Original Article

Does Fasting and High-Fatty Diet Effect Ossseointegration: An Experimental Study

CA Kaya, R Guler[1], MC Yavuz[2], EC Ozcan[3], A Bozoglan[4], S Dundar[4]

Department of Vegetable and Animal Production/ Milk and Fattening, Faculty of Diyarbakir Agricultural Vocational School, Dicle University, Diyarbakir, [1]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Dicle University, Diyarbakir, [2]Department of Periodontology, Faculty of Dentistry, Medeniyet University, Istanbul, [3]Department of Esthetic, Plastic and Reconsructive Surgery, Faculty of Medicine, Firat University, Elazig, [4]Department of Periodontology, Faculty of Dentistry, Firat University, Elazig, Turkey

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ABSTRACT

Background: Hyperlipidemia caused by a high-fat diet (HFD) has many adverse effects on the cardiovascular system, including vascular problems. In addition, a high-fat diet has significant adverse effects on bone health. **Aim:** This study aimed to investigate the levels of bone–implant connection in rats subjected to fasting and a high-fatty diet. **Methods:** This study utilized a sample size of 28 female Spraque–Dawley rats. The rats were divided into four groups, with 7 rats in each group; the control group on a normal diet (Group 1) (n = 7), the fasted group (Group 2) (n = 7), the high-fatty diet (HFD) group (Group 3) (n = 7), and the fasted and high-fat diet (Group 4) (n = 7). Machined surfaced titanium implants with a diameter of 2.5 mm and a length of 4 mm were placed in the right tibia bones of the subjects. All rats that continued the administered diet for 12 weeks were sacrificed at the end of the experimental period. The implants and the surrounding bone tissue were surgically removed and subjected to biomechanical analysis to assess bone–implant osteintegration. **Results:** There was no statistically significant difference in bone–implant osteointegration (P > 0,05) between the rats in the control group and the other three groups. **Conclusion:** This study determined that fasting or maintaining a high-fat diet does not adversely affect the bone–implant connection in rats' tibias.

KEYWORDS: *Fasting, high-fatty diet, implant, osteointegration*

INTRODUCTION

The amount of fat in the diet has increased rapidly in the last 20 years with the emergence of many cheap, delicious foods with high fat.[1] A high-fat diet (HFD) can induce obesity and metabolic diseases in the human metabolism.[2,3] For example, most atherogenic or high-fat diets (HFD) cause hyperlipidemia, characterized by high bloodstream lipids.[4] Hyperlipidemia has become a significant health problem for today's aging population. In a hyperlipidemic state, protein-bound lipid particles pass through the endothelial wall into the subendothelial space, where they are captured and oxidatively modified by reactive oxygen species produced by metabolically active adjacent smooth muscle cells and macrophages.[4-6] A similar cycle occurs in human osteoporotic bone. Oxidized protein-bound lipid particles accumulate in perivascular subendothelial areas. Osteoblast cells

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Address for correspondence: Dr. R Guler, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Dicle University, Postal Code - 21280, Campus, Diyarbakir, Turkey.
E-mail: ridvanguler06@gmail.com

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also oxidatively modify protein-bound lipid particles. Oxidized lipid products are detected in the bone marrow of hyperlipidemic mice.[4-7] Hyperlipidemia caused by HFD diet has many adverse effects on the cardiovascular system, including vascular problems.[4,7] In addition to the vascular issues of hyperlipidemia induced by HFD, adverse effects on bone reconstruction and bone metabolism are also known. HFD has been shown to reduce trabecular bone microarchitecture, increase osteoclast activity, and expand bone marrow fat, which could then lead to decreased bone mineral density and increased risk of fracture.[7]

The HFD diet also has significant adverse effects on bone health. This leads to lower bone mineral density and a higher risk of osteoporosis and bone fractures.[4,8] In the literature review, the detrimental effects of the HFD diet on osseointegration are explained by multiple mechanisms. At the cellular level, hyperlipidemic conditions lead to the inhibition of osteogenic remodelling signalling,[9] reduced formation of mature osteoblasts, higher expression of molecular markers of bone remodeling signaling,[9] reduced formation of mature osteoblasts, and higher expression of molecular markers of bone remodeling.[10] In addition, increasing osteoclast differentiation and activity[5] and increasing bone resorption are different mechanisms.[10] Moreover, hyperlipidemia significantly impairs bone healing, thus reducing bone surface and volume.[4] Similar studies have shown that high-fat diets negatively affect the initiation of osseointegration by reducing bone–implant contact and the biomechanical properties of the interface.[11,12] The link between diet and bone metabolism may be provided by the fact that osteoblasts and fat cells originate from a common mesenchymal stem cell in the bone marrow and lineage selection can be affected by both local and systemic changes.[13]

