Research Article / Araştırma Makalesi

Effect of Kefir Consumption on Lipid Metabolism and Adipokine Hormones in BALB/C Mice Fed A High-Fat Diet

Yüksek Yağlı Bir Diyetle Beslenen BALB/C Farelerde Kefir Tüketiminin Lipid Metabolizması ve Adipokin Hormonlar Üzerine Etkileri

Seren ORHAN [1], Hülya ÇIÇEK [1], Mustafa ÖRKMEZ [1], Mehmet Akif BOZDAYI [1]
Efsane YAVUZ [1], Davut Sinan KAPLAN [2], Ahmet Sarper BOZKURT [2]

[1]Gaziantep University, Faculty of Medicine, Department of Medical Biochemistry, Gaziantep, TÜRKİYE
[2]Gaziantep University, Faculty of Medicine, Department of Physiology, Gaziantep, TÜRKİYE

Abstract

Background: The imbalance in pro-inflammatory and anti-inflammatory hormones secreted by the increase in fat tissue causes chronic inflammation in the fat tissue. It is thought that this chronic inflammation causes metabolic complications resulting from obesity. Kefir is a type of probiotic that has recently attracted attention in the fight against obesity. This study aimed to examine the effects of kefir consumption on lipid profile and Adiponectin, Leptin, Resistin and Irisin/FNDC5 in the high fat diet fed BALB/C mouse model.
Materials and Methods: BALB/C strain male mice were divided into three groups: control group (n = 10), high fat diet (HFD) (n = 10) and HFD + Kefir (n = 10). Mice were fed specific dietary patterns for eight weeks. The control group was given standard pellet feed. The HFD group was given a high-fat diet containing 52% fat. In addition to the high-fat feed, 15 ml/kg kefir was given to the HFD+Kefir group via oral gavage. Lipid profile was measured on an autoanalyzer using commercial kits. Leptin, Adiponectin, Resistin and Irisin/FNDC5 levels were measured by enzyme-linked immunosorbent assay (ELISA) using commercially available kits.
Results: As a result of the experiment, there was no difference between the live weight gains of the groups. Epididymal fat weights in the HFD and HFD+Kefir groups were found to be statistically significantly higher than the control group. There was no significant difference between the epididymal fat weights of the HFD and HFD+Kefir groups HDL Cholesterol (HDL-C), LDL Cholesterol (LDL-C) values in the HFD and HFD+Kefir groups were found to be statistically significantly higher than the control group. No statistically significant difference was detected between the HFD+Kefir group and the HFD group in terms of HDL-C, LDL-C values. There was no difference between groups in triglyceride values. Adiponectin and Irisin/FNDC5 values of the HFD+Kefir group were found to be statistically significantly lower than the other groups. There was no statistically significant difference between the control group and the HFD group in terms of Adiponectin and Irisin/FNDC5 values. There was no significant difference between the groups in Leptin and Resistin values.
Conclusions: It was thought that kefir may have metabolic effects through adipokines in the high-fat diet nutrition model, and it would be useful to support this with human studies.

