ORİJİNAL MAKALE / ORIGINAL ARTICLE

Sağlık Bilimlerinde Değer / Sağlık Bil Değer
Value in Health Sciences / Value Health Sci
ISSN: 2792-0542 sabd@duzce.edu.tr 2023; 13(3): 451-457
doi: https://dx.doi.org/10.33631/sabd.1344751

Investigation of the Effects of Short, Medium, Long Chain Fatty Acids on Osteocalcin, Leptin and Insulin Levels

Cemre Nur EDİRNELİ [1], Ersin BEYAZÇİÇEK [1]

ABSTRACT

Aim: There are some studies on insülin released from pancreatic beta cells, both active and inactive osteocalcin in bone tissue, and leptin released in adipose tissue. However, data on the effects of combined short, medium, and long fatty acids on the serum/tissue concentration of hormones such as osteocalcin, leptin and insülin are scarce. This study aims to investigate the effects of combined use of butyric acid, caprylic acid and oleic acid on osteocalcin, leptin, and insulin secretion.

Material and Methods: Forty-nine male Wistar rats were used in the study. The rats were randomly divided into 7 subgroups as control group, butyric acid group, caprylic acid group, oleic acid group, butyric acid+caprylic acid group, butyric acid+oleic acid group, and caprylic acid+oleic acid group. Fatty acids were administered orally for 21 days. At the end of the study, osteocalcin, insulin, and leptin levels of serum samples taken from rats were determined by the ELISA method.

Results: While osteocalcin and leptin levels were found to be high in the group administered only butyric acid, insulin levels were found to be higher in the group treated with combined caprylic acid + oleic acid. The blood glucose level of the caprylic acid group was found to be higher than the other groups.

Conclusion: The relationship between osteocalcin, leptin, and insulin is quite complex. Different studies show that osteocalcin can have an effect on leptin resistance, consumption of different types of fatty acids, especially short-chain fatty acids, can contribute to insulin sensitivity by increasing the release of osteocalcin, can help reduce leptin resistance, and osteocalcin can reduce insulin resistance.

Keywords: Butyric acid; caprylic acid; insulin; leptin; oleic acid; osteocalcin.

Kısa, Orta, Uzun Zincirli Yağ Asitlerinin Osteokalsin, Leptin ve İnsülin Düzeylerine Etkilerinin Araştırılması

ÖZ

Amaç: Pankreatik beta hücrelerinden salınan insülin, kemik dokusunda hem aktif hem de inaktif salınan osteokalsin ve yağ dokusunda salınan leptin ile ilgili bazı çalışmalar bulunmaktadır. Ancak, kombine kısa, orta ve uzun yağ asitlerinin osteokalsin, leptin ve insülin gibi hormonların serum/doku konsantrasyonu üzerindeki etkilerine ilişkin veriler azdır. Bu çalışmanın amacı bütirik asit, kaprilik asit ve oleik asidin birlikte kullanımının osteokalsin, leptin ve insülin salgılanması üzerindeki etkilerini araştırmaktır.

Gereç ve Yöntemler: Çalışmada kırk dokuz erkek Wistar sıçan kullanılmıştır. Sıçanlar rastgele olarak kontrol grubu, bütirik asit grubu, kaprilik asit grubu, oleik asit grubu, bütirik asit+kaprilik asit grubu, bütirik asit+oleik asit grubu ve kaprilik asit+oleik asit grubu olmak üzere 7 alt gruba ayrıldı. Yağ asitleri 21 gün boyunca oral yoldan uygulanmıştır. Çalışma sonunda sıçanlardan alınan serum örneklerinde osteokalsin, insülin ve leptin düzeyleri ELISA yöntemiyle belirlendi.

Bulgular: Sadece bütirik asit uygulanan grupta osteokalsin ve leptin düzeyleri yüksek bulunurken, kaprilik asit+oleik asit kombinasyonu uygulanan grupta insülin düzeyleri daha yüksek bulunmuştur. Kaprilik asit grubunun kan glukoz seviyesi diğer gruplara göre daha yüksek bulunmuştur.

Sonuç: Osteokalsin, leptin ve insülin arasındaki ilişki oldukça karmaşıktır. Farklı çalışmalar osteokalsinin leptin direnci üzerinde etkili olabileceğini, farklı türde yağ asitlerinin, özellikle de kısa zincirli yağ asitlerinin tüketiminin osteokalsin salınımını artırarak insülin duyarlılığına katkıda bulunabileceğini, leptin direncini azaltmaya yardımcı olabileceğini ve osteokalsinin insülin direncini azaltabileceğini göstermektedir.

Anahtar Kelimeler: Bütirik asit; insülin; kaprilik asit; leptin; oleik asit; osteokalsin.

