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Investigation of The Effects of Fatty Acids on Growth Hormone, Insulin-like Growth Factor 1, and Insulin- and Hormone-sensitive Lipase Levels in Rats

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ABSTRACT

Objective: Several studies have investigated hormones such as growth hormone (GH), insulin (INS), insulin-like growth factor-1 (IGF-1), and hormone-sensitive lipase (HSL). However, there is insufficient data on the effects of the combination of short-, medium-, and long-chain fatty acids on hormone concentrations in serum/tissue, including GH, INS, IGF-1, and HSL. The purpose of this study was to investigate the effects of butyric acid (BA), caprylic acid (CA), and oleic acid (OA) alone or in combination on GH, INS, IGF-1, and HSL secretion.

Methods: Fifty-six male Wistar rats were used in the study. The animals were separated into 8 subgroups: control, BA, CA, OA, BA + CA, BA + OA, CA + OA, and BA + CA + OA groups. Fatty acids were administered orally to rats for 21 days. At the end of the study, GH, IGF, INS, and HSL levels were measured in serum using the enzyme-linked immunosorbent assay method.

Results: BA administration reduced GH, IGF-1, and INS levels but had no significant effect on HSL levels. CA administration increased HSL levels but had no significant effect on GH, INS, and IGF-1 levels. OA administration increased GH and HSL levels but had no significant effect on IGF-1 and INS levels.

Conclusion: The combined use of fatty acids increased GH levels while decreasing INS, IGF-1, and HSL levels.

Keywords: Butyric acid, caprylic acid, oleic acid

INTRODUCTION

Fatty acids are the building blocks of fats and contain carbon atoms ranging from 2 to 34 (1). They are classified based on the number of carbons in their structures. If the number of carbons is <6, they are classified as short-chain, approximately 6-12 as medium-chain, and >12 as long-chain fatty acids (LCFAs) (2).

Short-chain fatty acids (SCFAs) are predominantly produced by gut bacterial flora via the fermentation of unprocessed carbohydrates and dietary fiber. Acetic acid (C2), propionic acid (C3), butyric acid (BA) (C4), valeric acid (C5), and caproic acid (C6) are SCFAs with various carbon chain lengths that are produced in varying amounts depending on the diet and gut bacteria composition (3). BA is a 4-carbon, colorless, oily carboxylic acid with a characteristic odor. It is soluble in water and slightly volatile at room temperature. BA, also known as butter acid, is naturally found in milk. BA has been reported to play an important role in the modulation of many diseases (3).

Medium-chain fatty acids (MCFAs) consist of fatty acids with carbon chain lengths ranging from 6 to 12 m (2). They can be digested without the need for pancreatic enzymes and bile salts. Upon reaching the small intestine, they are already in the form of fatty acids. Therefore, they are quickly transported to the liver and metabolized there. MCFAs have recently been considered as alternative treatments for certain chronic diseases, such as type 2 diabetes mellitus, epilepsy, anorexia nervosa, disorders of lipid metabolism, obesity disorders, and inflammatory bowel diseases (1). Caprylic acid (CA) (C8), caproic acid (C6), and capric acid (C10) are medium-chain saturated fatty acids. MCFAs are unique nutrients present in certain fats, such as dairy products, date kernels, and coconut oils (4). The metabolic specificity of MCFAs is associated with beneficial physiological effects, such as increased catabolism in adipose tissue and reduced fat storage in tissues (5). Studies on overweight individuals have demonstrated that diets abundant in MCFAs lead to decreased fat storage and elevated energy expenditure compared with diets abundant in LCFAs, even when the caloric intake is matched (6).

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LCFAs are the primary source of energy for many organs, particularly the muscles and liver. Oleic acid (OA) is a monounsaturated fatty acid with 18 carbons. OA alone accounts for one-third or more of the lipids in breast milk. It serves as a significant energy source and can be synthesized within the body. In adults, OA reduces the total blood cholesterol concentration. Additionally, it regulates nutrition absorption in the gastrointestinal (GI) system, keeping blood glucose and INS levels within normal limits (7).