Key Words: High fat diet, Probiotic, Kefir, Adipokines

Öz

Amaç: Yağ dokusunun artmasıyla salgılanan proinflamatuvar ve antiinflamatuvar hormonlardaki dengesizliğin, yağ dokusunda kronik inflamasyona neden olduğu, bunun da obeziteye bağlı metabolik komplikasyonlara neden olduğu düşünülmektedir. Kefir son zamanlarda obeziteyle mücadelede dikkat çeken bir probiyotik türüdür. Bu çalışma, yüksek yağlı diyetle beslenen BALB/C fare modelinde kefir tüketiminin lipit profili ve Adiponektin, Leptin, Resistin ve Irisin/FNDC5 üzerindeki etkilerini incelemeyi amaçladı.
Materyal ve Metod: BALB/C suşu erkek fareler; kontrol grubu (n=10), yüksek yağlı diyet (YYD) (n=10) ve YYD+Kefir (n=10) olmak üzere üç gruba ayrıldılar. Fareler sekiz hafta boyunca belirli diyet kalıplarıyla beslendi. Kontrol grubuna standart pelet yem verildi. YYD grubuna %52 yağ içeren yüksek yağlı bir diyet verildi. YYD+Kefir grubuna yüksek yağlı yemin yanı sıra 15 ml/kg kefir oral gavaj yoluyla verildi. Lipid profili, ticari kitler kullanılarak bir otoanalizörde ölçüldü. Leptin, Adiponektin, Resistin ve İrisin/FNDC5 seviyeleri, ticari olarak temin edilebilen kitler kullanılarak enzim bağlı immünosorbent testi (ELISA) ile ölçüldü.
Bulgular: Deney sonucunda grupların canlı ağırlık artışları arasında fark saptanmadı. YYD ve YYD+Kefir gruplarında epididimal yağ ağırlıkları kontrol grubuna göre istatistiksel olarak anlamlı düzeyde yüksek bulunmuştur. YYD ve YYD+Kefir gruplarının epididimal yağ ağırlıkları arasında anlamlı fark yoktu. YYD ve YYD+Kefir gruplarında HDL Kolesterol (HDL-K), LDL Kolesterol (LDL-K), değerleri kontrol grubuna göre istatistiksel olarak anlamlı düzeyde yüksek bulunmuştur. YYD+Kefir grubu ile YYD grubu arasında HDL-K, LDL-K değerleri açısından istatistiksel olarak anlamlı bir fark saptanmadı. Trigliserit değerlerinde gruplar arasında fark yoktu. YYD+Kefir grubunun Adiponektin ve İrisin/FNDC5 değerleri diğer gruplara göre istatistiksel olarak anlamlı derecede düşük bulundu. Kontrol grubu ile YYD grubu arasında Adiponektin ve İrisin/FNDC5 değerleri açısından istatistiksel olarak anlamlı fark saptanmadı. Leptin ve Resistin değerlerinde gruplar arasında anlamlı fark yoktu.
Sonuç: Yüksek yağlı diyet ile beslenme modelinde kefir tüketiminin adipokinler aracılığıyla metabolik etkilere sahip olabileceği ve bunun insan çalışmaları ile desteklenmesinin faydalı olacağı düşünüldü.

Anahtar Kelimeler: Yüksek yağlı diyet, Probiyotik, Kefir, Adipokinler

Corresponding Author/Sorumlu Yazar

Dr. Seren ORHAN
Gaziantep University, Faculty of Medicine, Department of Medical Biochemistry, Gaziantep, TÜRKİYE

E-mail: serenkaleli@live.com

Received / Geliş tarihi: 04.10.2023

Accepted / Kabul tarihi: 26.12.2023

DOI: 10.35440/hutfd.1371056

This article was produced from thesis number 710565 at the National Thesis Center in 2022.

Introduction

Although the main function of adipose tissue is energy storage, it also secretes large amounts of hormones called adipokines (1). Adipokines secreted by white adipose tissue are involved in a wide variety of metabolic processes, including glucose and lipid metabolism, eating behavior and regulation of energy intake (2). Intestinal microbiota has been found to be associated with the pathogenesis of some metabolic diseases. Regulation of the intestinal microbiome is applied as a useful treatment in the treatment of these diseases. Probiotics are microorganisms that regulate and improve the microbial balance in the intestine with regular use intestinal microbiota has been found to be associated with the pathogenesis of some metabolic diseases (3). Studies in animal models and humans have shown that probiotics have beneficial effects on obesity and its complications (4). Kefir is a drinkable type of probiotic obtained by fermentation of milk (5). Studies have shown that kefir has many cancer-preventing, immune-regulating and improving effects on lipid metabolism. However, the effects of kefir on lipid metabolism and obesity and the mechanisms through which these effects occur are still a matter of curiosity (6). This study was planned to determine the effects of kefir on lipid parameters (LDL Cholesterol, HDL Cholesterol, Triglyceride) and Adiponectin, Leptin, Resistin and Irisin/FNDC5 in a mouse model fed with a high-fat diet.

Materials and Methods

This study was approved at the Gaziantep University Experimental Animals Local Ethics Committee meeting held on 25.12.2019 with decision number 2019/45. Additionally, this study was supported by Gaziantep University Scientific Research Projects Management.

