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Comparison of a dietary stilbene and a medium-chain fatty acid on visceral white adipose tissue CD36 expression and hepatic steatosis in diet-induced obesity

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Abstract

Background

High-fat/high-fructose diets (HFFD) are known to lead to visceral adiposity and hepatic steatosis. This study hypothesized that dietary interventions with resveratrol (RSV) or lauric acid (LA) could mitigate these effects of HFFD by modulating the expression of CD36 in visceral white adipose tissue (vWAT).

Methods

Male C57BL/6 mice, subjected to a six-week trial, were fed either a standard control diet (10% kcal fat) or an HFFD diet, which combined a high-fat diet (60% kcal fat) with 5% fructose-supplemented water. Additional to the HFFD diet, RSV (7.5 mg/kg) and LA (750 mg/kg) were orally supplemented. Dietary intakes, weight gain, body composition, vWAT CD36 levels, and hepatic histopathology were evaluated.

Results

Compared to the control, HFFD significantly increased total body weight gain and body fat percentage ($p < 0.05$). RSV supplementation attenuated HFFD-induced weight gain ($p < 0.05$), while both RSV and LA significantly reduced total body fat percentage ($p < 0.05$). HFFD led to a significant elevation in vWAT CD36 levels (1.51 ± 0.20 ng/mg protein) compared to the control (0.69 ± 0.07 ng/mg protein; $p < 0.05$). The vWAT CD36 levels of HFFD-RSV (0.98 ± 0.13 ng/mg protein) and HFFD-LA (0.76 ± 0.21 ng/mg protein) were lower than HFFD ($p < 0.05$). HFFD group demonstrated clear evidence of fat accumulation (microvesicular steatosis), alongside noticeable cellular degeneration within the hepatocytes ($p = 0.0001$), both of which were not seen by RSV and LA intake.

Conclusion

These findings indicate that dietary RSV and LA intake may protect against HFFD-induced adiposity and hepatic steatosis, and CD36 in vWAT may be a key mechanistic pathway.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) has gained prominence as a major metabolic complication of the obesity epidemic. The prevalence of NAFLD is shown to be higher in individuals with overweight and obesity (≈40%-60%) compared to the general adult population (25%) [1]. Currently, it is hypothesized that the link between fatty liver disease and metabolic dysfunction may be visceral obesity. Consequently, investigating the adipose tissue is critical to uncover the link between fatty liver pathophysiology and obesity [2].

Metabolic dysfunctions such as adipose tissue storage dysfunction and ectopic triglyceride accumulation in several non-adipose organs, most notably the liver are associated with visceral obesity [2]. One mechanistic link between obesity and hepatic steatosis is the dysregulated flux of plasma free fatty acids (FFA) and the redistribution of intracellular triglycerides from adipose tissue toward the liver. Under these pathological conditions, the membrane receptor CD36 (fatty acid translocase), may be an underlying mechanism. CD36 facilitates the excessive uptake of FFA in tissues, thereby accelerating adiposity and hepatic lipid deposition [3–5]. While previous studies have shown that hepatic CD36 expression is significantly upregulated by diets high in fat [5] and fructose [3–5], the impact of specific nutrients on adipose CD36 expression associated with hepatic steatosis remains poorly understood.

Dietary polyphenols, such as resveratrol (*trans*-3,4',5-trihydroxystilbene) have been shown to mitigate the effects of died-induced obesity in rodent models [6–8]. Resveratrol (RSV) is a polyphenolic compound in the diet (grapes, berries, red wine, and nuts) under the stilbene group. RSV has been shown to have anti-lipogenic effects in the liver associated with decreased *de novo* fatty acid synthesis, as well as triacylglycerol synthesis, and increased fatty acid oxidation [9]. Furthermore, RSV has been reported to protect against obesity by inhibiting adipogenesis and enhancing lipid mobilization in adipose tissue [10].

Concurrently, interest in the metabolic effects of lauric acid, the primary medium-chain fatty acid (MCFA) in coconut oil, is growing. Lauric acid (LA), which is also a saturated fatty acid (SFA) has been shown to prevent obesity and hepatic steatosis by preventing hepatic lipid accumulation, reducing inflammation, and mitigating insulin resistance [11]. However, reported positive effects of LA such as lowering inflammation in specific tissues, its health impact is controversial and its specific influence on adipose tissue has not been fully investigated [8, 11, 12].

Despite the known risks of diets high in fat and added sugars, there is a lack of data regarding the modulation of adipose CD36 and its association with hepatic steatosis in response to RSV or LA supplementation. Therefore, the objective of the current was to evaluate how RSV and LA supplementation influences obesity induced by HFFD, particularly concerning its impact on CD36 expression within visceral adipose tissue.

2. Material and Methods

2. 1. Animals and dietary interventions

Following the ARRIVE guidelines and with ethical approval from the Hacettepe University Animal Ethics Committee (Ankara, Turkey), this study utilized 32 male C57BL/6 mice. These animals, aged eight weeks and weighing between 24 and 27 g, were sourced from Hacettepe University Experimental Animal Research and Husbandry Unit (Ankara, Turkey). Throughout the experiment, mice were housed in a climate-controlled environment (22 ± 1°C temperature, 45 ± 5% humidity) with a 12:12-hour light-dark cycle. Both standard chow and water were provided ad libitum. Due to an unexplained death, the final sample size for the HFFD-RSV group was adjusted to n = 7 (total n = 31).