1 Duzce University, Faculty of Medicine, Department of Physiology, Duzce, Türkiye

Sorumlu Yazar / Corresponding Author: Ersin BEYAZÇİÇEK, e-mail: beyazcicek13@gmail.com
Geliş Tarihi / Received: 17.08.2023, Kabul Tarihi / Accepted: 03.09.2023

INTRODUCTION

The skeletal system is considered an endocrine organ that affects energy metabolism (1). Osteocalcin, a bone matrix protein produced in the skeletal system, has hormonal effects. It leads to various hormonal influences on energy and glucose metabolism (2). It has been demonstrated that osteocalcin, responsible for many skeletal functions, has a circadian rhythm and is a unique hormone (3). It has been found through animal and experimental models that osteocalcin is released into the circulatory system and exerts biological effects on pancreatic beta cells and adipose tissue (2). Based on the observation that obesity is inversely related to osteoporosis, there has long been suspicion of a connection between bone and energy metabolism(1). This connection between bone and energy metabolism arises from osteocalcin's support of insulin secretion, which regulates energy metabolism (3). Insulin also acts in the opposite direction to stimulate osteocalcin synthesis in osteoblasts. The balance between osteocalcin and insulin plays a significant role in obesity and diabetes (3). Osteocalcin production is regulated not only by insulin but also by leptin. One of the fundamental principles of endocrinology is that hormonal regulation is under tight positive and negative control. In humans, osteocalcin has been negatively associated with insulin resistance, and leptin has been negatively correlated with osteocalcin levels in both cross-sectional and longitudinal analyses (4). Leptin activates the sympathetic tone that inhibits insulin secretion and stimulates Esp expression in osteoblasts (via activation of the adrenergic beta 2 receptor). Esp inhibits osteocalcin, thereby reducing insulin expression. Leptin inhibits pancreatic insulin. Insulin, in turn, stimulates leptin expression in white adipose tissue (4). In conclusion, osteocalcin production is regulated by the control of insulin and leptin hormones. Insulin released from pancreatic beta cells stimulates both active and inactive osteocalcin synthesis in bone tissue. Active osteocalcin released from bone tissue, in turn, stimulates insulin secretion in the pancreas. There is no feedback mechanism in the relationship between insulin and osteocalcin. Therefore, the leptin hormone released from adipocytes regulates the production of osteocalcin and insulin through the hypothalamus (4).

Short-chain fatty acids (SCFA) are primarily the end products of the fermentation of undigested sugars and dietary fiber by the gut microbiota. Butyric acid, a 4-carbon, colorless, characteristically odorous, fatty carboxylic acid, is one of the main byproducts. It is soluble in water and slightly volatile at room temperature. Butyric acid, also known as 'butter acid,' is naturally present in milk. It is reported to play a significant role in modulating various diseases (5).

Caprylic acid (octanoic acid, C8:0), caproic acid (C6:0), and capric acid (C10:0) belong to the class of medium-chain saturated fatty acids (MCFAs) (6). MCSFAs are characteristic nutrients found in dairy products and specific oils like palm kernel and coconut oil. The metabolic specificity of MCSFAs has been associated with beneficial physiological effects, leading to high catabolism in adipose tissue and low tissue deposition (7). In overweight individuals, diets rich in MCSFAs have been shown to reduce fat accumulation and increase energy expenditure compared to diets rich in long-chain fatty acids (LCFAs) with equal calories (8).

Oleic acid (C18:1) is a monounsaturated fatty acid with a total of 18 carbons and a double bond between the 9th and 10th carbons. It constitutes 1/3 or more of the lipids in breast milk. Oleic acid is an essential energy source and can be synthesized within the body. It is recognized as a primary energy source in breast milk, along with lactose, for newborns. Recent studies have focused on the effects of oleic acid on lipoprotein metabolism. In adults, oleic acid consistently increases the HDL/LDL ratio and reduces the concentration of total blood cholesterol.

Furthermore, it regulates the absorption of nutrients in the gastrointestinal system by maintaining blood glucose and insulin concentrations within normal limits. As far as we know, there is limited data on the effects of combined short, medium, and long-chain fatty acids on the serum/tissue concentration of hormones such as osteocalcin, leptin, and insulin. Moreover, no published study evaluating the synergistic effects of different types of fatty acids on the secretion of osteocalcin, leptin, and insulin has been identified. The aim of this study is to investigate the effects of fatty acids such as butyric acid, caprylic acid, and oleic acid on osteocalcin, leptin, and insulin levels.

MATERIAL AND METHODS

Animals

"The animals utilized in this research were sourced from the Duzce University Experimental Animals Application and Research Center. A total of 49 male Wistar rats, aged 2-3 months and weighing 230±30 g, were housed in a laboratory setting. The rats were maintained at a room temperature of 23 ºC, with a humidity level of 60±5%, and a light-dark cycle of 12:12. Throughout the study, the rats had unrestricted access to food and water. To evaluate the impact of fatty acid administration on the rats' weight changes, their weights were measured both at the commencement and conclusion of the study. This investigation received ethical clearance from the Duzce University Animal Experiments Local Ethics Committee, under Decision No: 2021/03/04."