In this study, BALB/C male mice obtained from Gaziantep University Experimental Animal Research Center were used. Mice were fed for 12 hours during the day and 12 hours at night in an environment with 23°C room temperature and 50-60% relative humidity. Mice were randomly divided into three groups and fed with the following dietary patterns for eight weeks (56 days).

Standard diet (control) group (n=10): Healthy mice fed with standard pellet feed and water ad libutum were given 15ml/kg of water by oral gavage.

High-fat diet group (HFD) (n=10): Prepared HFD and water were given ad libutum. Water was given by oral gavage at 15ml/kg.

Kefir + High fat diet group (Kefir+HFD) (n=10): 15ml/kg kefir prepared daily was given via oral gavage to mice fed with HFD ad libutum.

High Fat Diet (HFD)

Standard pellet feed was purchased from a specialized commercial feed manufacturer. In standard pellet feed, 14% of the energy is obtained from fats, 59% from carbohydrates and 27% from protein. A high-fat diet was prepared by the researcher by adding 40 g of butter to 100 g of standard pellet feed (7). The result of the analysis of the high-fat diet is as follows: Carbohydrate 21.91 g/100 g, protein 8.35 g/100 g, fat 52.01 g/100 g, energy 589.37 kcal/100 g, moisture 11.27 g/100 g and ash content 6.46 g/100 g. In the high-fat diet used in our study, 80% of the energy is obtained from fats, 14% from carbohydrates and 5% from protein.

Preparation of Kefir

A total of 100 g of live kefir grains were used to ferment one liter of pasteurized milk. Milk and kefir grains were cultured in a glass container in a dark environment at 25 °C for 24 hours. Kefir grains were obtained from Danem Milk and Dairy Products (Isparta, Turkey). After 24 hours, the cultured milk was filtered through a sterile plastic strainer. Kefir milk was prepared daily throughout the experimental period. Lactic acid bacteria, molds and yeasts in the prepared kefir milk are counted and listed in the Table 1.

Table 1. Counting of microorganisms in kefir milk

Microorganism	Quantity
Total Lactic Acid Bacteria count	$1.4x10^6$ (kob/mL)
Total Aerobic Mesophilic Bacteria Count	$1.15x10^8$ (kob/mL)
Total Yeast and Mold Count	$1.9x10^8$ (kob/mL)
Total Coliform count	not found

Measuring Body Weight and Visceral Fat Weight

Feeds were prepared daily. All mice were weighed manually at the same time on the same day every week. To determine the visceral fat weight, epididymal visceral adipose tissues were removed from the anterior, lateral and dorsolateral parts of the prostate of the mice after euthanasia and their weights were weighed using a precision scale.

Biochemical Parameters

At the end of the experiment, male BALB/C mice were anesthetized intraperitoneally with 60 mg/kg ketamine and 10 mg/kg xylazine, and blood samples were taken intracardiacly and transferred to yellow-capped biochemistry tubes. After 30 minutes, blood samples were centrifuged (4000 rpm, 10 minutes). Serum samples were stored in Eppendorf tubes at −80 °C. LDL Cholesterol (LDL-C), HDL Cholesterol (HDL-C) and Triglyceride levels were measured on the Beckman Coulter AU5800 (Japan) autoanalyzer using Beckman Coulter commercial kits (Ireland). The method uses an enzymatic method to measure. Leptin, Adiponectin, Resistin, Irisin\FNDC5 levels of serum samples were measured by enzyme-linked immunosorbent measurement (ELISA) method using a commercially available kit (USCN, China).

Statistical Method

The suitability of the data for normal distribution was determined by the Shaphiro Wilk test. One-way ANOVA and LSD multiple comparison tests were used to compare normally distributed numerical variables in three groups, and Kruskal Wallis and Dunn multiple comparison tests were used for non-normally distributed characteristics. Mean median and standard deviation values were given as descriptive statistics. Analyzes were performed with the help of the SPSS statistical software package (version 24.0 for Windows, SPSS Inc., USA) and p<0.05 was considered significant.