Growth hormone (GH) is produced by somatotropic cells located in the anterior pituitary gland. Its primary role is to promote linear growth (8). It exerts its hormonal effects via insulin-like growth factor-1 (IGF-1). GH stimulates amino acid uptake. It directly accelerates mRNA transcription and translation, leading to increased protein synthesis. It also facilitates the use of fats as an energy source, thereby reducing protein breakdown (9).

IGFs are small peptides that exert their effects primarily locally and stimulate growth in specific cells. Their primary amino acid sequences are similar to each other and to human proinsulin. Structurally and functionally, they belong to the growth factor family (10). They are peptides that are dependent on GH. IGFs lead to the anabolic effects of GH and the effects that enable cell division through mitosis (9).

Insulin hormone is produced by pancreatic beta cells and is stored in granules. It is then released into the bloodstream. Elevated blood glucose levels prompt beta cells to release insulin. Glucose is the most important factor that stimulates the synthesis and release of INS (11). Insulin stimulates lipoprotein lipase activity and facilitates the clearance of chylomicrons containing excess triglycerides from circulation (12).

Hormone-sensitive lipase (HSL) is an intracellular enzyme with neutral properties that can degrade various lipid substrates, including triacylglycerols, diacylglycerol, monoacylglycerol, cholesterol esters, and other lipid and water-soluble compounds (13).

Limited literature exists concerning the impact of combined SCFAs, MCFAs, and LCFAs on hormone concentrations in serum or tissues, including GH, IGF-1, INS, and HSL. Moreover, no published research has explored the synergistic effects of different fatty acid types on the secretion of GH, IGF, INS, and HSL. This study aimed to examine the effects of SCFAs, MCFAs, and LCFAs on GH, IGF, INS, and HSL levels.

METHODS

Animals

The rats were obtained from the Düzce University Animal Research and Application Center. Fifty-six male Wistar rats aged 4-5 months and weighing approximately 390±30 grams, were accommodated under ideal environmental conditions. These conditions included a room temperature of 23 °C, humidity maintained at 60±5% and a 12-hour light-dark cycle. The rats were provided *ad libitum* access to both food and water. All study methods were reported in accordance with the Animal Research: Reporting of *in Vivo* Experiments guidelines and approved by Düzce University Local Ethics Committee on Animal Testings (decision no: 2022/07/03, meeting date: 27.07.2022).

Substances and Dosages

BA, CA, and OA were procured from Sigma (Sigma-Aldrich, Inc., St. Louis, MO, US). Each of these fatty acids was orally administered at a dose of 100 mg/kg. As an anesthetic, 90 mg/kg ketamine hydrochloride and 10 mg/kg xylazine hydrochloride were intramuscularly administered (i.m.).

Experimental Design

The rats were divided into 8 groups, each consisting of 7 rats: control (CONT), BA, CA, OA, BA + CA, BA + OA, CA + OA, and BA + CA + OA. All substances were given orally by gavage. The CONT group received only 1 mL/kg saline for 21 days. Only the BA, CA, and OA groups received either 100 mg/kg of BA, CA, or OA fatty acids for 21 days. The dual-fatty acid combination (BA + CA, BA + OA, and CA + OA) groups received a combination of 100 mg/kg of BA, CA, or OA fatty acids for 21 days. Similarly, the triple combination (BA + CA + OA) group received a combination of 100 mg/kg of BA, CA, and OA fatty acids for 21 days. Throughout the study, to examine the effects of fatty acid administration on weight changes in the animals, their weights were measured at the beginning and end of the study.

Termination of the Study

The animals in each group were subjected to cardiac puncture under ketamine/xylazine anesthesia 24 hours after the last treatment to collect blood from the heart. Subsequently, the animals were euthanized under anesthesia by cervical dislocation. The blood samples were centrifuged at 4000 revolutions per minute (rpm) for 15 minutes to separate the serum, which was subsequently stored at a temperature of -80 °C until further analysis.