Substances and Doses

Three different fatty acids were used in the study: butyric acid, caprylic acid and oleic acid (Sigma Aldrich Chemical Co., St. Louis, Missouri, US). A 100 mg/kg of each of these fatty acids was given orally. As anesthetics, 90 mg/kg ketamine hydrochloride (Keta-Control, Mefar İlaç Sanayi A.Ş., Istanbul, Turkey) and 10 mg/kg xylazine hydrochloride (Vetaxyl, VET-AGRO Sp. z o.o., ul. Lublin, Polonia) were used intramuscularly (i.m). All drugs were prepared daily.

Experimental Groups and Routes of Administration of the Substances

Rats were randomly divided into 7 subgroups as Control, Butyric Acid, Caprylic Acid, Oleic Acid, Butyric Acid+Caprylic Acid, Butyric Acid+Oleic Acid, Caprylic Acid+Oleic Acid. In the control group, only saline was administered orally at 1 ml/kg for 21 days. The fatty acid groups were administered 100 mg/kg fatty acid orally for 21 days.

Ending the Study

After the last application, blood was taken from the heart of the animals in the groups by cardiac puncture method under ketamine/xylazine anesthesia. The animals were then sacrificed by cervical dislocation under anesthesia. Blood samples underwent centrifugation at 4000 rpm for a duration of 15 minutes. Following centrifugation, the serum was carefully separated and preserved at a temperature of -80 ℃ until the time of analysis.

Determination of Biochemical Parameters

Osteocalcin, insulin and leptin levels were determined by ELISA (enzyme-linked immunosorbent assay) method in the collected serum samples. ELK (ELK biotechnology CO., LTD, Hubei, CHINA) brand ELISA kits for rat osteocalcin (Cat. *ELK2391*), rat insulin (Cat: *ELK2370*) and rat leptin (Cat: *ELK8904*) were obtained. All parameters were measured with an ELISA reader (Epoch Microplate Spectrophotometer, BioTek Instruments, Inc., Winooski, VT, USA) according to the kit procedure. In addition, blood glucose level was determined with OPTIMA (OK Biotech CO., LTD., Taiwan) blood glucose meter and strips.

Statistical Analysis

The Kruskal-Wallis test was used to compare the groups in terms of serum osteocalcin, insulin and leptin levels, and homogeneous subgroups multiple comparison method was used to determine the different groups. Body weights were analyzed by Two-Way ANOVA. $P \leq 0.05$ was accepted as statistical significance level. GraphPad Prism (version 9.0, La Jolla, California, USA) program was used for analysis.

RESULTS

The Effects of Fatty Acids on Osteocalcin Levels

When the groups were compared in terms of osteocalcin levels, a statistically significant difference was determined between the groups (P<0.001) (Figure 1). When the results were examined in more detail, it was found that the osteocalcin level values of the Butyric Acid group were statistically higher than the Control, Caprylic Acid, Oleic Acid, Butyric Acid+Caprylic Acid, Butyric Acid+Oleic Acid**,** and Caprylic Acid+Oleic Acid groups (p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, p<0.001 and p=0.001, respectively). Although the mean osteocalcin levels of the other groups were higher than the control group, it was not statistically significant (P>0.050).

The Effects of Fatty Acids on Leptin Levels

There was a statistically significant difference between the groups in terms of leptin levels (p<0.001) (Figure 2). When the results were examined in more detail, it was found that the leptin level values of the butyric acid group were statistically higher than the control, caprylic acid, oleic acid, butyric acid+caprylic acid, butyric acid+oleic acid and caprylic acid+oleic acid groups (p<0.001, p<0.001, p<0.001, p=0.004, p<0.001, p=0.009 and p<0.001, respectively). Although the mean leptin level of butyric acid+oleic acid group was higher than the other groups (except butyric acid group), it was not statistically significant (p>0.050).