Results

There was no statistically significant difference between the last week average weights of the groups and the average weight gains of the groups (p>0.05) (Table 2). A significant difference was found between the epididymal fat weights of the groups (p = 0.001). Epididymal fat weights of the HFD group and HFD+Kefir group were found to be significantly higher than the control group. There was no significant difference between the epididymal fat weights of the HFD and HFD+Kefir groups (p>0.05) (Figure 1).

Table 2. Comparison of weights and weight changes between groups

Variables	Control (n=9)	HFD (n=9)	HFD+Kefir (n=10)	
	Mean± SD	Mean± SD	Mean± SD	p
Week 1 weight (gr)	24,88 ± 4,22	29,56 ± 3,24	24,3 ± 2,11	0,003
Week 9 weight (gr)	28,38 ± 2,56	31 ± 3,67	28,7 ± 2,63	0,155
Week 1-9 weight change (gr)	3,5 ± 3,85	1,44 ± 4,56	4,4 ± 3,6	0,284

HFD: High Fat Diet, SD: Standard Deviation, p <0.05.

A statistically significant difference was found between the groups in HDL-C, LDL-C values (p=0.001). There was no statistical difference between the groups in triglyceride values (p>0.05). HDL-C and LDL-C values were found to be higher in the HFD and HFD+Kefir groups than in the control group, and there was no difference between the HFD+Kefir group and the HFD group (Figure 2, Figure 3, Figure 4) . There was no statistically significant difference between the groups in Leptin and Resistin values (p>0.05). A statistically significant difference was found between the groups in Adiponectin and Irisin/FNDC5 values (p=0.001). Adiponectin and Irisin/FNDC5 values of the HFD+Kefir group were found to be lower than the other groups. There was no difference between the control group and the HFD group (p>0.05) (Table 3).

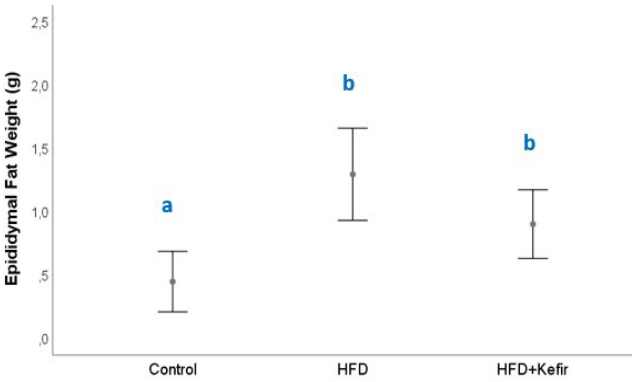

Figure 1. Comparision of the epididymal fat weights between groups. Different superscript letters between bars indicate significant difference (p<0.05).

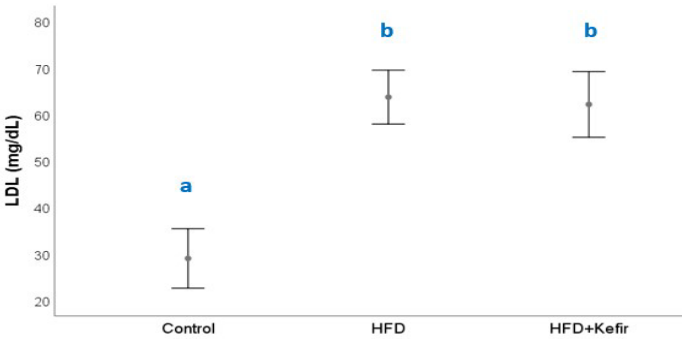

Figure 3. LDL-C values of Control, HFD, HFD+Kefir groups. Different superscript letters between bars indicate significant difference (p<0.05).

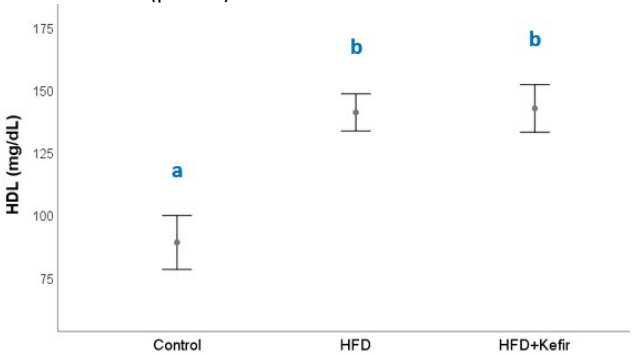

Figure 2. HDL-C values of Control, HFD, HFD+Kefir groups. Different superscript letters between bars indicate significant difference (p<0.05).

