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Comparison of Lipid Profile and Insulin Sensitivity in Rabbits Fed with High-Fat or High Fructose Diets

Allah Bux Kachiwal[1], Raheela Mangi[2], Mool Chand Malhi[1], Mehboob Alam Syed[2]

[1]Department of Veterinary Physiology and Biochemistry, Sindh Agriculture University, Tandojam, Sindh, Pakistan.
[2]Department of Pharmacology, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre (JPMC), Karachi, Sindh, Pakistan.

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Corresponding Author: Allah Bux Kachiwal,
Department of Veterinary Physiology and Biochemistry, Sindh Agriculture University, Tandojam, Sindh, Pakistan.
Email: kachiwal2003@gmail.com

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ABSTRACT

Obesity and metabolic syndrome are significant global health challenges influenced by dietary and lifestyle factors. This study aimed to develop an experimental rabbit model of obesity and metabolic syndrome using high-fat and high-fructose diets over 11 weeks. Rabbits were divided into three groups: group A (control) fed a basal diet, group B fed a high-fat diet, and group C fed a high-fructose diet. Key metrics assessed included body weight, fat mass, basal glycemia, glucose infusion rate (GIR), total cholesterol, triacylglycerol (TAG), and non-esterified fatty acid (NEFA) levels.
Group B (high-fat diet) showed the highest body weight (2640±70g) and fat mass (90±12.2g), while group A (control) had the lowest values (2420±40g and 63.3±9.5g, respectively). Group C (high-fructose diet) exhibited the highest basal glycemia (5.52±0.31 mmol/l) and TAG levels (2±0.30 mmol/l). GIR was highest in group A (18.5±1.2 mg/kg/min) and lowest in group B (12.9±2.0 mg/kg/min). Total cholesterol was highest in group A (2.04±0.14 mmol/l) and lowest in group C (1.83±0.14 mmol/l). NEFA levels peaked in group C (0.41±0.04 mmol/l) and were lowest in group A (0.3±0.04 mmol/l).
The study demonstrated that high-fat and high-fructose diets induce distinct metabolic changes in rabbits, modeling key features of obesity and metabolic syndrome. These findings highlight the differential impacts of these diets, providing a basis for further research into the mechanisms and dietary influences driving these conditions.

INTRODUCTION

The incidence of obesity has been steadily increasing on a global scale in recent decades, to the extent that it is now categorized as a pandemic. As per the World Health Organization (WHO), by the year 2035, an estimated 39% of individuals in contemporary society will be impacted by obesity [1]. That is why there is a growing demand for the development of new public policies focused on prevention and primary healthcare [2]. Obesity is characterized by the abnormal or excessive accumulation of body fat that can have detrimental effects on one's health[3].While the root cause has been linked to an imbalance in energy intake and expenditure due to subpar dietary choices and inadequate physical activity, it is actually a complex interplay of various elements, including genetics, hormones, and environmental factors.[4].

Consumption of a diet high in fats has been linked to dyslipidemia and an increased risk of cardiovascular disease. Research has demonstrated

that excessive consumption of dietary fats can result in heightened levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG), while often reducing levels of high-density lipoprotein cholesterol (HDL-C) [5]. Rabbits that were fed a high-fat diet containing abundant saturated fats displayed notable changes in their lipid profile, mirroring patterns seen in individuals with atherosclerosis [6]. Furthermore, these alterations in lipid parameters have been associated with underlying mechanisms related to hepatic lipid synthesis and impaired lipoprotein metabolism [7].

Numerous dietary approaches have been employed to induce obesity, insulin sensitivity (IS) reduction, and dyslipidemia in rabbits. Previous studies have associated high-fat diets with a range of metabolic issues, although the extent of metabolic alterations varied significantly [8]. Research conducted [9] has demonstrated that high-fructose diets can also lead to decreased IS and varying degrees of dyslipidemia. Comparing these studies has been complicated by the differences in dietary interventions, including food composition and duration. Identifying the most effective dietary regimen for inducing obesity in an animal model that closely mimics the human condition poses a significant challenge. The optimal diet for promoting obesity and its related conditions may be identified through long-term research.