Determination of Biochemical Biomarkers

The levels of GH, IGF-1, INS, and HSL in the collected serum samples were measured using enzyme-linked immunosorbent assay (ELISA). For this purpose, ELISA kits for rat GH (Cat. 201-11-0552), rat INS (Cat: 201-11-0708), rat IGF-1 (Cat: 201-11-710), and rat HSL (Cat: SRB-T-84624) were procured from SunRed (Shanghai SunRed Biological Technology, China). All parameters were measured using an ELISA reader according to the kit procedure. Additionally, blood glucose levels were determined using blood glucose measurement devices and strips.

Statistical Analysis

In comparing the groups based on serum GH, IGF-1, INS, HSL, GH, and glucose levels, One-Way Analysis of Variance (ANOVA) and the Tukey-Kramer Multiple Comparison test were utilized to determine the different groups. To compare body weights, Two-Way ANOVA was employed, and groups showing significant differences were identified using the Šídák Multiple Comparison test. A statistical significance level of $p \leq 0.05$ was considered. Prism 9 software was used for the analyses.

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RESULTS

Effects of Fatty Acids on Biochemical Parameters

A significant difference in GH levels among the groups was evident upon comparison (p<0.001) (Figure 1). The study found that the OA, BA + CA, BA + OA, and BA + CA + OA groups had significantly greater mean GH levels than the CONT group (p<0.001, p=0.02, p<0.001, and p=0.005, respectively). The BA group had significantly lower mean GH levels than the CA, OA, BA + CA, BA + OA, CA + OA, and BA + CA + OA groups (p=0.02, p<0.001, p<0.001, p=0.002, and p<0.001, respectively). Similarly, the mean GH level of the CA group was found to be statistically lower than that of the BA + OA group (p=0.03).

A significant disparity in INS levels among the groups was evident upon comparison (p=0.001) (Figure 2). Upon closer examination of the results, we determined that the INS levels of the BA, CA + OA, and BA + CA + OA groups were statistically lower than those of the CONT group (p=0.02, p=0.02, and p=0.03, respectively). Additionally, the mean INS levels of the BA + OA and CA + OA groups were lower than those of the CA group (p=0.04 and p=0.04, respectively).

The groups exhibited a statistically significant difference in IGF-1 levels (p<0.001) (Figure 3). Upon closer examination of the results, we found that the IGF-1 levels of the BA + CA + OA group were statistically lower than those of the CONT, CA, OA, and BA + CA groups (p=0.02, p=0.001, p<0.001, and p=0.02, respectively). Similarly, the IGF-1 levels of the BA group were statistically lower than those of the CA and OA groups (p=0.01 and p=0.005). Additionally, it was determined that the IGF-1 levels of the BA + CA group were statistically lower than those of the OA group (p=0.04).

There was a substantial difference in HSL levels between the groups (p<0.001) (Figure 4). Upon detailed examination of the results, The BA + CA + OA group had significantly lower mean HSL levels than the CONT, BA, CA, OA, BA + CA, and BA + OA groups (p=0.04, p<0.001, p<0.001, and p=0.03, respectively). In contrast, the mean HSL level of the CA group was significantly higher than that of the CONT, BA, BA + OA, and CA + OA groups (p<0.001). The OA group showed significantly higher mean HSL levels than the CONT, BA, and BA + OA groups (p<0.001, p=0.002,

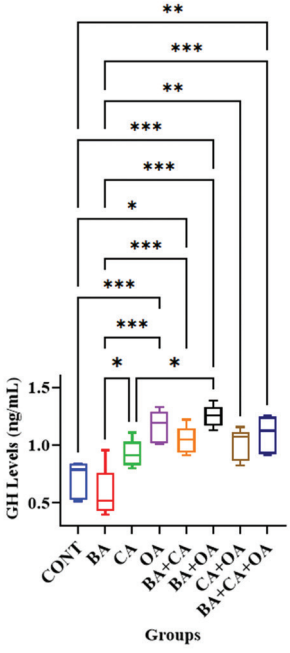

Figure 1. The effect of fatty acids on GH levels (*p<0.05, **p<0.01 and ***p<0.001)