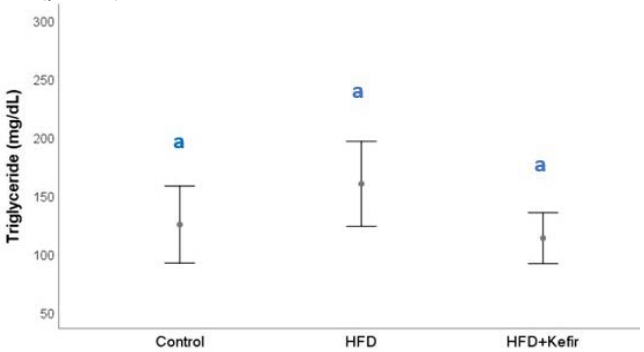

Figure 4. Triglyceride values of Control, HFD, HFD+Kefir groups. Different superscript letters between bars indicate significant difference (P<0.05).

Table 3. Comparison of Resistin, Adiponectin, Leptin, FNDC5/Irisin values between groups

Variables	Control (n=9)	HFD (n=9)	HFD+Kefir (n=10)	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**p**
Resistin (ng/mL)	55,27 ± 30,97	45,68 ± 22,54	52,87 ± 17,65	0,683
Adiponectin (ng/mL)	22,64 ± 8,60	22,06 ± 5,01	9,56 ± 7,39	0,001
Leptin (ng/mL)	236,14 ± 171,79	214,36 ± 181,74	283,7 ± 134,17	0,649
	Median (%25-%75)	**Median (%25-%75)**	**Median (%25-%75)**	
FNDC5/Irisin (ng/mL)	886,61 (599,61-1425)	1228 (851,9-1833,7)	356,56 (170,3-1311,3)	0,001

HFD: High Fat Diet, SD: Standard Deviation, p <0.05.

Discussion

In humans or animal models, excess fat from high-fat diets leads to obesity. In general, diets in which more than 30% of the total energy comes from fat cause obesity (8). In mice fed a high-fat diet, increased lipid molecules in the body are stored in the liver and fatty tissues (9). Therefore, measuring body fat in mice is a more sensitive indicator in determining obesity (10).

Li et al. compared the weight gain and lipid parameters of mice using four different mouse strains fed HFD. While Kunming and ICR mice gained significantly more body weight than control, C57BL/6 and BALB/C mice fed HFD, which is frequently used in obesity studies, did not show a significant increase in body weight compared to the control group. In our study, no significant difference was found between the body weights of the HFD group and HFD+Kefir group compared to the control. The lack of significant weight gain in mice despite HFD feeding may depend on the type and metabolic functions of the mice (9). According to our study, epididymal fat tissue weight in mice fed HFD and HFD+Kefir was found to be higher than the control group. It was observed that the epididymal fat weight in the HFD+Kefir group was lower than the HFD group, but this difference was not statistically significant.

However, one study investigated the effects of four different kefirs (three conventional and one commercial) on weight gain, plasma cholesterol, and triglycerides in a mouse model of high-fat diet-induced obesity (10). The study showed that kefir consumption in a high-fat diet could reduce plasma cholesterol and triglyceride levels and weight gain. However, they have shown that different types of kefir have different levels of effects on weight gain and cholesterol levels. This has shown that differences in the microbial population of kefir are important in determining the effect of kefir on health (10). Considering similar results in the literature, it is thought that the effect of kefir consumption on visceral fat is related to the application time of kefir and the microbiological content of kefir (11).

It is generally accepted that HFD feeding disrupts the lipid profile by increasing triglyceride and LDL-C levels and decreasing HDL-C levels (12). LDL-C values increased in the HFD and HFD+Kefir groups, but no effect of kefir on LDL-C was observed. HDL-C values of HFD and HFD+Kefir groups were found to be significantly higher than the control group.