The consumption of high-fructose diets, often fueled by the ubiquitous availability of sugary beverages and processed foods, has been linked to the onset of insulin resistance and dyslipidemia. Studies have revealed that rabbits exposed to high-fructose diets demonstrated increased levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG), coupled with reduced levels of high-density lipoprotein cholesterol (HDL-C) [10]. Changes in lipid metabolism induced by fructose are believed to arise from modified hepatic lipid processing and lipogenesis, contributing to the emergence of non-alcoholic fatty liver disease (NAFLD) and atherogenic dyslipidemia [11].

Studying high-fat and high-fructose diets helps understand how they affect metabolic health differently. Both diets lead to dyslipidemia and heart issues, but their effects on lipids may vary. Knowing these differences is crucial for creating targeted interventions to reduce risks from fats or fructose. Researching these diets on rabbits' lipid profiles provides insights into how diet affects lipid metabolism. The changes in rabbit lipids are similar to those in human disorders, showing the study's relevance. Understanding the mechanisms behind these diet impacts can help promote healthier eating habits and lower heart disease risks. The study aimed to compare lipid profiles and insulin sensitivity in rabbits on high-fat or high-fructose diets.

MATERIALS AND METHODS

Animal Groups and Diets

Twelve-week-old male Albinos were randomly assigned to one of three groups (fifteen per group): control, high fat, or high fructose. The rabbits were divided into groups and provided with a control diet for 10 weeks (comprising 39.7% maize starch, 20.0% dextrose, 5.8% sunflower oil, and 20.5% casein by weight), a high-fat diet for 11 weeks (consisting of 12.7% maize starch, 6.5% dextrose, 3.9% sunflower oil, 31.3% lard, and 28.6% casein by weight), or a high-fructose diet (composed of 59.7% fructose). The rabbits were housed individually in cages with unrestricted access to food and water. They were maintained at a controlled temperature ranging from 22 to 28°C and subjected to a 12-hour light/12-hour dark cycle. The rabbits were regularly monitored for changes in weight, food intake, and overall health throughout the study period. After the designated feeding period, blood samples were collected for biochemical analysis.

Body Weight and Body Fat Mass

Weekly body weight measurements were taken throughout the study. Body fat mass was evaluated using isotope dilution with deuterium oxide (2 H2O) at the onset of the 10-week dietary intervention (week 1) and upon completion (week 11). Blood samples (1 ml) were collected before and two hours after the administration of a deuterium oxide injection (500 mg/kg body weight). The concentration of deuterium oxide in the plasma was analyzed using Fourier-transform infrared spectroscopy.

Euglycaemic–hyperinsulinaemic Clamp Technique

Prior to and following the 11-week dietary

intervention, the euglycaemic-hyperinsulinaemic clamp technique was employed. An unfed animal was surgically implanted with a catheter in its jugular vein while under anesthesia. Blood glucose levels were monitored at five-minute intervals while insulin was administered [72 mU/kg (500 pmol/kg) for 1 minute, followed by 18 mU/kg per minute (125 pmol/kg per minute) for 3 hours]. A 20% glucose solution was infused at varying rates, with adjustments made to the glucose infusion rate (mg/kg per minute) to achieve and sustain baseline glycemia. The glucose infusion rate, a reliable indicator of insulin sensitivity under hyperinsulinemic conditions, was used to measure insulin-mediated glucose uptake. Blood glucose levels were assessed using the glucose oxidase method, while insulin levels were determined using ELISA.

Plasma Lipid Profiles

Enzymatic techniques were used to measure the basal plasma concentrations of total cholesterol, NEFA, and TAG before and after the 10-week diet period. For each group and each time period (weeks 1 and 11), the plasma samples were combined, and the plasma lipoproteins were separated using a fast-protein liquid chromatography system. Each fraction's cholesterol content was measured.

Statistical Analysis

A completely randomized design (CRD) was employed for this experiment, with three treatments (diets) and six replicates per treatment. Data were analyzed using analysis of variance (ANOVA) followed by Tukey's post-hoc test to determine significant differences between groups. The significance level was set at $p < 0.05$, and results were expressed as mean ± standard error (SE).