CONT: control, BA: butyric acid, CA: caprylic acid, OA: oleic acid, GH: growth hormone

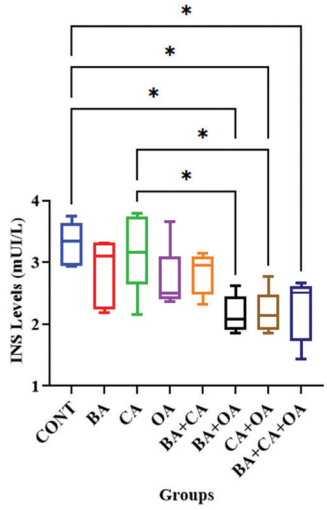

Figure 2. The effect of fatty acids on INS levels (*p<0.05)

CONT: control, BA: butyric acid, CA: caprylic acid, OA: oleic acid, INS: insulin

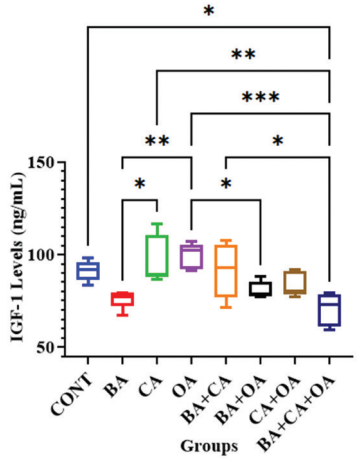

Figure 3. The effect of fatty acids on IGF-1 levels (*p<0.05, **p<0.01 and ***p<0.001)

CONT: control, BA: butyric acid, CA: caprylic acid, OA: oleic acid, IGF-1: insulin-like growth factor-1

and p<0.001, respectively). The BA + CA group had significantly higher mean HSL levels than the CONT, BA + OA, and CA + OA groups (p<0.001).

There was a substantial difference in blood glucose levels among the groups (p<0.001) (Figure 5). The BA + CA group had significantly lower mean glucose levels than the CONT, BA, CA, OA, BA + OA, CA + OA, and BA + CA + OA groups (p<0.001, p<0.001, p=0.01, p<0.001, p<0.001, and p<0.001, respectively). The mean glucose level in the CA group was significantly higher than that in the BA, BA + OA, and BA + CA + OA groups (p=0.02, p=0.01, and p=0.02, respectively).

Evaluation of the Effects of Fatty Acids on Body Weight Changes

When comparing the mean weights of the groups before and after the experiment, no significant difference was observed among them (p=0.07) (Figure 6). Overall, although the weights obtained from post-experiment measurements were higher than those obtained from pre-experiment measurements, they were not statistically significant (p>0.05). Conversely, although the weights of the CA and BA + OA groups were lower after the experiment compared with before the experiment, they were not statistically significant (p>0.05).

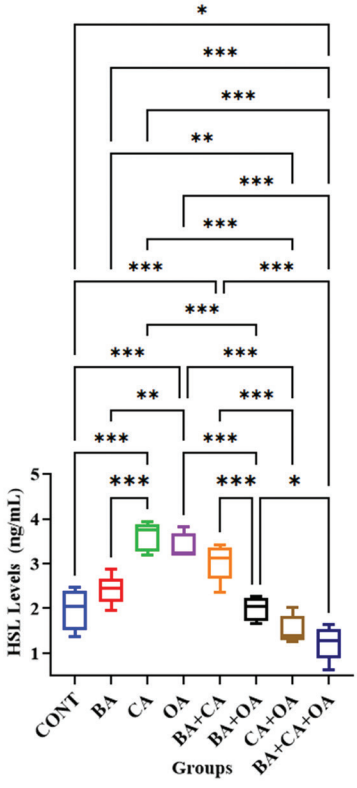

Figure 4. The effect of fatty acids on HSL levels (*p<0.05, **p<0.01 and ***p<0.001)
CONT: control, BA: butyric acid, CA: caprylic acid, OA: oleic acid, HSL: hormone-sensitive lipase