HDL-C is thought to be a beneficial factor in reducing blood lipid levels. HDL-C is generally expected to decrease in HFD-fed mice. Some studies in the literature are compatible with our current results (13-15). Li et al. created a high-fat diet-induced obesity model using four mouse strains and compared their lipid values. Interestingly, in this study, they found that obese mice had higher HDL-C than control mice in 3 mouse strains, including the BALB\C strain. Little information is available in the literature to explain the increased HDL-C values in obese mice. In our study, carbohydrate and protein rates are quite low compared to the standard diet due to the added fat to the diet. It is classified as a low-carbohydrate diet with a carbohydrate content of less than 26% of total energy (16). According to the results of a meta-analysis, applying a high-fat and low-carbohydrate diet increased LDL-C and HDL-C levels and decreased triglyceride levels (17, 18). According to a review examining the effect of diet on cardiovascular disease and lipid and lipoprotein levels, dietary saturated fatty acids predominantly increase LDL-C levels, with a modest increase in HDL-C (17).

Leptin controls body weight by controlling energy intake and energy expenditure. Serum Leptin concentrations generally correlate with body fat percentage, and higher serum levels have been found in obese individuals (19). Resistin is a hormone that has been proven to be associated with insulin resistance in rodents (20). Resistin is thought to be less associated with insulin resistance in humans than in rodents. Resistin plays a more active role in regulating inflammatory processes in humans (21). In our study, no statistically significant difference was found between groups in Resistin and Leptin levels.

Adiponectin mediates insulin function and glucose homeostasis, and circulating Adiponectin levels are negatively correlated with body fat mass and insulin resistance (20). Adiponectin values of the HFD+Kefir group were found to be lower than the other groups. Unexpectedly, there was no difference in Adiponectin values between the control group and the HFD group. Cipryan et al. examined leptin and lipid parameters in a study in which healthy individuals applied a high-fat and low-carbohydrate diet for 12 weeks. It was observed that Adiponectin levels increased significantly and Leptin levels decreased in the high fat low carbohydrate fed group

(22). In our study, the fact that Adiponectin remained constant despite the high fat content in the diet may be due to the decrease in carbohydrate content in the diet . The effects of probiotics on circulating Adiponectin in humans are uncertain. While some studies show that certain probiotics increase serum Adiponectin levels (23), Zhang et al. showed in their study in diabetic nephropathy patients that probiotics can significantly reduce Adiponectin levels (24). Oksaharju et al. also reported in their study that HFD increased Adiponectin levels and probiotic application prevented this increase (14). It found no consistent effect of probiotics specifically on Adiponectin and leptin. It was thought that the most important reason for the inconsistency between studies was the different effects of the probiotic types and doses used (23).

Irisin is an adipomyokine encoded from the Fibronectin Type III Domain 5 (FNDC5) gene and activated after cleavage of the protein of the same name. Irisin is secreted primarily by muscle and in small amounts by adipose tissue (25). FNDC5/Irisin protects individuals from metabolic diseases by promoting the conversion of white adipose tissue into brown adipose tissue (26). Some studies have examined the connection between irisin and obesity in humans, but the results are not consistent. some studies found a positive correlation between serum irisin levels, body mass index (BMI) and adiposity (27-29). It has been observed that the level of irisin in circulation decreases with weight loss after dietary changes. The reason for the increase in irisin in obesity may be due to the development of irisin resistance or the increase in the amount of irisin secreted from adipose tissue due to the increase in the amount of fat in the body (25). In our study, it was thought that the decrease in the amount of irisin due to kefir use may be due to the breaking of the resistance of this irisin or the decrease in the amount of epididymal fat. This made us think that there may be a relationship between probiotic use and FNDC5/Irisin levels.

Since there are limited studies on this subject in the literature, the effects of kefir on adipokine hormones in HFD nutrition have not yet been elucidated. It is thought that determining the effects of probiotic supplements on adiposity and lipid metabolism and understanding the mechanisms behind them will be useful in the treatment of obesity-related metabolic diseases. In our study, only blood levels of hormones were determined. In addition, it is thought that determining the expression levels of genes related to the production of these hormones in further studies will give us more detailed information. We also think that the lack of carbohydrate metabolism data in the study is one of the limitations of our study. It was thought that kefir may have metabolic effects through adipokines in the high-fat diet nutrition model, and it would be useful to support this with human studies.