Following a seven-day standardization phase on standard chow, mice were randomized into four distinct treatment groups. The control group (n = 8) was maintained on a standard diet (Research Diets #D12450J, 4.4 g fat/100 g, 3.82 kcal/g;), while the remaining groups - HFFD (n = 8), HFFD-RSV (n = 7), and HFFD-LA (n = 8) - were transitioned to a high-fat diet (Research Diets #D12492, 34.9 g fat/100 g, 5.21 kcal/g;) supplemented with 5% (w/v) fructose in their water. To evaluate the bioactive compounds, RSV (7.5 mg/kg/bw, Solgar Inc., New Jersey, USA) [7] and (750 mg/kg/bw, Merck & Co., New Jersey, USA) [13], were administered via daily oral gavage, prepared fresh in 0.9% NaCl. Control and HFFD mice received a corresponding vehicle gavage (0.9% NaCl) to standardize for handling stress. This 6-week intervention utilized diets sourced from Arden Research & Experiment Co., Ltd., adhering to NRC and OpenSource Diets guidelines (Table 1).

Table 1
Composition of the diets administrated with feed, water and gavage during the dietary study

Diet Composition **	**Experimental Diet Groups***			
	Control	**HFFD**	**HFFD-RSV**	**HFFD-LA**
Energy (kcal/g)				
Energy, feed (kcal/g)	3.83	5.21	5.21	5.21
Carbohydrate (% energy)				
Carbohydrate, feed (% energy)	70	20	20	20
Fat (% energy) ***	10	60	60	60
Protein (% energy)	20	20	20	20
Carbohydrate source (g/100 g chow)				
Corn starch	52.13	-	-	-
Maltodextrin	14.22	16.15	16.15	16.15
Sucrose	-	8.89	8.89	8.89
Cellulose	4.74	6.46	6.46	6.46
Fat source (g/100 g chow)				
Palm oil	4.26	-	-	-
Butter (anhydrous)	-	34.89	34.89	34.89
Protein source (g/100 g chow)				
Casein	18.95	25.85	25.85	25.85
L-cysteine	0.28	0.39	0.39	0.39
Others (g/100 g chow)				
Mineral mix	0.95	1.29	1.29	1.29
Vitamin mix	0.95	1.29	1.29	1.29
Choline chloride	0.19	-	-	-
Choline bitartrate	-	0.26	0.26	0.26
Dicalcium phosphate	1.23	1.68	1.68	1.68
Calcium carbonate	0.52	0.71	0.71	0.71
Potassium citrate	1.56	2.13	2.13	2.13

Diet Composition **	Experimental Diet Groups*			
	Control	HFFD	HFFD-RSV	HFFD-LA
Energy (kcal/mL)				
Energy, water (kcal/mL)	-	0,2	0,2	0,2
Carbohydrate (% energy)				
Added fructose, water (% energy)	-	100	100	100
Resveratrol (mg/kg)	-	-	7,5	-
Lauric acid (mg/kg)	-	-	-	750

* Control is the standard chow diet; HFFD is the high fat high fructose diet; HFFD-RSV is the resveratrol added high fat high fructose diet; HFFD-LA is the lauric acid added high fat high fructose diet.

** The diet composition was divided into 3 parts that are; feed, water, and gavage subsequently.

*** The energy from lauric acid was ignored due to very low contribution.

2.3. Collection of tissues

Upon completion of the intervention, 16-week-old mice underwent a 5-hour fast. Anesthesia was induced using a subcutaneous cocktail of ketamine and xylazine (0.1 and 0.02 mg/g body weight, respectively) [4, 5, 8]. Following euthanasia, the liver and various visceral fat tissues (specifically mesenteric, retroperitoneal, and epididymal adipose tissues) were dissected. These samples were immediately snap-frozen in liquid nitrogen and transferred to -80°C storage. The remaining carcasses were likewise kept at -80°C for subsequent analysis of total body fat and protein [4, 14].

2.4. Body composition analysis

The body total water, protein and fat composition was analyzed in the carcasses of all mice. To determine the body water content the carcasses were oven-dried as previously described [15]. The dehydrated carcasses were homogenized and sampled for estimation of protein content by the Kjeldahl method estimated nitrogen content [14] and for fat content by Soxhlet extraction [4, 14].

2.5. Measurement of CD36 in visceral white adipose tissue

Visceral white adipose tissue (vWAT), comprising epididymal, retroperitoneal, and mesenteric fat depots, was collected and analyzed as a pooled sample. Levels of vWAT CD36 were measured using commercial ELISA kits (Bioassay Technology Laboratory, China), following the manufacturer's established protocol using an Absorbance Microplate Reader (ChromMate 4300, Awareness Technology Inc, USA). The vWAT samples were prepared as previously described [4, 5, 8]. The concentration of vWAT CD36 was expressed as ng/mg protein.

2.5. Histological procedure for the liver

Following the 6-week dietary intervention, consistent liver segments were excised and preserved in a 10% formaldehyde solution. For histological preparation, these specimens underwent a dehydration sequence using ascending grades of alcohol, followed by xylene clearing. The tissues were subsequently paraffin-embedded, and 5 µm sections were generated. These sections were then mounted on polylysine-coated slides and subjected to Hematoxylin and Eosin (H&E) staining to facilitate morphological assessment [16].