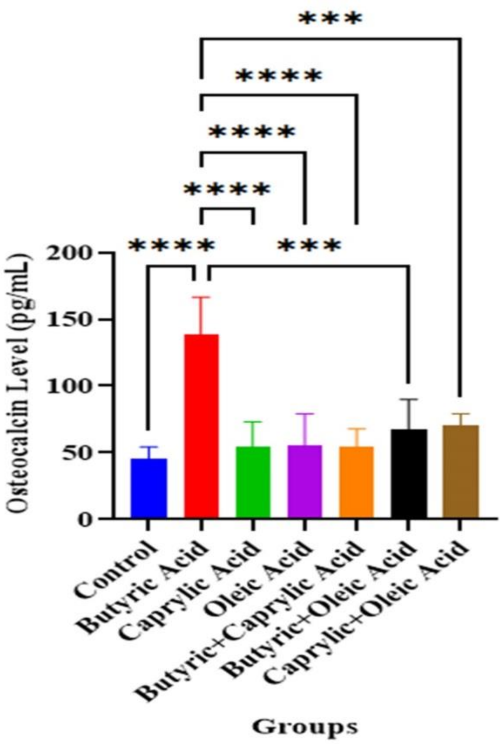

Figure 1. The effect of fatty acids on osteocalcin level (***p=0.005 and ****p<0.001).

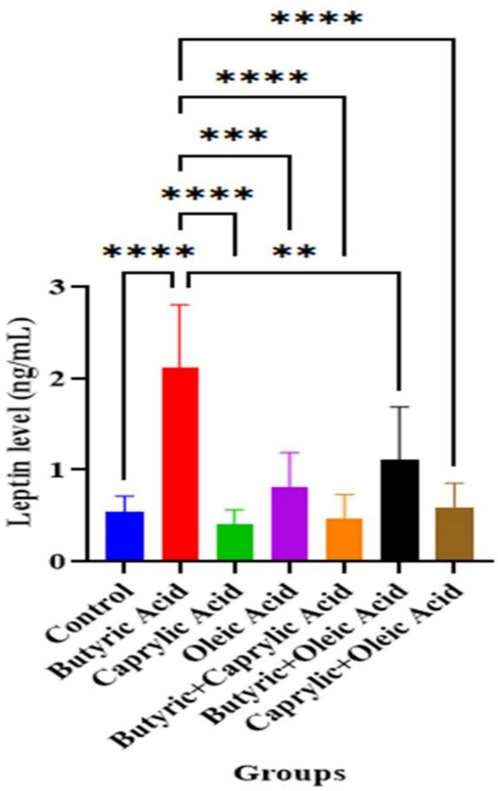

Figure 2. The effect of fatty acids on leptin level (**p=0.010, ***p=0.005 and ****p<0.001)

The Effects of Fatty Acids on Insulin Levels

When the groups were compared in terms of insulin levels, a statistically significant difference was determined between the groups (P<0.001) (Figure 3). When the results were analyzed in more detail, it was found that the mean insulin level of the Caprylic+Oleic Acid group was statistically higher than the Control, Butyric Acid, Caprylic Acid, Oleic Acid and Butyric Acid+Caprylic Acid groups (p<0.001, p<0.001, p<0.001, p<0.001, p<0.001 and p<0.002, respectively). At the same time, the mean insulin level values of the Butyric Acid+Oleic Acid group were significantly higher than those of the Control, Butyric Acid and Caprylic Acid groups (P=0.005, P=0.043 and p=0.009, respectively). When the groups were analyzed in detail, although the mean insulin level values of the Control group were lower than those of the Butyric Acid, Caprylic Acid, Oleic Acid and Butyric Acid+Caprylic Acid groups, they were not statistically significant (P>0.050).

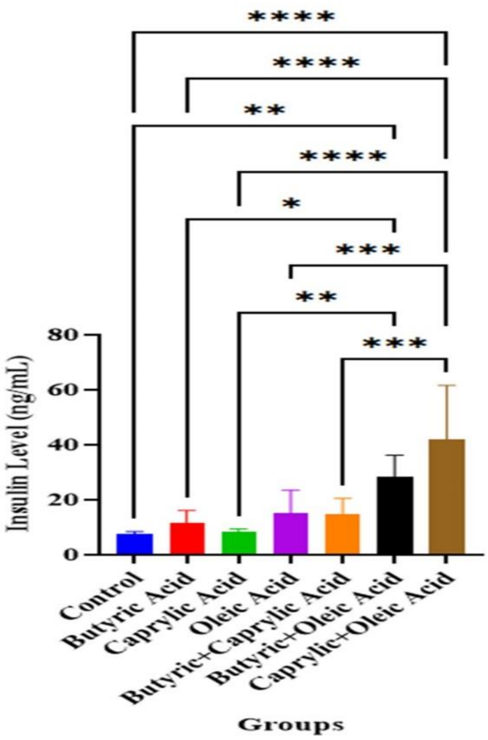

Figure 3. The effect of fatty acids on insulin level (*p<0.050, **p<0.010, ***p<0.005 and ****p<0.001).