Ethical Approval: *This study was planned at Gaziantep University, Department of Medical Biochemistry and was approved by the Gaziantep University Experimental Animal Local Ethics Committee meeting dated 25.12.2019 with decision number 2019/45.*

Author Contributions:
Concept: S.O. ,H.Ç., M.Ö.
Literature Review: S.O.
Design : S.O. H.Ç. M.Ö.
Data acquisition: S.O. ,M.A.B., E.Y., A.S.B., D.S.K.
Analysis and interpretation: S.O, H.Ç
Writing manuscript: S.O.
Critical revision of manuscript: H.Ç, M.Ö
Conflict of Interest: *The authors have no conflicts of interest to declare.*
Financial Disclosure: *This study was supported by Gaziantep University Scientific Research Projects Management Unit: TF.UT.20.15..*

References

1. Koebnick C, Black MH, Wu J, Shu YH, MacKay AW, Watanabe RM, et al. A diet high in sugar-sweetened beverage and low in fruits and vegetables is associated with adiposity and a pro-inflammatory adipokine profile. The British journal of nutrition. 2018;120(11):1230-9.
2. Rouhani MH, Hadi A, Ghaedi E, Salehi M, Mahdavi A, Mohammadi H. Do probiotics, prebiotics and synbiotics affect adiponectin and leptin in adults? A systematic review and meta-analysis of clinical trials. Clinical nutrition (Edinburgh, Scotland). 2019;38(5):2031-7.
3. Kim DH, Kim H, Jeong D, Kang IB, Chon JW, Kim HS, et al. Kefir alleviates obesity and hepatic steatosis in high-fat diet-fed mice by modulation of gut microbiota and mycobiota: targeted and untargeted community analysis with correlation of biomarkers. The Journal of nutritional biochemistry. 2017;44:35-43.
4. Gérard P. Gut microbiota and obesity. Cellular and molecular life sciences : CMLS. 2016;73(1):147-62.
5. Azizi NF, Kumar MR, Yeap SK, Abdullah JO, Khalid M, Omar AR, et al. Kefir and Its Biological Activities. Foods (Basel, Switzerland). 2021;10(6).
6. Choi JW, Kang HW, Lim WC, Kim MK, Lee IY, Cho HY. Kefir prevented excess fat accumulation in diet-induced obese mice. Bioscience, biotechnology, and biochemistry. 2017;81(5):958-65.
7. Vitaglione P, Mazzone G, Lembo V, D'Argenio G, Rossi A, Guido M, et al. Coffee prevents fatty liver disease induced by a high-fat diet by modulating pathways of the gut–liver axis. 2019;8.
8. Hariri N, Thibault L. High-fat diet-induced obesity in animal models. Nutrition research reviews. 2010;23(2):270-99.
9. Li J, Wu H, Liu Y, Yang L. High fat diet induced obesity model using four strainsof mice: Kunming, C57BL/6, BALB/c and ICR. Experimental animals. 2020;69(3):326-35.
10. Peluzio M, Dias MME, Martinez JA, Milagro FI. Kefir and Intestinal Microbiota Modulation: Implications in Human Health. Frontiers in nutrition. 2021;8:638740.
11. Rosa DD, Grześkowiak ŁM, Ferreira CL, Fonseca ACM, Reis SA, Dias MM, et al. Kefir reduces insulin resistance and inflammatory cytokine expression in an animal model of metabolic syndrome. 2016;7(8):3390-401.
12. Li J, Pang B, Shao D, Jiang C, Hu X, Shi J. Artemisia sphaerocephala Krasch polysaccharide mediates lipid metabolism and metabolic endotoxaemia in associated with the modulation of gut microbiota in diet-induced obese mice. International journal of biological macromolecules. 2020;147:1008-17.
13. Li J, Wu H, Liu Y, Yang L. High fat diet induced obesity model