Hematoxylin Eosin (HE) staining procedure

After the liver sections were kept in the oven, the excess paraffin was removed by taking xylene. It was then passed through a series of decreasing grades of alcohol and washed with water. Sections washed with water after being kept in hematoxylin dye solution were taken into Eosin solution. The sections, which were washed with water again, were passed through a series of increasing grades of alcohol and kept in xylene. After staining, sections were examined and hepatocyte degeneration, microvesicular steatosis, inflammatory cell infiltration, lobular and portal areas were scored. Scoring was performed as 0 (absent), 1 (mild), 2 (moderate), and 3 (severe) and all data was analyzed statistically.

2.8. Statistical Analysis

Sample size was determined using G*Power software. Based on a calculated effect size of 0.5685 (derived from the expected variance between the highest and lowest group means), a total of 32 mice (n = 8 per group) was required to achieve a power of 80% (1 − β) with a type I error rate (α) of 0.05 [8]. Values are presented as the mean ± standard error (SEM). For variables following a normal distribution, a one-way ANOVA was implemented to evaluate differences across the four experimental groups, with Tukey's post-hoc test utilized for pairwise comparisons. In cases where data points were collected longitudinally (i.e. weekly body weight, feed, water, and energy intakes), we applied a repeated-measures ANOVA. Significant differences in these data were further analyzed using the Bonferroni post-hoc correction. All computations were executed in SPSS software (v.23; IBM Corp.), with a p-value threshold of 0.05 set for statistical significance.

3. Results

Food, water, energy intakes and body weight changes

Throughout the study, the control group maintained a significantly higher daily feed intake compared to all HFFD-based groups ($p < 0.05$). Conversely, daily water consumption remained consistent across all experimental groups ($p > 0.05$). Analysis of total daily energy and macronutrient profiles revealed that mice on the HFFD, HFFD-RSV, and HFFD-LA diets consumed more total energy and fat than control mice ($p < 0.05$). While carbohydrate intake was elevated in the control group ($p < 0.05$), fructose consumption was exclusively higher in the three HFFD groups due to the absence of fructose in the control diet.

Interestingly, protein intake was significantly greater in the HFFD and HFFD-RSV groups compared to the HFFD-LA and control mice ($p < 0.05$, Table 2).

Table 2
Feed, water, energy, and macronutrient intake

Feed intake (g/day)	**Control**	**HFFD**	**HFFD-RSV**	**HFFD-LA**	**p value**
	4.88 ± 0.13[a]	**4.09 ± 0.37[b]**	**4.12 ± 0.31[b]**	**3.93 ± 0.32[b]**	**< 0.0001***
Water intake (mL/day)	9.32 ± 0.24	8.87 ± 0.37	9.46 ± 0.26	9.70 ± 0.35	0.809
Energy intake (kcal/day)	18.63 ± 0.50[a]	21.51 ± 1.94[b]	21.63 ± 1.62[b]	20.68 ± 1.68[b]	< 0.0001*
Carbohydrate intake (g/day)	3.47 ± 0.09[a]	1.73 ± 0.13[b]	1.76 ± 0.10[b]	1.71 ± 0.11[b]	< 0.0001*
Fructose intake (g/day)	-	1.02 ± 0.06	1.05 ± 0.05	1.03 ± 0.05	< 0.0001*
Protein intake (g/day)	0.94 ± 0.02[a]	1.07 ± 0.09[b]	1.08 ± 0.08[b]	1.03 ± 0.08[ab]	0.018*
Fat intake (g/day)	0.21 ± 0.01[a]	1.43 ± 0.13[b]	1.43 ± 0.11[b]	1.37 ± 0.11[b]	< 0.0001*

The data is presented as mean ± standard error of the mean (M ± SEM).

One-Way ANOVA test was performed between groups.

[ab] Different symbols in the same line is presented differences between the groups (Tukey HSD post-hoc test was performed).

* Refers to the statistically significant difference between all groups.

Control is the standard chow diet; HFFD is the high fat high fructose diet; HFFD-RSV is the resveratrol added high fat high fructose diet; HFFD-LA is the lauric acid added high fat high fructose diet.

Beyond nutrient intake, we assessed the proportional contribution of each macronutrient to total daily energy. In line with the experimental design, the percentage of energy derived from fat was significantly greater in the HFFD, HFFD-RSV, and HFFD-LA groups compared to the control ($p < 0.05$). Conversely, the control group derived a larger fraction of its daily energy from protein and carbohydrates than the HFFD-based groups ($p < 0.05$). Furthermore, while the control group consumed no fructose, the HFFD-based groups obtained approximately 20% of their daily calories from this sugar ($p < 0.05$; Fig. 1A).

To assess whether the food and drink intake have influenced weight changes, body weights were followed throughout the study. The dietary intervention significantly influenced the body weight and weekly body weight gains of the mice ($p < 0.001$). Additionally, the weekly body weights and the mean

body weights of the dietary intervention weeks were not different between the groups (Fig. 1B). However, the total body weight gain of the dietary intervention groups at the end of the experiment was higher in the HFFD group than the control group ($p < 0.005$). The HFFD-RSV group had a lower total body weight gain than the HFFD group ($p < 0.05$) (Fig. 1C).