The Effects of Fatty Acids on Blood Glucose Levels

When the groups were compared in terms of blood glucose levels, a statistically significant difference was determined between the groups (P=0.0010) (Figure 4). When the results were analyzed in more detail, it was found that the mean blood glucose levels of the Butyric Acid+Caprylic Acid group were statistically lower than those of the Cotrol, Caprylic Acid, and Caprylic Acid+Oleic Acid groups (p values were p=0.0141, p=0.0003 and p=0.0360, respectively). In addition, the mean blood glucose level of the Oleic Acid group was significantly lower than that of the Caprylic Acid group (P=0.0300). Although the blood glucose levels of the Butyric Acid and Butyric Acid+Oleic Acid groups were higher than the Butyric Acid+Caprylic Acid group, they were not statistically significant (p=0.2478 and p=0.1110, respectively).

The Effects of Fatty Acids on Body Weight

When the pre- and post-experimental mean weights were compared within the groups, a statistically significant difference was found between them (p=0.008) (Table 1 and Figure 5). When the groups were analyzed in more detail, it was determined that the post-experimental mean weight values of the control group were statistically higher than the pre-experimental mean weight values (p<0.001). Conversely, no statistically significant disparities were observed within the remaining groups (p>0.050).

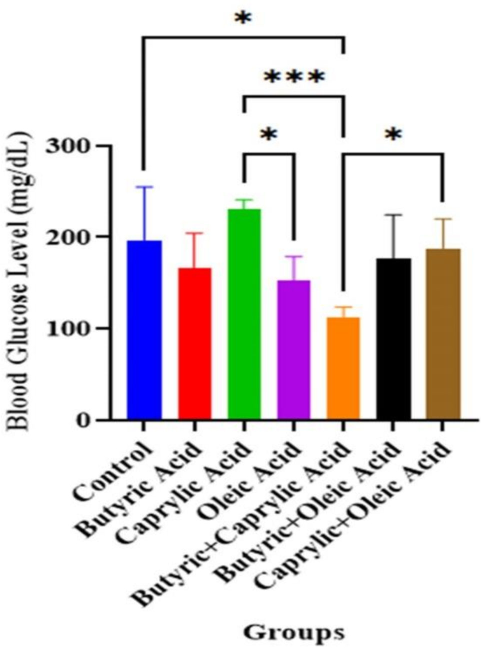

Figure 4. The effect of fatty acids on blood glucose level (*p<0.050, ***p<0.005).

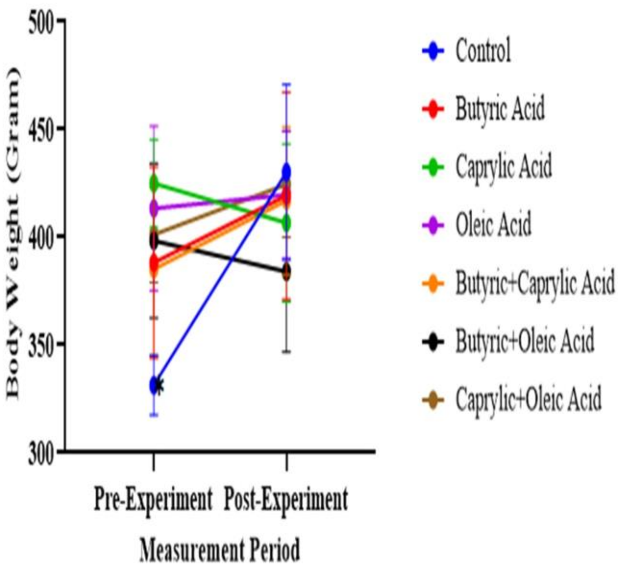

Figure 5. The effects of Fatty Acids on body weight (*p<0.050)

Table 1. Effects of different fatty acids on body weight and P value for comparison of groups

Group	Time	Mean (g) ±SD	Min (g)	Max (g)	P value
Control	Pre	331,4±13,9	315	347	**0,008**
	Post	430,2±40,6	383	493	
Butyric Acid	Pre	388,2±44,3	315	436	0,702
	Post	419,3±47,9	340	471	
Caprylic Acid	Pre	425,0±20,4	400	451	0,917
	Post	406,8±36,6	355	457	
Oleic Acid	Pre	413,4±38,2	357	453	0,999
	Post	419,8±29,4	389	457	
Butyric+Caprylic Acid	Pre	385,2±39,7	321	428	0,683
	Post	417,0±34,4	356	436	
Butyric+Oleic Acid	Pre	398,4±35,9	341	437	0,993
	Post	384,0±37,3	333	431	
Caprylic+Oleic Acid	Pre	401,2±22,2	367	428	0,908
	Post	424,6±24,6	392	461	

(Pre; pre-experiment, Post; Post-experiment)

DISCUSSION

Osteocalcin, leptin, and insulin are hormones that play a significant role in regulating metabolic functions in the body. Additionally, different types of fatty acids present in foods can also impact metabolic functions (9). Short-chain fatty acids, medium-chain fatty acids, and long-chain fatty acids are metabolized differently in the body and have various metabolic effects. Recent studies have shown the benefits of short and medium-chain fatty acids, particularly in the form of dietary supplements like medium-chain triglycerides added to foods, for promoting healthy weight control and metabolic health due to their distinct aroma and taste. In this study, the relationship between SCFAs, MCFAs, and LCFAs and osteocalcin, leptin, and insulin is investigated.