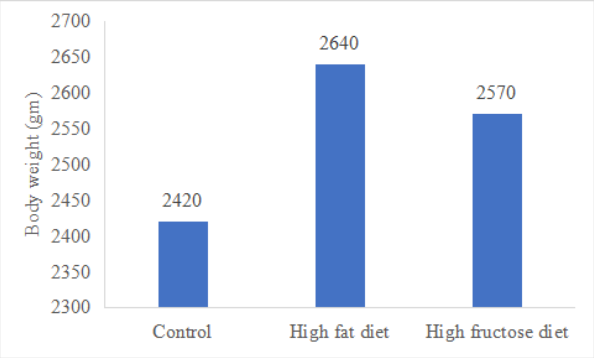
RESULTS

Live Body Weight (g)

Data indicates that maximum body weight (2640±70g) was noted in group B rabbits fed on high fat diet as compared to group C rabbits fed on high fructose diet (2570±55g). Minimum body weight (2420±40g) was recorded from group A (control; basal diet). According to Tukey's HSD test there was three distinct group which were significantly different from each other.

Figure 1

Body weight (g) of rabbits.



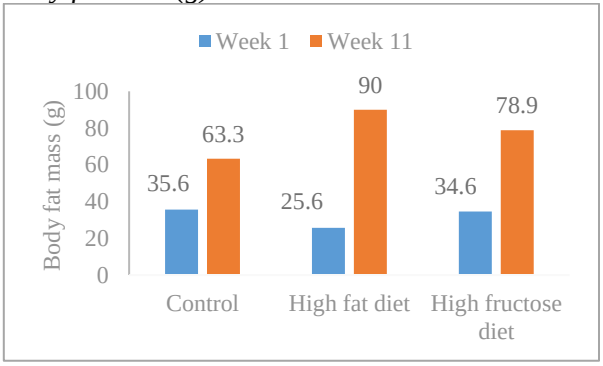
Different alphabets among the mean values shows significant difference at P<0.05

Body Fat Mass (g)

The body fat mass was increased in all groups. Maximum body fat mass (90±12.2g) was noted in group B rabbits fed on high fat diet as compared to group C rabbits fed on high fructose diet (78.9±11.8g). Minimum body fat mass (63.3±9.5g) was recorded from group A (control; basal diet). According to Tukey's HSD test there was three distinct group which were significantly different from each other.

Figure 2

Body fat mass (g).

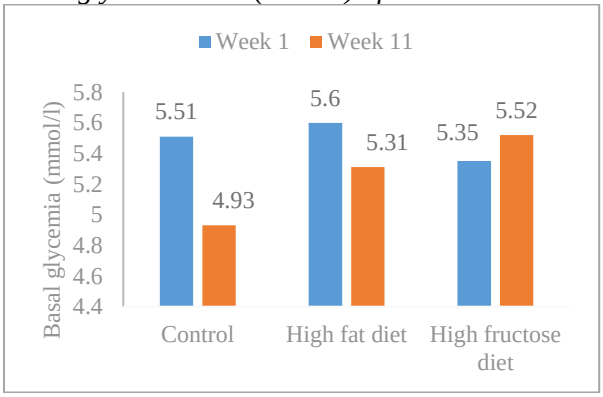


Different alphabets among the mean values shows significant difference at P<0.05

Basal Glycemia Level (mmol/l)

The basal glycemia level was decreased in all groups. Maximum basal glycemia level (5.52±0.31 mmol/l) was noted in group C rabbits fed on high fructose diet as compared to group B rabbits fed on high fat diet (5.31±0.19 mmol/l). Minimum basal glycemia level (4.93±0.25 mmol/l) was recorded from group A (control; basal diet).

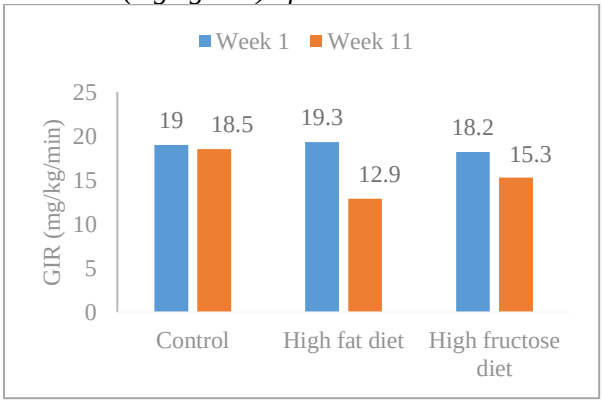
Figure 3
Basal glycemia level (mmol/l) of rabbits



Same alphabet among the mean values shows no significant difference at P>0.05

Glucose Infusion Rate (GIR) level (mg/kg/min)
The GIR level was decreased in all groups. Maximum GIR level (18.5±1.2 mg/kg/min) was noted in group A (control; basal diet) as compared to group C rabbits fed on high fructose diet (15.3±1.4 mg/kg/min). Minimum GIR level (12.9±2.0 mg/kg/min) was recorded from group B rabbits fed on high fat diet.