DISCUSSION

Various fatty acids are present in human nutrition, circulating in the bloodstream, and within human cells and tissues. SCFAs, MCFAs, and LCFAs serve as energy sources and membrane components. They possess biological activities that influence cellular and tissue metabolism, function, and sensitivity to hormonal and other signals. Although there has traditionally been an interest in the impact of fatty acids on health related to cardiovascular disease, it is now known that fatty acids also affect a range of other diseases, including metabolic diseases, such as type 2 diabetes, inflammatory diseases, and cancer (14). This study examined the relationships of SCFAs, MCFAs, and LCFAs with GH, IGF-1, INS, and HSL.

Substantial interactions occur between fatty acids and the endocrine system, with hormones exerting influence on fatty acid metabolism and tissue lipid composition. Insulin and GH

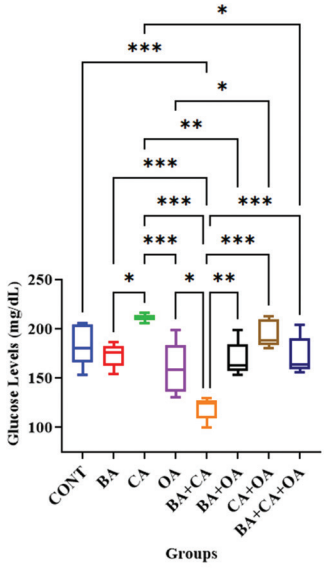

Figure 5. The effect of fatty acids on glucose levels (*p<0.05, **p<0.01 and ***p<0.001)
CONT: control, BA: butyric acid, CA: caprylic acid, OA: oleic acid

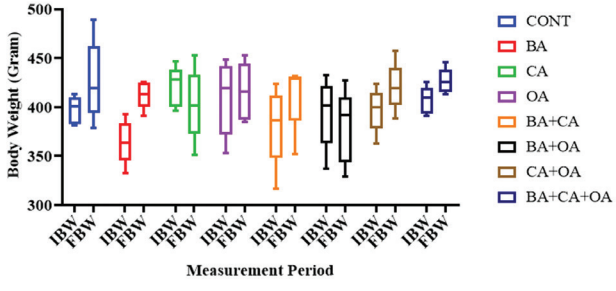

Figure 6. The effect of fatty acids on body weight
IBW: initial body weight, FBW: final body weight, CONT: control, BA: butyric acid, CA: caprylic acid, OA: oleic acid

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are prominent hormones involved in lipid metabolism. Their concentrations fluctuate in chronic degenerative conditions like diabetes and cardiovascular disease, thereby affecting tissue lipid profiles (15).

SCFAs have critical functions in intestinal epithelial cells. SCFAs also regulate diverse processes within the GI tract, including the absorption of electrolytes and water (16). A previous study found that BA, an SCFA, increased GH secretion in pituitary cells via GPR41/43 activation and intracellular Ca^{+2} accumulation (17). This suggests that BA may serve as a secondary mediator in the metabolic adaptations of GH during fasting, primarily involving increased lipolysis and protein retention (18). GH stimulates the release and oxidation of free fatty acids (FFAs). The most prominent metabolic effect of GH is a significant increase in lipolysis and FFA levels (19). The composition of the plasma membrane affects cell sensitivity to metabolically significant hormones like INS and vasoactive intestinal peptides. In a study investigating the impact of lipid and modified plasma membrane composition on the activation of the growth hormone secretagogue receptor (GHSR), it was noted that polyunsaturated fatty acids (PUFAs) enhance membrane fluidity by disrupting their structure. Long-term exposure (96 hours) to 18-carbon PUFAs, specifically oleic and linoleic acid, significantly heightened the sensitivity of GHSR cells to ghrelin, whereas acute treatment did not yield the same effect (20). Ghrelin, a hormone regulated by metabolism, activates the G protein-coupled receptor GHSR-1a, not only in the pituitary gland but also in peripheral tissues such as the pancreas, stomach, and T-cells in circulation (20). It has been shown that CA octanoylated ghrelin, the only known orexigenic peptide hormone (21). In the present study, we observed that OA, BA + CA, BA + OA, and BA + CA + OA applications increased GH levels. These data are consistent with the literature. However, only the BA group showed a decrease in GH levels. This difference is likely due to the fact that most studies in the literature are conducted on cell lines, as numerous uncontrolled mechanisms come into play in the *in vivo* environment, leading to different results from those obtained *in vitro*.