Organ weights and body composition

The calculated differences in dietary energy and macronutrient intakes may lead to changes in the body compositions and specific organs like liver and adipose tissue. Therefore, organ weights, body composition, adipose CD36 and histological analysis of the liver were analyzed. At the end of the intervention period the weights of brain, kidneys, heart and total white adipose tissue were not different between all the mice groups ($p > 0.05$). Moreover, liver organ weights were lower in the HFFD (4.50 ± 0.09%BW) and HFFD-LA (4.46 ± 0.09%BW) groups than the control (5.12 ± 0.19%BW) group ($p < 0.05$), and the HFFD-RSV (5.02 ± 0.11%BW) liver weight showed no difference than the other groups ($p > 0.05$). In addition, at the end of the intervention the Lee index did not show any difference between diet groups ($p > 0.05$) (Table 3). Furthermore, the body composition of the animals only showed significant difference in the percentage of fat weight as it was higher in the HFFD group compared to the control group ($p < 0.05$). To add, both groups of HFFD-RSV and HFFD-LA showed lower total body fat weights (%) compared to HFFD ($p < 0.05$) (Fig. 2).

Table 3
Organ weight. fat depot mass relative to body weight and lee index in mice

Brain	**Control**	**HFFD**	**HFFD-RSV**	**HFFD-LA**	**p value**
	1.68 ± 0.09	**1.50 ± 0.05**	**1.57 ± 0.06**	**1.58 ± 0.04**	**0.456**
Liver	5.12 ± 0.19[a]	4.50 ± 0.09[b]	5.02 ± 0.11[ab]	4.46 ± 0.09[b]	0.006[*]
Kidneys	1.37 ± 0.03	1.31 ± 0.04	1.38 ± 0.03	1.31 ± 0.03	0.458
Heart	0.56 ± 0.01	0.67 ± 0.06	0.64 ± 0.04	0.69 ± 0.04	0.317
Total visceral white adipose tissue[#]	4.22 ± 0.32	5.69 ± 0.75	4.42 ± 0.48	5.46 ± 0.93	0.469
Lee index (g/cm^3)	313.64 ± 2.41	317.41 ± 2.46	315.76 ± 2.09	315.12 ± 2.41	0.734

The data is presented as mean ± standard error of the mean (M ± SEM).

One-Way ANOVA test was performed between groups.

Lee index was calculated by the formula $\text{Lee index}\left(\frac{\text{g}}{\text{cm}^3}\right) = \frac{\sqrt[3]{\text{Body weight (g)}}}{\text{Body lenght (cm)}} \text{x} 1000$

[ab] Different symbols in the same line is presented differences between the groups (Tukey HSD post-hoc test was performed).

* Refers to the statistically significant difference between all groups.

[#] Total white adipose tissue was calculated by the total of epididymal fat, retroperitoneal fat, and mesenteric fat weights relative to body weight.

Control is the standard chow diet; HFFD is the high fat high fructose diet; HFFD-RSV is the resveratrol added high fat high fructose diet; HFFD-LA is the lauric acid added high fat high fructose diet.

Visceral white adipose tissue (vWAT) CD36 levels

Level of vWAT CD36 in the HFFD (1.51 ± 0.20 ng/mg protein) group was significantly higher than the control (0.69 ± 0.07 ng/mg protein) group ($p < 0.05$). The vWAT CD36 levels of the HFFD-RSV (0.98 ± 0.13 ng/mg protein) and HFFD-LA (0.76 ± 0.21 ng/mg protein) groups were lower than the HFFD group ($p < 0.05$) (Fig. 3).

Liver Histopathology and morphological assessment

In addition to vWAT CD36 levels, the presence of fatty liver was evaluated since it may be linked to high fat and fructose diets. Liver hepatocyte degeneration and microvesicular steatosis was detected in the HFFD group compared to the control ($p = 0.0001$), however these disorders were not seen in the HFFD-RSV and HFFD-LA ($p > 0.05$). The lobular and portal inflammatory infiltration were not different between groups ($p > 0.05$) (Fig. 4).

4. Discussion

Obesity and its associated metabolic disorders remain a major global health challenge, largely driven by dietary factors. Western-type diets, characterized by high intakes of fat and added sugars such as fructose and sucrose, are strongly associated with visceral adiposity and hepatic steatosis [4, 5, 8, 14, 17], partly through disruptions in lipid metabolism and increased ectopic fat accumulation. In this context, bioactive dietary compounds have emerged as potential modulators of obesity-related pathways. Resveratrol has been shown to attenuate metabolic disturbances in diet-induced obesity models and reduce hepatic lipogenesis [6–9], while LA, the predominant fatty acid in coconut oil, may exert beneficial effects on lipid accumulation, inflammation, and insulin resistance [11, 12]. Previous studies have demonstrated that CD36 mediates lipid accumulation and hepatic steatosis, acting as a fatty acid transporter that links adipose tissue and liver metabolism [3]. Therefore, in this research we evaluated RSV and LA supplementation to a HFFD-induced obesity model, focusing on CD36 expression in vWAT and its association with adiposity and hepatic alterations.