Short-chain fatty acids offer benefits such as maintaining healthy gut functions and preventing inflammation (10). Moreover, it has been suggested that short-chain fatty acids could enhance the production of the leptin hormone, consequently reducing appetite and aiding in weight loss (11). Butyric acid is a short-chain fatty acid produced by specific bacterial species in the gut. It has demonstrated anti-inflammatory effects and is believed to contribute to protection against various diseases, including inflammatory bowel disease and type 2 diabetes (12). A study conducted by Hamer et al. shows that butyric acid has a positive impact on gut motility and mucosal barrier function (12). In addition, butyric acid has been reported to potentially play a significant role in bone health due to its ability to enhance the production of the osteocalcin hormone. Osteocalcin is a hormone produced by bone cells and is involved in the regulation of energy metabolism. Specifically, it has been shown that osteocalcin increases insulin secretion and sensitivity, improves glucose tolerance, and reduces the risk of type 2 diabetes. Leptin is a hormone secreted by fat cells and plays a crucial role in regulating energy balance, appetite control, and metabolism. When leptin levels are high, it enhances the sensation of fullness in the brain, suppressing appetite and increasing energy expenditure. As a result, individuals with leptin resistance may struggle with weight control (13). However, the effects of butyric acid on leptin levels in humans are still not clear, despite some animal studies suggesting an increase in leptin levels due to this fatty acid. Furthermore, more research is needed to fully comprehend the effects of butyric acid on weight control (13–16). In the present study, it was observed that only the groups receiving butyric acid exhibited significantly higher levels of osteocalcin and leptin, as reported in the literature. Insulin levels were relatively higher in the butyric acid-treated groups compared to the control group, but the difference was not statistically significant. Similarly, although the blood glucose levels were lower in the groups treated with butyric acid compared to the control group, the difference was not statistically significant. In conclusion, the relationship between butyric acid, osteocalcin, insulin, and leptin is significant due to its potential effects on gut health and weight control. However, further research is needed to better understand these relationships.

Medium-chain fatty acids are metabolized more rapidly than other fatty acids and are converted into energy more efficiently (17). Therefore, medium-chain fatty acids are thought to have the potential to be used for weight control and increasing energy expenditure (18). Caprylic acid is an unsaturated fatty acid found in natural sources like various food items and certain oils. It is utilized for energy production in the body and also offers some health benefits. Particularly, caprylic acid has been shown to have an impact on osteocalcin, insulin, and leptin hormones. (19–21). It is believed that caprylic acid might have a positive impact on bone health by increasing osteocalcin synthesis. Additionally, caprylic acid also influences insulin sensitivity. Insulin is a hormone secreted to regulate blood sugar levels in the body. Insulin sensitivity defines the body's response to insulin. Caprylic acid could contribute to better blood sugar control by increasing insulin sensitivity. Moreover, it is thought that caprylic acid could aid in weight control by enhancing leptin release. In a study, the effects of caprylic acid on insulin sensitivity in obese mice were investigated (20). The researchers have reported that caprylic acid treatment improves insulin sensitivity by increasing glucose uptake and glycogen synthesis in skeletal muscles. They have suggested that these effects could be attributed to the activation of AMP-activated protein kinase (AMPK), a key regulator of energy metabolism, which is activated by AMP. In the current study, although the application of caprylic acid increased osteocalcin, leptin, and insulin levels compared to the control group, these changes were not found to be statistically significant. However, the combined application of caprylic acid with oleic acid significantly increased insulin levels. In addition, the groups that underwent caprylic acid application exhibited higher blood glucose levels. In conclusion, the relationships between caprylic acid and osteocalcin, insulin, and leptin are significant with regards to bone health, blood sugar control, and weight management. Moreover, the effects of caprylic acid on these hormones remain unclear, and further research is required. However, more research is needed in this area.