IGFs interact with GH during embryonic development and postnatal growth. IGF-1 directly enhances muscle mass, bone density, and bone structure. The intestinal microbiota triggers the secretion of IGF-1, which supports the development and remodeling of bones. SCFAs produced in microbial fermentable fibers induce the secretion of IGF-1, explaining how microbial activity affects bone health through IGF-1. Additionally, IGF-1 has both direct and indirect glucose-lowering effects. It increases FFA oxidation in muscles, reduces the flow of FFAs to the liver, enhances INS signaling, decreases hepatic glucose output, and improves INS sensitivity (22). The results of the present study indicate that the combined application of all three fatty acids reduces IGF-1 levels. This result is likely due to the increase in GH levels induced by fatty acids. Elevated blood GH levels may inhibit IGF-1 expression. However, because there are no studies in the literature regarding the effects of MCFAs and LCFAs on IGF-1, comparisons cannot be made.

Studies have shown that a high-fat diet supplemented with propionic acid and BA improves INS sensitivity and protects against the development of obesity and INS resistance (23,24). Additionally, a reduction in fat content was observed in obese mice treated with BA (23,24). This is consistent with weight loss and improved INS tolerance, suggesting a role for BA in the treatment of diet-induced obesity. SCFAs also inhibit lipolysis, a complex metabolic process performed by adipocytes during nutrient deprivation and stress, by releasing FAs and glycerol from triacylglycerol storage droplets, increasing glucose uptake stimulated by INS (25,26). Recent studies have shown that fatty acids induce INS resistance in skeletal muscle by blocking the activation of phosphatidylinositol 3-kinase (PI3-kinase) associated with insulin receptor substrate-1 (27). According to the results of a study, GPR40, a G-protein-coupled receptor abundantly expressed in the pancreas, functions as a receptor for LCFAs. Furthermore, LCFAs enhance glucose-stimulated INS secretion from pancreatic β cells by activating GPR40 (28). Acute increases in FFAs stimulate INS secretion, but long-term lipid exposure impairs β-cell function both *in vitro* and *in vivo* animal studies (29). Obesity and high FFA levels reduce INS clearance. A study examined the effects of some common FFAs and their acyl-coenzyme A thioester on partially purified INS-degrading enzymes in the livers of male Sprague-Dawley rats (30). The results of the study suggest that increased intracellular LCFA concentrations directly affect INS metabolism and alter INS action in intact cells, potentially contributing to hyperinsulinemia and INS resistance observed in high fatty acid and obesity (30). However, there are no studies on the effects of MCFAs on INS. In the present study, when groups were examined in terms of INS levels, we found that the groups treated with BA, CA + OA, and BA + CA + OA had lower INS levels. These findings are consistent with the literature.

HSL is a key enzyme in mobilizing fatty acids from intracellular stores (31). SCFAs regulate lipid metabolism when substrates are provided for lipid synthesis. SCFAs activate AMP-activated protein kinase (AMPK) (31). AMPK has been shown to positively regulate lipolysis by affecting HSL and adipose triglyceride lipase (32,33). A previous study reported that triglycerides containing MCFAs increased HSL activity and expression in the white adipose tissue of c57bl/6j mice (34). HSL knockout studies have shown that the removal of HSL disrupts lipolysis and leads to a significant decrease in lipogenesis (35). There are no studies in the literature regarding the effects of LCFAs on HSL. In the present study, when the groups were examined in terms of HSL levels, it was observed that the application of BA, CA, and OA alone increased HSL levels, whereas their combined application had the opposite effect. This may be due to the administration of high-dose fatty acid formulations (200 or 300 mg/kg) over a long period.