Adiposity and steatosis induced by HFFD

The current study validates previous data of increased energy [4, 18], fat [17] and fructose [4, 17, 18] intakes due to HFD [17], high fructose diets [4, 17, 18], and HFFD along with their contribution to energy (fat-, fructose-), leads to increased obesity [4, 14, 17, 19–21] and adiposity [14, 20–22] along with fat accumulation/steatosis [17, 23] in liver histopathological examinations. Further, the increased body fat percentage due to HFFD (60% of energy fat, 20% energy fructose) may be associated with increased fatty acid flux and enhanced lipid storage in adipose tissue [4].

Along with the previous data, CD36 was evaluated whether it could serve as a potential novel biomarker in obesity. In addition, increased levels of vWAT CD36 via HFFD may be [5, 17] associated with obesity and systemic inflammation also previously reported [24].

Lauric acid supplementation to HFFD

Lauric acid [25] is a emerging topic and some studies have investigated its monoglyceride form glycerol monolaurate since it is often used as a food additive (emulsifier) [26, 27]. The present study has shown that LA supplementation may protect against HFFD-induced obesity/adiposity and hepatocyte degeneration and microvesicular steatosis and that total body fat of HFFD-LA is a separating factor from HFFD. These findings are in line with previous studies reporting reduced body weight gain and total body fat [28, 29] as well as decreased hepatic lipid accumulation and improved hepatic lipid metabolism [29], following glycerol monolaurate (300–1600 mg/kg/day) supplementation to HFD (45–60%kcal fat).

Consistent with our findings, LA has been reported to ameliorate hepatic steatosis and improve metabolic parameters, including lipid profile, oxidative stress, and inflammation in HFD models [30]. However, the metabolism of the middle-chain SFA LA is still not well known. It is proposed to act both as a long-chain fatty acid and enter the lymphatic circulation and as a middle-chain fatty acid, and enter the liver following the portal vein although, the portal vein absorption of LA is shown to be less than one-fourth of the lymphatic absorption [31]. Interestingly, although LA may increase adiposity under HFD, it appears to induce less adipose tissue inflammation and metabolic dysfunction compared to long-chain SFA such as palmitic acid [12].

To our knowledge, the effects of LA or coconut oil on adipose tissue CD36 expression have not been directly investigated, highlighting a novel aspect of the present study. Previous on monolaurate [28] or coconut oil [32, 33] has reported reduced levels of CD36 in the liver [28, 32], white adipose tissue [33]), whether administered alone or alongside to a HFD (39–45%kcal fat). Such reductions are proposed as protective against fatty liver disease [28, 32] and obesity [33]. In line with these findings, the reduced vWAT CD36 levels observed in the present study may reflect a potential mechanism underlying the beneficial effects of LA. Furthermore, recent evidence also suggests that LA modulates adipose tissue metabolism by promoting lipolysis and altering the expression of key regulators of lipid turnover and energy homeostasis [11].

Resveratrol supplementation to HFFD

Resveratrol has been studied commonly in different areas of studies when compared to LA. Studies on mice have shown that RSV supplementation (5–25 mg/kg/bw or 400 mg/kg/chow) to HFD (45–60%kcal fat) [7, 34] and HFFD (52%kcal fat, 20% w/v fructose) [23] protected against obesity and adiposity by leading to reduced body weight [7, 34], brown adipose tissue weights [23] and relative abdominal, epididymal and perirhemtric fat weights [34], similarly in the present study. Nevertheless, hepatocyte degeneration and microvesicular steatosis due to HFFD was attenuated by HFFD-RSV. Correspondingly, studies on rodents have shown modulated hepatic lipid metabolism [29], diffused fat accumulation in hepatocytes [23], and anti-steatosis effects [34, 35] by protecting mitochondrial functions, inhibiting the dysfunctional lipid metabolism [35] and regulation of PPARα mRNA activity [34] after supplementation with RSV [23, 34], high RSV consisting *polygonum cuspidatum* [35] to HFD (45–60%kcal fat) [35] and HFFD (52%kcal fat, 20% w/v fructose) [23].

Furthermore, while RSV has been widely studied in the context of obesity, its effects on CD36 expression in adipose tissue remain insufficiently explored. Reduced levels of CD36 in adipose tissue of rats supplemented RSV (15 mg/kg/bw) indicated reduced fatty acid uptake for triglyceride mobilization as a protective effect against obesity [6], also shown in the present study. Adipose CD36 levels also is a separating factor between RSV and LA intake.

In conclusion, the detrimental effects of high-fat/high-fructose diets extend beyond excess body weight, leading to broader metabolic disturbances, including adipose tissue dysfunction and hepatic steatosis. The current findings offer original preclinical insights highlighting the role of adipose tissue CD36 in diet-induced obesity and its modulation by the stilbene resveratrol and the fatty acid lauric acid. The findings support the potential of resveratrol as a promising nutritional intervention in diet-induced obesity, discovering future clinical translation given its favorable safety profile. In parallel, although research on lauric acid is expanding, its metabolic pathways, interactions with other components of coconut oil, and effects in humans require further investigation. Overall, the observed beneficial effects of resveratrol and lauric acid suggest that targeted dietary strategies may contribute to the prevention or attenuation of obesity and hepatic steatosis.

Abbreviations

CD36
cluster of differentiation 36/ fatty acid translocase
FFA
free fatty acids
HFFD
high-fat/high-fructose diet
LA
lauric acid
RSV
resveratrol

SFA
saturated fatty acid
vWAT
visceral white adipose tissue.

Declarations

Data availability statement

Data available on request from the corresponding author.