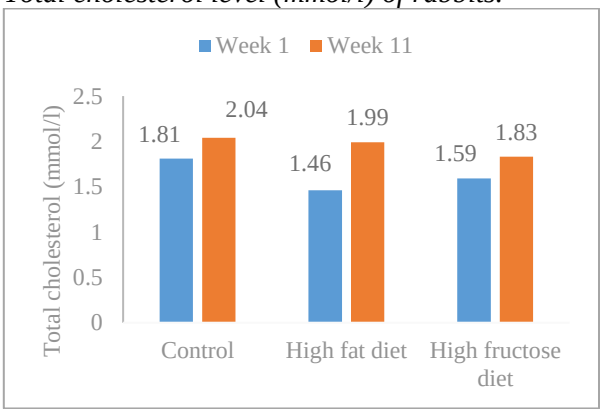
Figure 4
GIR level (mg/kg/min) of rabbits.



Same alphabet among the mean values shows no significant difference at P>0.05

Total cholesterol level (mmol/l)
The total cholesterol level was increased in all groups. Maximum total cholesterol level (2.04±0.14 mmol/l) was noted in group A (control; basal diet) as compared to group B rabbits fed on high fat diet (1.99±0.17 mmol/l). Minimum total cholesterol level (1.83±0.14 mmol/l) was recorded from group C rabbits fed on high fructose diet.

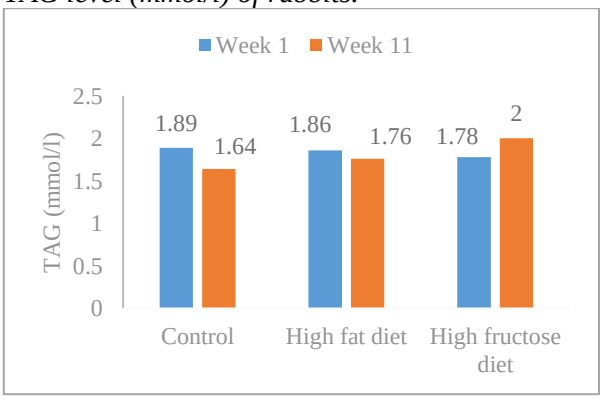
Figure 5
Total cholesterol level (mmol/l) of rabbits.



Same alphabet among the mean values shows no significant difference at P>0.05

TAG level (mmol/l)
The TAG level was decreased in A & B groups and increased in C group. Maximum TAG level (2±0.30 mmol/l) was noted in group C rabbits fed on high fructose diet as compared to group B rabbits fed on high fat diet (1.76±0.09 mmol/l). Minimum TAG level (1.64±0.10 mmol/l) was recorded from group A (control; basal diet).

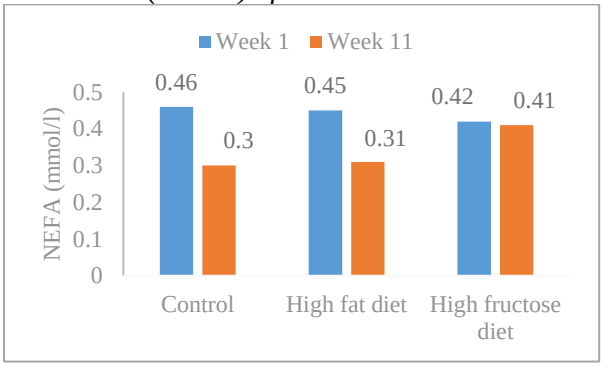
Figure 6
TAG level (mmol/l) of rabbits.



Different alphabet among the mean values shows significant difference at P<0.05

NEFA level (mmol/l)
The NEFA level was decreased in all groups. Maximum NEFA level (0.41±0.04 mmol/l) was noted in group C rabbits fed on high fructose diet as compared to group B rabbits fed on high fat diet (0.31±0.04 mmol/l). Minimum NEFA level (0.3±0.04 mmol/l) was recorded from group A (control; basal diet).

