 3.67	56 ± 5.09

The disparity in body weight gain between the two groups under investigation intensified during the second week ($p < 0.001$), and this distinction was sustained until the conclusion of the study. Specifically, the average elevation (%) in body weight for the treatment group reached approximately 56% upon completion of the sixth week of the study, whereas the control group exhibited an estimated elevation of 47% in this index. The cholesterol levels exhibited no notable variation between the control and treatment groups. In contrast, the HFD mice exhibited lower LDL-cholesterol levels and higher HDL-cholesterol concentrations, although these variations failed to achieve statistical importance. Conversely, the measurement of TG levels demonstrated a significant increase in the treatment group ($p < 0.01$; Table 3).

Table 3. A comparative analysis of cholesterol, TG, HDL-C, and LDL-C levels in control and treatment groups.

Types of lipids (mg/dL)	Cholesterol	TG	HDL-C	LDL-C
Control	321 ± 41.78*	284 ± 22.71**	60 ± 10.33*	127 ± 15.81*
Treatment	310 ± 34.12*	398 ± 12.05**	73 ± 18.14*	112 ± 18.43*

Note: The statistical significance levels for the observed results are indicated by * ($p > 0.05$) and ** ($p < 0.01$) respectively.

The comparison of testicular tissue slides between the control and treatment groups revealed no significant difference in terms of the counted spermatogenic cells and tissue structure (Table 4; Fig. 2). Similarly, the assessment of liver tissue slides did not indicate significant alterations in the studied indices and tissue structure when comparing the control and treatment groups (Table 5; Fig. 3). In addition, the analysis of kidney tissue slides did not uncover any noteworthy distinctions across the control and treatment groups regarding pertinent parameters and tissue architecture (Table 6; Fig. 4).

Table 4. A comparative analysis of testicular tissue cell counts in control and treatment groups.

Cell counts	Spermatogonia A	Spermatogonia B	Primary	Sertoli cells	Leydig cells
Control	3.5 ± 1.34	4.1 ± 1.78	5.0 ± 1.26	1.9 ± 0.67	3.1 ± 1.17
Treatment	2.0 ± 0.84	3.4 ± 1.52	4.2 ± 1.03	1.87 ± 0.84	2.0 ± 0.73

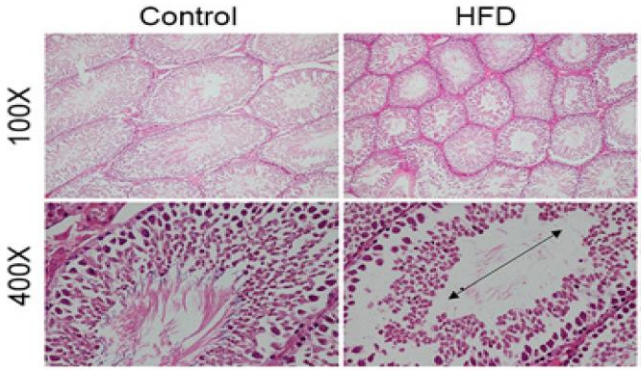
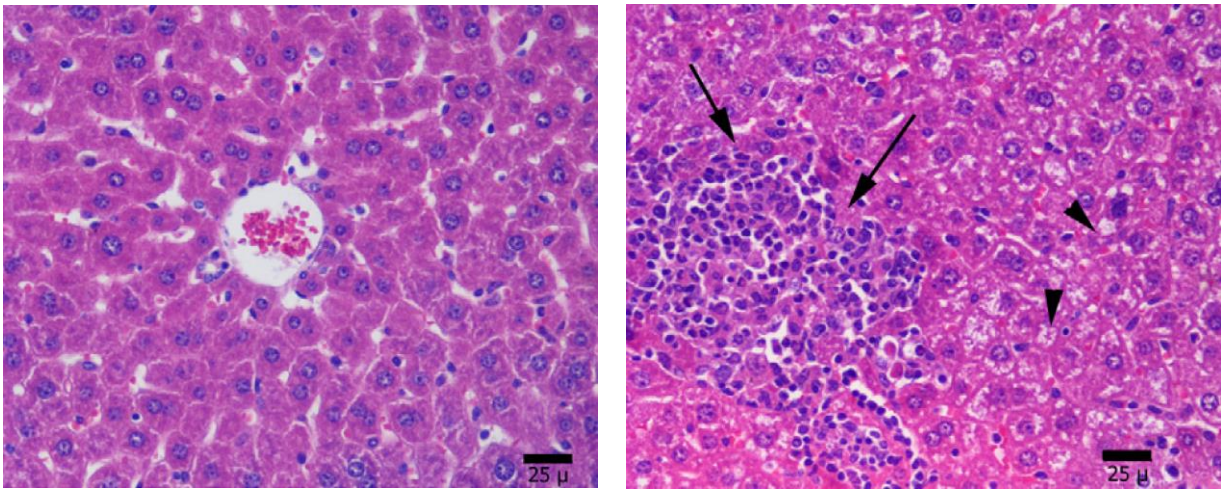