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Conflict of interest

The authors declare no conflict of interest.

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Ethics Approval

All animals received ethical and human care within the provisions of the “National Ministry of Food, Agriculture, and Livestock Regulations on the Protection and Welfare of Animals Used for Experimental and Other Scientific Purposes” and Institutional guidelines. Experiments were approved by the Regional Animal Ethics Committee of Hacettepe University, Ankara, Turkey (IRB Number: 2020/10-09).

CRediT authorship contribution statement

Betul Kisioglu-Halis: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing-original draft, Writing – review & editing, Visualization, Project administration. **Esra Onal:** Investigation**. Derya Karabulut:** Investigation. **Ilyas Onbasilar:** Methodology. **Asli Akyol:** Conceptualization, Methodology, Writing – review & editing, Visualization, Supervision, Project administration. All authors read and approved the final manuscript.

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Figures

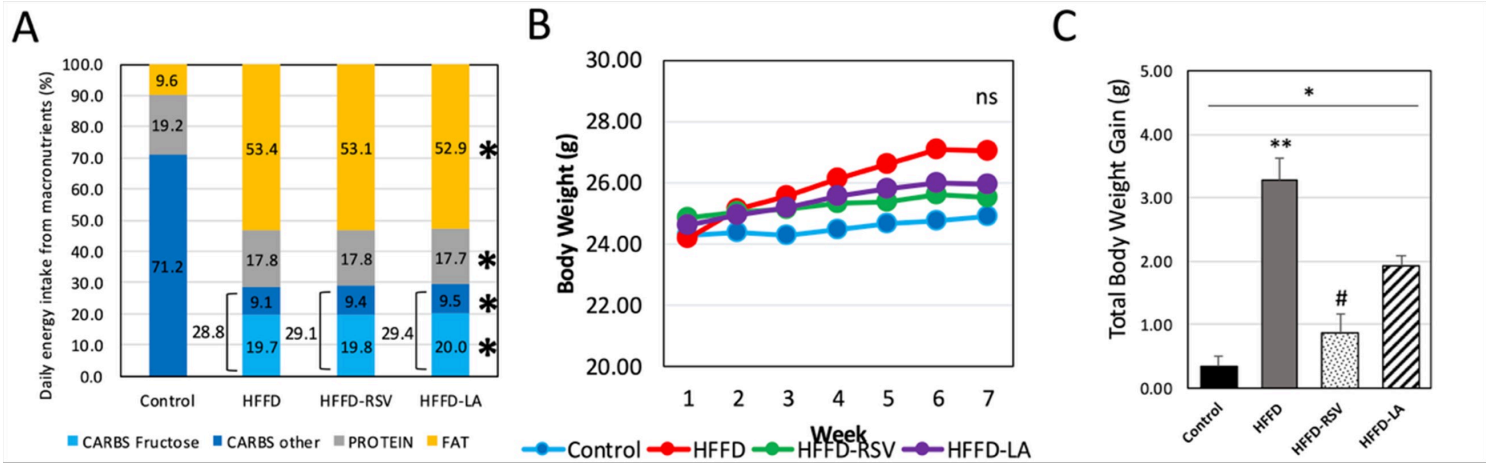


Figure 1

The body weight changes, macronutrient composition, body composition changes of mice. A) Macronutrient composition of the diets; **B)** Body weight changes; **C)** Body weight gain. Mean ± SEM. *p<0.05 One-Way ANOVA; **p<0.05 versus control; #p<0.05 versus HFFD; NS: not significant; Control: Control diet; HFFD: High fat high fructose diet; LA: lauric acid; RSV: resveratrol.