In a study investigating the effects of FFAs on glucose uptake and utilization in healthy women, acute increases in plasma FFA within the high physiological range for 4 h led to approximately 40% inhibition of INS-stimulated glucose uptake and glycogen synthesis in healthy normal-weight individuals (36). Another study

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involving seven pregnant women found that FFAs inhibited INS-stimulated glucose uptake by 42% (37). Another study also found that high fatty acid concentrations inhibit glucose utilization (36). An *in vitro* study conducted on isolated hepatocytes and perfused rat liver showed that SCFAs and MCFAs modulate the hepatic metabolism of carbohydrates and lipids. BA and CA inhibited glycolysis (38). In another study, it was demonstrated that MCFAs in rodents have protective effects against glucose homeostasis following high-fat overfeeding. In addition, small numbers of MCFAs in the diet were found to provide protection against INS resistance in humans during caloric excess (39). In the present study, we found that rats treated with BA + CA had lower blood glucose levels. In contrast, treatment with only CA increased blood glucose levels.

MCFAs (except for lauric acid) predominantly belong to the fast-metabolizing group (40). A recent systematic review showed that diets rich in MCFAs resulted in significantly higher high density lipoprotein-cholesterol levels compared with those rich in LFAs, but had no effect on triglycerides, low density lipoprotein-cholesterol, or total cholesterol concentrations (41). MCFAs in the diet have gained nutritional interest because of their easier absorption from dietary medium-chain triacylglycerols compared with LCFAs derived from vegetable oils (42). MCFAs can be directly absorbed and provide rapid energy, promoting intestinal epithelial cell renewal and repair, maintaining intestinal mucosal barrier function integrity, and reducing inflammation and stress (43). Animal and human studies have shown that the rapid oxidation rate of MCFAs leads to increased energy expenditure. Most animal studies have shown that MCFAs result in higher energy expenditure than LCFAs, leading to less weight gain and reduced adipose tissue size after several months of consumption (6). Additionally, both animal and human experiments indicate that medium-chain triglycerides have a greater satiating effect than long-chain triglycerides (6). All three major SCFAs (propionate, acetate, and butyrate) provide protection against diet-induced obesity (44). However, in the present study, although the weights obtained from post-experimental measurements were generally higher than those obtained from pre-experimental measurements, no significant difference was observed. Only groups treated with CA or BA + OA showed a non-significant decrease in weight compared with pre-experimental measurements.

Study Limitations

Due to financial restrictions, molecular parameters at the tissue level were not evaluated.

CONCLUSION

BA application resulted in a decrease in GH, IGF-1, and INS levels, but no significant effect was observed on HSL levels. CA application increased HSL levels but did not show a significant effect on GH, insulin, and IGF-1 levels. OA application increased GH and HSL levels but did not significantly affect IGF-1 and INS. CA application increased glucose levels, whereas BA and OA applications did not significantly affect glucose levels. The combined application of fatty acids increased GH levels while decreasing INS, IGF-1, and HSL levels. In conclusion, longer-term and comprehensive studies are needed to elucidate the effects of SCFAs, MCFAs, and LCFAs on GH, IGF-1, HSL, and INS.

Ethics Committee Approval: All study methods were reported in accordance with the Animal Research: Reporting of *in Vivo* Experiments guidelines and approved by Düzce University Local Ethics Committee on Animal Testings (decision no: 2022/07/03, meeting date: 27.07.2022).

Informed Consent: Experimental animal study.

Author Contributions: Surgical and Medical Practices - A.E., Ö.B., E.B., A.G.; Concept - Ö.B., E.B.; Design - A.E., Ö.B., E.B., A.G.; Data Collection and/or Processing - A.E., Ö.B., E.B., A.G.; Analysis and/or Interpretation - Ö.B., E.B.; Literature Search - A.E., Ö.B., E.B., A.G.; Writing - A.E., Ö.B., E.B., A.G.

Conflict of Interest: The authors have no conflict of interest to declare.

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