Fig. 2. Histological examination of testis tissue from rats fed an HFD. Arrowheads indicate seminiferous tubule diameter.

Table 5. A comparative analysis of liver tissue cell counts and parameters in control and treatment groups.

Cell counts/ Parameters	Hepatocytes	Hepatocytes diameter (µm)	Portal diameter (µm)	Binucleated cells	Multinucleate cells
Control	33 ± 1.56	37 ± 1.61	48 ± 7.88	7 ± 0.44	4 ± 0.18
Treatment	41 ± 2.35	39 ± 1.07	69 ± 4.12	8 ± 0.46	4 ± 0.21



(a) (b)

Fig. 3. Comparative liver histology in mice subjected to standard pellet diet and HFD. arrowheads indicate small fat droplets in hepatocytes, while arrows indicate inflammatory cell clusters. (a) control group, (b) treatment group.

Table 6. A comparative analysis of kidney tissue parameters in control and treatment groups.

Parameters	Glomeruli	Glomeruli diameter (µm)	Collecting tubule diameter (µm)
Control	7 ± 0.99	69 ± 8.56	44 ± 4.86
Treatment	6 ± 0.87	60 ± 7.61	49 ± 4.65

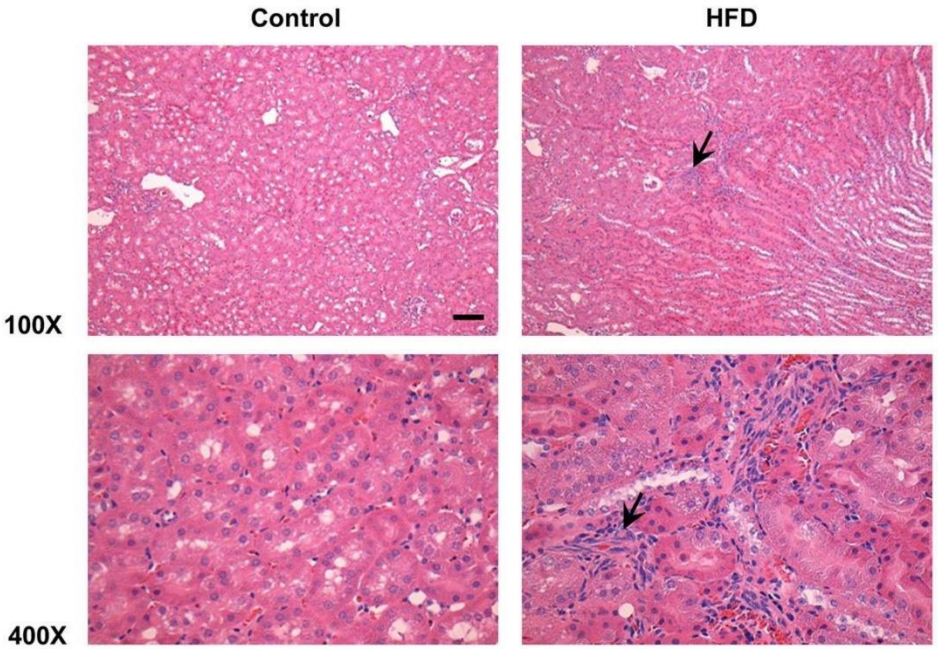


Fig. 4. Histological staining of mouse kidneys: comparison between control group and treatment group (HFD). Arrows point to inflammatory foci.