Long-chain fatty acids, on the other hand, are primarily utilized for energy storage purposes and have been associated with obesity (22). Oleic acid, a monounsaturated fatty acid, holds several beneficial health effects for the body. The relationship between oleic acid and osteocalcin, insulin, and leptin has been explored in recent research studies. (23–27). Oleic acid has been shown to have positive effects on bone health. In a study, it was observed that mice supplemented with oleic acid experienced an increase in bone mineral density and enhanced bone structure. Furthermore, supplementation of oleic acid has been demonstrated to increase osteocalcin production and bone mineralization in bone cells (28). In a study, it was observed that providing obese mice with oleic acid supplementation resulted in a reduction in insulin resistance (29). Additionally, a study conducted on humans revealed that consumption of olive oil reduced insulin resistance and regulated blood sugar levels (30). The impact of oleic acid on insulin resistance can be explained through mechanisms at the cellular level. Oleic acid improves cellular membrane functions and enhances insulin receptor activity by altering the lipid composition of the cell membrane (31). Additionally, oleic acid enhances mitochondrial functions, thereby increasing cellular energy production and insulin sensitivity. Some studies have indicated that long-chain fatty acids could potentially increase insulin resistance (32). In a study, it was found that mice lacking osteocalcin exhibited leptin resistance (32). These findings suggest the potential influence of osteocalcin on leptin resistance. In another study, it was demonstrated that increasing osteocalcin secretion in mice had a positive impact on insulin sensitivity (18). In the current study, despite the fact that oleic acid application led to an increase in osteocalcin, insulin, and leptin levels compared to the control group, these changes were not found to be statistically significant. However, the combined application of oleic acid and caprylic acid resulted in an elevation of insulin levels. Additionally, the groups receiving oleic acid exhibited lower blood glucose levels compared to the control group. Nonetheless, further research is needed to fully understand the impact of oleic acid on insulin resistance. Some studies suggest that oleic acid enhances insulin sensitivity, while others propose the opposite (33). Furthermore, the influence of other factors related to insulin resistance, such as obesity and levels of physical activity, should also be taken into consideration.

In conclusion, the relationship between osteocalcin, leptin, and insulin is quite intricate. Various studies suggest that osteocalcin might have an impact on leptin resistance, different types of fatty acids—especially short-chain fatty acids—could potentially enhance osteocalcin secretion, thereby contributing to insulin sensitivity, assisting in reducing leptin resistance, and potentially lowering insulin resistance. However, the interplay of these factors is complex and further research is needed to fully comprehend the intricate mechanisms at play.

Authors's Contributions: Idea/Concept: E.B.; Design: E.B., C.N.E.; Data Collection and/or Processing: E.B., C.N.E.; Analysis and/or Interpretation: E.B.; Literature Review: E.B., C.N.E.; Writing the Article: E.B.; Critical Review: E.B.

REFERENCES

1. Reinehr T, Roth CL. A new link between skeleton, obesity and insulin resistance: Relationships between osteocalcin, leptin and insulin resistance in obese children before and after weight loss. Int J Obes. 2010; 34(5): 852-8.
2. Zanatta LCB, Boguszewski CL, Borba VZC, Kulak CAM. Osteocalcina, metabolismo energético e da glicose. Arq Bras Endocrinol Metabol. 2014; 58(5): 444-51.
3. Al-Suhaimi EA, Al-Jafary MA. Endocrine roles of vitamin K-dependent- osteocalcin in the relation between bone metabolism and metabolic disorders. Rev Endocr Metab Disord. 2020; 21(1): 117-25.
4. Paz-Filho G, Wong ML, Licinio J, Mastronardi C. Leptin therapy, insulin sensitivity, and glucose homeostasis. Indian J Endocrinol Metab. 2012; 16(9): 549.
5. Çağlar A, Tomar O, Ekiz T. Butyric acid: structure, properties and effects on health. Kocatepe Vet Derg. 2017; 3(10): 213-25.
6. Jensen RG, Ferris AM, Lammi-Keefe CJ, Henderson RA. Lipids of bovine and human milks: a comparison. J Dairy Sci. 1990; 73(2): 223-40.
7. Takeuchi H, Sekine S, Kojima K, Aoyama T. The application of medium-chain fatty acids: Edible oil with a suppressing effect on body fat accumulation. Asia Pac J Clin Nutr. 2008; 17 (Suppl. 1): 320-3.
8. Tsuji H, Kasai M, Takeuchi H, Nakamura M, Okazaki M, Kondo K. Dietary medium-chain triacylglycerols suppress accumulation of body fat in a double-blind, controlled trial in healthy men and women. Journal of Nutrition. 2001; 131(11): 2853-9.
9. Yun SL, A YK, Jin WC, Kim M, Yasue S, Hee JS, et al. Dysregulation of adipose glutathione peroxidase 3 in obesity contributes to local and systemic oxidative stress. Molecular Endocrinology. 2008; 22(9): 2176-89.