Figure 7
NEFA level (mmol/l) of rabbits.



Same alphabet among the mean values shows no significant difference at P>0.05

DISCUSSION

The study aimed to evaluate the effects of high-fat and high-fructose diets on obesity-related disorders in rabbits using a longitudinal approach. Baseline values were consistent with typical rabbit values. No previous research examined all baseline values and the relationship between obesity and insulin sensitivity. Groups were randomly created, but differences in plasma cholesterol levels were observed at baseline. Statistical analysis was conducted to account for these differences. The timing of diet exposure initiation is also important. Adult rabbits consuming a high-fructose diet have demonstrated manifestations of the metabolic syndrome, unlike their younger counterparts [2]. Consequently, the researchers opted to conduct the present study utilizing adult rabbits.

At the culmination of the 10-week period, we observed consistent body weights among all cohorts. In contrast to the control rabbits, those subjected to a high-fat diet displayed elevated body fat mass. An augmentation in adiposity has been observed in rabbits consuming a high-fat diet, which has been associated with an escalation in weight gain [13, 14, 15, 16, 8]. Obesity may arise due to various factors, including alterations in body composition, and is not solely indicated by an increase in body weight.

Since lard was employed as the primary source of dietary fat in this investigation, the escalation in body fat mass indicated the obesogenic capacity of the high-fat diet [17, 18]. The body's adipose tissue functioned as a reservoir for this excess fat. When comparing rabbits fed a high-fructose diet to control rabbits, no disparity in body weight or body fat mass was observed [9, 19, 12, 20, 21]. Previous studies [9, 20, 22] illustrated that the consumption of a diet rich in fructose (60 percent by weight) for approximately 10 weeks resulted in weight gain. Despite the increased weights of retroperitoneal, mesenteric, and subcutaneous fat depots in adult rats fed fructose, [12] noticed no alteration in body weight. This suggests that obesity is not an inevitable consequence of a high-fructose diet.

As previously elucidated in various studies [13, 23], rabbits subjected to a high-fat diet exhibited decreased insulin sensitivity (evaluated through the glucose infusion rate, a reliable indicator of insulin sensitivity as it gauges insulin-mediated glucose uptake under hyperinsulinemic conditions). Moreover, compromised insulin sensitivity has been associated with an accumulation of epididymal fat [24, 25], and the current data showing that rabbits on a high-fat diet had increased body fat mass align with previous research. However, basal blood glucose and insulin levels remained unchanged. Diminished insulin sensitivity has been correlated with hyperinsulinemia [24, 25, 23] and hyperglycemia [23] in specific trials employing a high-fat diet (lard or safflower oil). We posit that the duration of the current experiment might have been sufficient for the onset of insulin resistance but not diabetes, as the euglycemic-hyperinsulinemic clamp technique could have been employed to assess impaired insulin sensitivity prior to the manifestation of hyperglycemic and hyperinsulinemic conditions.

Conversely, when rabbits were subjected to a high-fructose diet, there were no discernible changes in their insulin sensitivity, baseline glycemia, or insulinaemia. Various other studies [19, 20, 21, 9] have reported instances of hyperglycemia; however, Nakagawa et al.[19] did not observe any alterations in glycemia following the consumption of a high-fructose meal. The occurrence of hyperglycemia can be mitigated by the increased hepatic glycogen content observed in rats on a high-fructose diet [19, 26]. Additionally, the high-fructose diet led to decreased insulin sensitivity and was associated with elevated plasma TAG and NEFA levels, as indicated by other studies [19, 22, 21, 9]. These heightened concentrations in response to a high-fructose diet,

by inhibiting the insulin signaling pathway, may significantly contribute to the development of impaired insulin sensitivity[27]. Nevertheless, the absence of dyslipidemia aligns with the preserved insulin sensitivity. Moreover, a high-sucrose diet has been shown to induce decreased insulin sensitivity in the liver prior to muscle in rat studies [28]. The euglycemic-hyperinsulinemic clamp technique, recognized as the gold standard method for directly measuring whole-body insulin sensitivity [29] was employed to assess insulin sensitivity. We propose that although a high-fructose diet did not result in impaired insulin sensitivity throughout the body, it may have caused some impairment in insulin action in the liver.