When comparing the weight of abdominal fat between the control and treatment groups, it was found that there was a significant increase in the treatment group. The control group exhibited an average weight of 0.6 ± 0.05 g, while the treatment group displayed an average weight of 1.3 ± 0.21 g. This difference was statistically significant

with a p-value of less than 0.001. Specifically, the weight of abdominal fat in the treatment group was estimated to be twice as much as that of the control group.

DISCUSSION

The purpose of this study was to pinpoint a cost-effective and efficient method to induce obesity in adult male Swiss mice swiftly. The findings revealed that the treatment group achieved a 56% elevation in body weight, with abdominal fat weight in this group being twice that of the control group. Notably, the control group experienced a 47% elevation in body weight throughout the study period. Previous studies required more time to induce obesity in laboratory models. In a study with HFD over a duration of 19 weeks, the New Zealand Obese (NZO) mice exhibited a weight gain of 24.08%, while the SJL mice experienced a mere 6.21% weight increase (Korovila *et al.* 2021). The diet administered to the mice provided an energy content of 7.14 J. In a previous study conducted by Masetto Antunes *et al.* (2022), a diet resembling the one employed in the current research was administered to male Swiss mice for a duration of 16 weeks. Through this approach, the mice exhibited a significant 96.61% elevation in body weight, while the control group experienced an estimated 61.04% upraise in body weight. Lee *et al.* (2022) conducted a study to examine the effects of a fructose-enriched diet, a fat-enriched diet, and a combination of both diets on the body weight gain of C57BL/6 mice over a three-month period. The groups that were fed HFD and the combination of the two diets exhibited a significant elevation in body weight, approximately 49.74% and 61.07% respectively, compared to the control group which experienced an approximately 12% upraise in body weight during the study duration. These findings, as depicted in the aforementioned tables, intriguingly contradict the results obtained from the group that solely consumed HFD. Notably, consumption of fructose alone did not result in a significant upraise in the body weight of the mice. In the present study, when evaluating various biochemical parameters, it was observed that only the blood serum TG levels exhibited a marked elevation in the treatment group compared to the control. Fat cells primarily serve as repositories for glycerides, and consequently, an upsurge in adipose tissue contributes to elevated plasma fatty acid levels, a characteristic of obesity. Conversely, the involvement of these compounds in cholesterol synthesis appears to be relatively less significant (Djeziri *et al.* 2018; Teng *et al.* 2018). Numerous studies have consistently documented elevated TG levels during the initial phases of obesity. For instance, Lewis *et al.* (2022) administered HFD to obese female mice for a duration of 75 days, resulting in notable increases in body weight, plasma TG levels, and cholesterol levels. In the present study, no significant variations were noted in terms of structural alterations related to cell size, cell number, or other parameters in liver, kidney, and testis tissues. However, it is important to acknowledge that previous studies have also reported instances of obesity without associated complications or abnormal clinical conditions, except for fat accumulation. Our observations can be attributed to the likelihood that the duration of the HFD employed in our study was insufficient to induce notable tissue alterations. This aligns with the findings of Eleazu *et al.* (2021), who reported that the utilization of HFD in male Sprague-Dawley rats displayed a significant impact on various biochemical parameters, while not affecting testis morphology.

CONCLUSION

In conclusion, this study demonstrates that feeding adult male Swiss mice HFD for six weeks results in significant weight gain and abdominal fat accumulation compared to control mice fed a standard diet. The HFD group experienced a 56% elevation in body weight and exhibited twice as much abdominal fat by weight compared to controls. Biochemical analysis revealed a notable elevation in serum triglyceride levels in the HFD group, indicating early metabolic alterations associated with obesity development. However, there were no notable histological changes observed in the liver, kidney, or testis between the groups. Overall, the study revealed important insights into the rapid induction of obesity achievable through high-fat feeding in the Swiss mouse model. The mice exhibited substantial weight gain and fat accumulation within six weeks, without developing obesity-related pathologies in metabolic or reproductive organs. This suggests that the mice were at the outset of weight gain, making this an optimal model for understanding the progression of obesity and testing potential treatments. The swift onset of weight gain allows for efficient future research within reasonable time frames. Furthermore, the lack of complications provides the opportunity to study obesity in isolation during its initial phases. In summary, this study suggests an effective dietary protocol to promptly induce obesity in male Swiss mice, serving as a valuable tool for obesity research focused on early intervention and therapeutic strategies.

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