using four strainsof mice: Kunming, C57BL/6, BALB/c and ICR. Exp Anim. 2020;69(3):326-35.
14. Ivanovic N, Minic R, Dimitrijevic L, Radojevic Skodric S, Zivkovic I, Djordjevic B. Lactobacillus rhamnosus LA68 and Lactobacillus plantarum WCFS1 differently influence metabolic and immunological parameters in high fat diet-induced hypercholesterolemia and hepatic steatosis. Food & function. 2015;6(2):558-65.
15. Lee HS, Nam Y, Chung YH, Kim HR, Park ES, Chung SJ, et al. Beneficial effects of phosphatidylcholine on high-fat diet-induced obesity, hyperlipidemia and fatty liver in mice. Life sciences. 2014;118(1):7-14.
16. Feinman RD, Pogozelski WK, Astrup A, Bernstein RK, Fine EJ, Westman EC, et al. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. Nutrition (Burbank, Los Angeles County, Calif). 2015;31(1):1-13.
17. Feingold KR. The Effect of Diet on Cardiovascular Disease and Lipid and Lipoprotein Levels. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext. South Dartmouth (MA): MDText.com, Inc. Copyright © 2000-2023, MDText.com, Inc.; 2000.
18. Burén J, Ericsson M, Damasceno NRT, Sjödin A. A Ketogenic Low-Carbohydrate High-Fat Diet Increases LDL Cholesterol in Healthy, Young, Normal-Weight Women: A Randomized Controlled Feeding Trial. Nutrients. 2021;13(3).
19. Kapar FS, Ciftci G. The effects of curcumin and Lactobacillus acidophilus on certain hormones and insulin resistance in rats with metabolic syndrome. J Diabetes Metab Disord. 2020;19(2):907-14.
20. Zorena K, Jachimowicz-Duda O, Ślęzak D, Robakowska M, Mrugacz M. Adipokines and Obesity. Potential Link to Metabolic Disorders and Chronic Complications. International journal of molecular sciences. 2020;21(10).
21. Haluzik M, Haluzikova D. The role of resistin in obesity-induced insulin resistance. Current opinion in investigational drugs (London, England : 2000). 2006;7(4):306-11.
22. Cipryan L, Dostal T, Plews DJ, Hofmann P, Laursen PB. Adiponectin/leptin ratio increases after a 12-week very low-carbohydrate, high-fat diet, and exercise training in healthy individuals: A non-randomized, parallel design study. Nutrition research (New York, NY). 2021;87:22-30.
23. Noormohammadi M, Ghorbani Z, Löber U, Mahdavi-Roshan M, Bartolomaeus TUP, Kazemi A, et al. The effect of probiotic and synbiotic supplementation on appetite-regulating hormones and desire to eat: A systematic review and meta-analysis of clinical trials. Pharmacological research. 2023;187:106614.
24. Zhang Y, Meng X, Ma Z, Sun Z, Wang Z. Effects of Probiotic Supplementation on Nutrient Intake, Ghrelin, and Adiponectin Concentrations in Diabetic Hemodialysis Patients. Alternative therapies in health and medicine. 2023;29(4):36-42.
25. Perakakis N, Triantafyllou GA, Fernández-Real JM, Huh JY, Park KH, Seufert J, et al. Physiology and role of irisin in glucose homeostasis. Nature reviews Endocrinology. 2017;13(6):324-37.
26. Arhire LI, Mihalache L, Covasa M. Irisin: A Hope in Understanding and Managing Obesity and Metabolic Syndrome. 2019;10(524).
27. Park KH, Zaichenko L, Brinkoetter M, Thakkar B, Sahin-Efe A, Joung KE, et al. Circulating irisin in relation to insulin resistance and the metabolic syndrome. The Journal of clinical endocrinology and metabolism. 2013;98(12):4899-907.
28. Liu JJ, Wong MD, Toy WC, Tan CS, Liu S, Ng XW, et al. Lower circulating irisin is associated with type 2 diabetes mellitus. Journal of diabetes and its complications. 2013;27(4):365-9.
29. Stengel A, Hofmann T, Goebel-Stengel M, Elbelt U, Kobelt P, Klapp BF. Circulating levels of irisin in patients with anorexia nervosa and different stages of obesity--correlation with body mass index. Peptides. 2013;39:125-30.