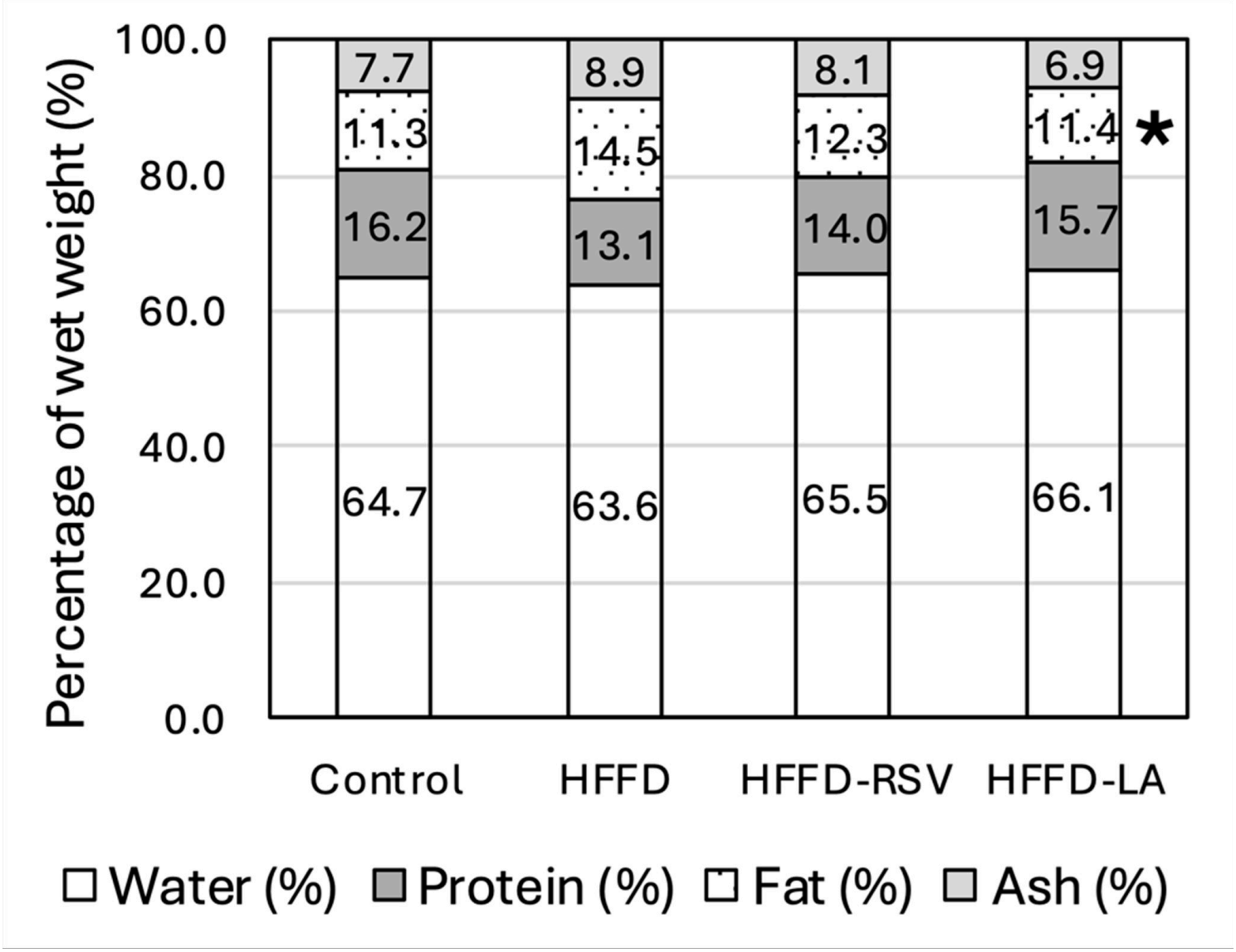


Figure 2

The body composition of the mice. Mean ± SEM. *p<0.05 One-Way ANOVA; **p<0.05 versus control; #p<0.05 versus HFFD; NS: not significant; Control: Control diet; HFFD: High fat high fructose diet; LA: lauric acid; RSV: resveratrol.