Although there was no disparity between the groups regarding plasma total cholesterol concentration, there was a significant increase over time, regardless of the diet. This increase could be attributed to aging, yet the absence of dietary cholesterol could be a factor in the lack of a noticeable impact of the diet. In a study involving hamsters, a higher intake of dietary fat, regardless of type, did not influence plasma cholesterol levels in the absence of dietary cholesterol[30]. The minimal amount of dietary cholesterol in lard might have contributed to the insignificant elevation in plasma total cholesterol observed in the rabbit subjects of the current study who were fed a high-fat diet. However, previous studies have shown that high-fructose diets have varying effects on plasma total cholesterol levels [9, 19, 20, 21, 31] and even identical high-fructose diets can display differences in outcomes. Therefore, drawing definitive conclusions about the impact of a high-fructose diet on cholesterol levels is complex. Moreover, the quantity of fat and dietary cholesterol in a high-fructose diet may influence plasma cholesterol levels. Furthermore, we observed no discrepancies in the levels of cholesterol in plasma lipoproteins, contradicting the findings of Sinitskaya et al. [14]. Conversely, Mohamed Salih et al. [21] discovered that towards the end of a high-fructose diet, VLDL and LDL cholesterol increased while HDL cholesterol decreased. The current results regarding lipoprotein cholesterol concentrations align with stable plasma total cholesterol levels, suggesting that the absence of dietary cholesterol could be the reason for the unchanged cholesterol levels.

The plasma-basal NEFA concentration did not differ between the groups. Previous studies have associated a high-fat diet with fluctuations in plasma NEFA levels [13, 14,15,16]. The results of our study, which involved administering high-fructose diets to rabbits, contradicted certain other research findings [19, 20, 21, 9]. We hypothesize that the lack of variation in plasma NEFA concentration may be attributed to the liver's potential increase in hepatic TAG storage [26] due to the sequestration of a significant amount of plasma NEFA.

In none of the groups did the plasma basal TAG concentration change. While some studies with a similar fat content did not show alterations [14, 15], others with comparable fat content did [13, 23]. Rats subjected to a high-fructose diet exhibited varying responses in plasma baseline TAG content [9,19, 21, 31, 32, 33]. Some studies have indicated that rats on a high-fructose diet displayed higher postprandial TAG concentrations, yet their baseline TAG concentrations showed no significant changes in either the short-term (2 weeks) or long-term (11 months) [33, 31]. Our present study exclusively focused on the basal TAG levels. We postulate that the rats in our research may have exhibited higher postprandial TAG concentrations compared to those observed in overnight fasted animals.

Feeding 12-week-old rabbits high-fat diets for 10 weeks causes obesity and insulin sensitivity issues. High-fructose diet doesn't improve obesity-related problems. Further research on specific fats, oils, and fatty acids is needed to understand the differences in study outcomes.

CONCLUSION

This study highlights the differential impact of high-fat and high-fructose diets on obesity-related metabolic parameters in rabbits. The findings indicate that a high-fat diet is more obesogenic, as evidenced by significant increases in body weight and fat mass. In contrast, the high-fructose diet did not lead to notable changes in body weight or fat mass but was associated with specific alterations in lipid metabolism, including increased triglycerides and non-esterified fatty acids.

While both diets induced dyslipidemia, the underlying mechanisms appeared distinct. The high-fat diet was linked to increased adiposity and

lipid storage, likely reflecting its impact on hepatic lipid synthesis and storage capacity. Conversely, the high-fructose diet led to a greater disruption in lipid metabolism, characterized by altered lipogenesis and lipoprotein metabolism, contributing to insulin resistance and the potential onset of metabolic syndrome.

These findings underscore the importance of understanding the metabolic effects of specific dietary components. High-fat and high-fructose diets influence lipid profiles and insulin sensitivity differently, suggesting that tailored dietary interventions may be required to mitigate the risks associated with each. Future studies are needed to explore the long-term implications of these dietary patterns on metabolic health and their relevance to human conditions such as obesity, dyslipidemia, and cardiovascular disease. This research provides a foundational understanding that can guide the development of targeted nutritional strategies and public health policies to combat the obesity epidemic effectively.

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