10. Tedelind S, Westberg F, Kjerrulf M, Vidal A. Anti-inflammatory properties of the short-chain fatty acids acetate and propionate: A study with relevance to inflammatory bowel disease. World J Gastroenterol. 2007; 13(20): 2826-32.
11. Chambers ES, Viardot A, Psichas A, Morrison DJ, Murphy KG, Zac-Varghese SEK, et al. Effects of targeted delivery of propionate to the human colon on appetite regulation, body weight maintenance and adiposity in overweight adults. Gut. 2015; 64(11): 1744-54.
12. Hamer HM, Jonkers D, Venema K, Vanhoutvin S, Troost FJ, Brummer RJ. Review article: The role of butyrate on colonic function. Aliment Pharmacol Ther. 2008; 27(2): 104-19.
13. Den Besten G, Van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res. 2013; 54(9): 2325-40.
14. Zhang YJ, Li S, Gan RY, Zhou T, Xu DP, Li H Bin. Impacts of gut bacteria on human health and diseases. Int J Mol Sci. 2015; 16(4): 7493-519.
15. Friedman JM. The function of leptin in nutrition, weight, and physiology. Nutr Rev. 2002; 60(10 I): 1-14.
16. Cani PD, Bibiloni R, Knauf C, Neyrinck AM, Delzenne NM. Changes in gut microbiota control metabolic diet–induced obesity and diabetes in mice. Diabetes. 2008; 57(6): 1470-81.
17. St-Onge MP, St-Onge MP, Bosarge A, Goree LLT, Darnell B. Medium chain triglyceride oil consumption as part of a weight loss diet does not lead to an adverse metabolic profile when compared to olive oil. J Am Coll Nutr. 2008; 27(5): 547-52.
18. Mumme K, Stonehouse W. Effects of medium-chain triglycerides on weight loss and body composition: A meta-analysis of randomized controlled trials. J Acad Nutr Diet. 2015; 115(2): 249-63.
19. He J, Zhang P, Shen L, Niu L, Tan Y, Chen L, et al. Short-chain fatty acids and their association with signalling pathways in inflammation, glucose and lipid metabolism. Int J Mol Sci. 2020; 21(17): 1-16.
20. Page KA, Williamson A, Yu N, McNay EC, Dzuira J, McCrimmon RJ, et al. Medium-chain fatty acids improve cognitive function in intensively treated type 1 diabetic patients and support in vitro synaptic transmission during acute hypoglycemia. Diabetes. 2009; 58(5): 1237-44.
21. Milanski M, Degasperi G, Coope A, Morari J, Denis R, Cintra DE, et al. Saturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamus: Implications for the pathogenesis of obesity. Journal of Neuroscience. 2009; 29(2): 359-70.
22. Stefan N, Kantartzis K, Häring HU. Causes and metabolic consequences of fatty liver. Endocr Rev. 2008; 29(7): 939-60.
23. Garcia-Galiano D, Borges BC, Allen SJ, Elias CF. PI3K signalling in leptin receptor cells: Role in growth and reproduction. J Neuroendocrinol. 2019; 31(5): 1-8.
24. Lee N, Sowa H, Hinoi E, Ferron M, Cell JA, 2007 undefined. Endocrine regulation of energy metabolism by the skeleton. Cell. 2007; 3(130): 456-69.
25. Mera P, Laue K, Ferron M, Confavreux C, Wei J, Galan-Diez M, et al. Osteocalcin signaling in myofibers is necessary and sufficient for optimum adaptation to exercise. Cell Metab. 2016; 23(6): 1078-92.
26. Ducy P, Amling M, Takeda S, Priemel M, Schilling AF, Beil FT, et al. Leptin inhibits bone formation through a hypothalamic relay: A central control of bone mass. Cell. 2000; 100(2): 197-207.
27. Mera P, Laue K, Wei J, Berger JM, Karsenty G. Osteocalcin is necessary and sufficient to maintain muscle mass in older mice. Mol Metab. 2016; 5(10): 1042-7.
28. Cheng CW, Tang KT, Fang WF, Lin JD. Synchronized expressions of serum osteopontin and B cell–activating factor in autoimmune thyroid disease. Eur J Clin Invest. 2019; 49(7): 1-10.
29. Pastor R, Bouzas C, Tur JA. Beneficial effects of dietary supplementation with olive oil, oleic acid, or hydroxytyrosol in metabolic syndrome: Systematic review and meta-analysis. Free Radic Biol Med. 2021; 172(June): 372-85.
30. Schwingshackl L, Lampousi AM, Portillo MP, Romaguera D, Hoffmann G, Boeing H. Olive oil in the prevention and management of type 2 diabetes mellitus: A systematic review and meta-analysis of cohort studies and intervention trials. Nutr Diabetes. 2017; 7(4): e262-6.
31. Chavez JA, Summers SA. A ceramide-centric view of insulin resistance. Cell Metab. 2012; 15(5): 585-94.
32. Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, Confavreux C, et al. Endocrine Regulation of Energy Metabolism by the Skeleton. Cell. 2007; 130(3): 456-69.
33. Zambiazi RC, Przybylski R, Zambiazi MW, Mendonça CB. Fatty acid composition of vegetable oils and fats. Boletim do Centro de Pesquisa de Processamento de Alimentos. 2007; 25(1): 111-20.