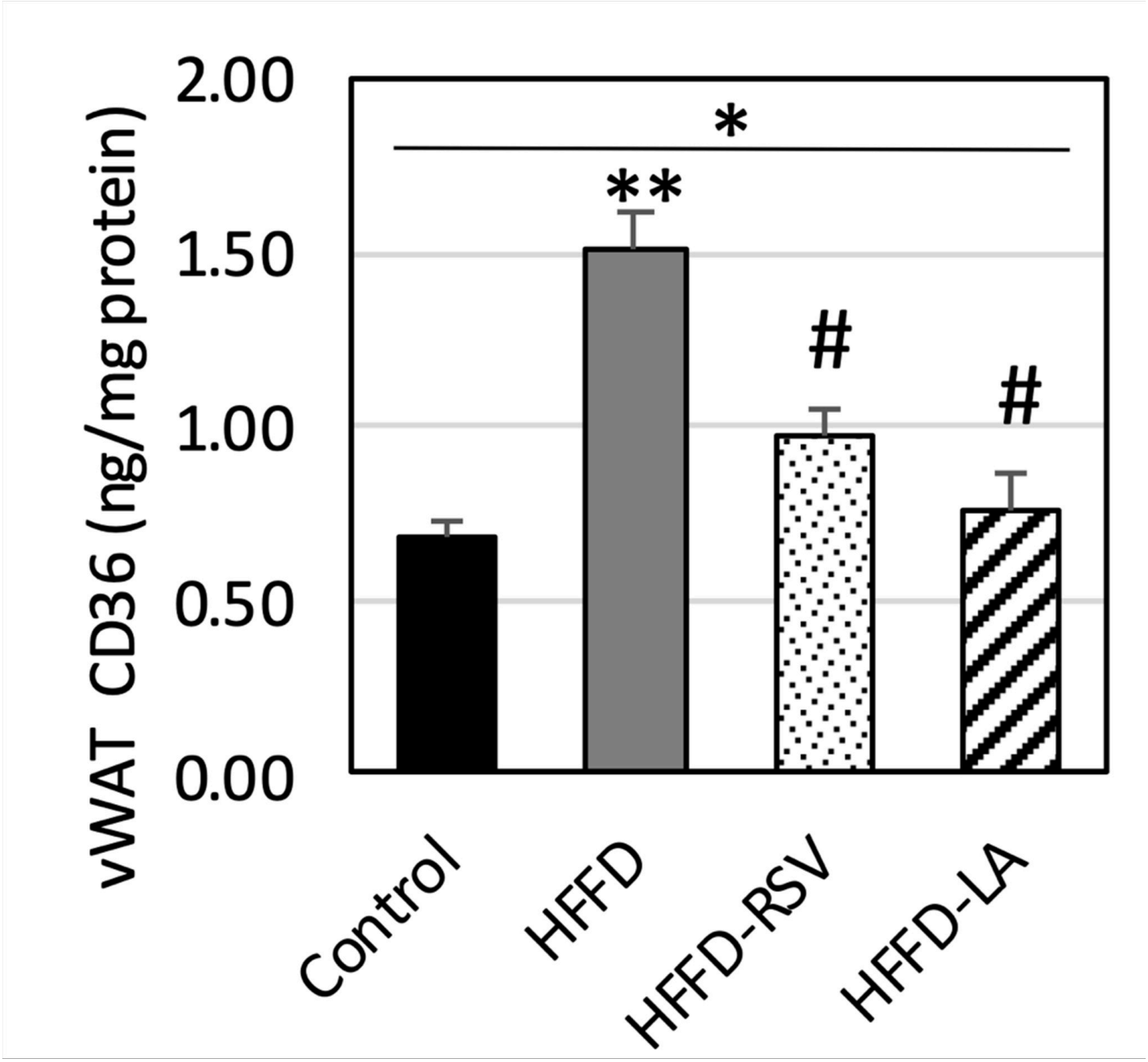


Figure 3

Visceral white adipose tissue CD36 levels of the diets. Mean ± SEM. *p<0.05 One-Way ANOVA; **p<0.05 versus control; #p<0.05 versus HFFD; NS: not significant; Control: Control diet; HFFD: High fat high fructose diet; LA: lauric acid; RSV: resveratrol; vWAT: visceral white adipose tissue.

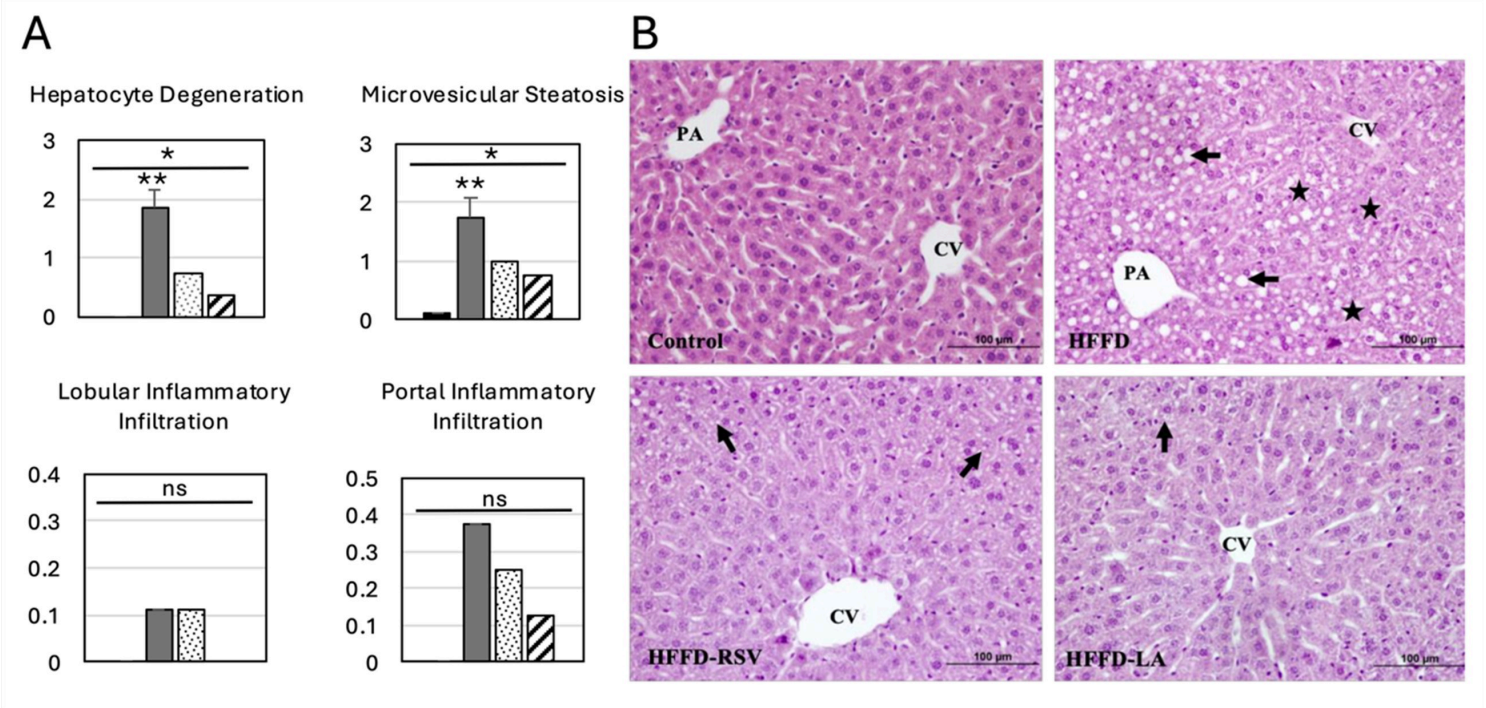


Figure 4

The hepatic lipid accumulation of the diets. A) Graphs of liver tissue histological evaluation; **B)** H&E staining of liver tissue showing hepatocyte degeneration (stars) and microvesicular steatosis (black arrows). Mean ± SEM. *p<0.05 One-Way ANOVA; **p<0.05 versus control; #p<0.05 versus HFFD; NS: not significant; Control: Control diet; HFFD: High fat high fructose diet; LA: lauric acid; RSV: resveratrol.