According to the National Health and Nutrition Examination Survey, 63% of osteoporotic patients have hyperlipidemia.[4] Additionally, numerous reports indicate that obesity is a risk factor for osteoporosis in humans.[4,5,14-16] In epidemiological studies, statistically significant inversely proportional results were obtained between serum cholesterol level, bone mineral parameters, and density, regardless of age and body mass index. In experimental animal studies, HFD consumption is associated with bone mineral content (BMC) and bone mineral density (BMD) reductions.[4]

Dietary modulations, particularly starvation or food restrictions, are believed to beneficially increase resistance to various chronic and acute stressors in all mammals.[17,18] Metabolic stress due to starvation initiates an allostatic mode in the body, various stress responses that stimulate the production of acute phase proteins, which protects the individuals from further oxidative and cellular damage.[17,19] Results of studies in model organisms suggest that reducing caloric intake, also known as dietary restriction, and changes in dietary composition (e.g., protein content) or timing of food intake (e.g., intermittent fasting) may be beneficial in preventing chronic diseases including cancer.[20,21]

Food deprivation, caloric restriction, periodic starvation, or moderate food deprivation can increase the ability of vertebrates to fight diseases.[22] Experimental studies have shown that fasting in rodents strengthens the immune system, reduces inflammation, and is an effective method for longevity.[21] During fasting, a delicate homeostatic balance occurs in energy consumption.[23] The balance between energy stores and spent energy is maintained by the delicate balance between carbohydrate, lipid and protein metabolisms. Exposure to starvation manifests itself with an alarming state in the body and encourages the body to create acute phase proteins that have the potential to protect the body from oxidative stress and take part in cell renewal.[21-23]

Dental implant-supported dentures are a widely used and scientifically accepted treatment option for partial and complete edentulism. However, factors such as the patient's systemic condition, daily diet, bone quality, implant characteristics, and smoking habits are crucial for the success of dental implant treatment.[7,10] Although increasing evidence suggests that a high-fat diet negatively impacts bone healing, the effects of HFD on the bone–implant connection have not yet been thoroughly investigated in the literature and, therefore, remain controversial.[10-13] Thus, the relationship between titanium implant osseointegration in high-fat diets and fasting rats remains unclear. Previous research has focused mainly on the isolated effects of diet or fasting on bone health. This has led to a critical gap in understanding the combined effects of high-fat diet and fasting on the osseointegration process. Clarifying this issue is important in improving dietary guidelines and management strategies for patients undergoing dental implant procedures and increasing implant success rates. To address this gap, the current study investigates the combined effects of fasting and a high-fat diet on osseointegration, an area that remains underexplored despite its significant implications for clinical practices surrounding dental implants.

This study aims to directly address these gaps by investigating how intermittent fasting combined with a high-fat diet influences osseointegration, thereby providing needed insights into how to fill this gap. Filling this gap not only advances our understanding

of dietary impacts on bone healing but also may offer new therapeutic insights into managing bone health in patients with dietary restrictions or preferences.

Material-Method

Animals and study design

All surgical and experimental procedures were performed at the Firat University Experimental Research Center (Elazığ, Turkey). Approval for the study was received from the Firat University Animal Experiments Local Ethics Committee (Elazig/Turkiye) (2019/112). The rats used in the experiment were obtained from the same centre, Firat University Experimental Research Center. All animal experiments were performed by the Declaration of Helsinki regarding the care and welfare of animals. Sprague–Dawley rats were selected due to their physiological and genetic parallels with human metabolism, particularly in how they process high-fat diets, making them an ideal model for exploring the effects of osseointegration. In addition, these rats were used in the study because they are readily available and inexpensive. Studies in the literature were taken as examples when determining the specific diet formulation applied in the experiment.[24,25] Especially, the high-fat diet composition was modeled after Sahin *et al*.,[24] and Yavuz *et al*.,[25] who demonstrated its efficacy in inducing hyperlipidemia, a key factor in studying its impact on bone health and osseointegration. A total of 28 female Spraque–Dawley rats, with an average age of 1 year, were used in the study. To ensure the standardization, a vaginal smear test was applied to the rats included in the study to ensure that they were in the same estrus period. Animals were randomly distributed into experimental groups. Their average body weights on the experimental period's first day were 250 to 300 g. The rats were kept in plastic cages, and their room temperature was checked daily 12-h dark and 12-h light cycle and free access to feed and water was ensured.

The number of animals required for the experimental setup was determined and calculated by power analysis; deviation was calculated as 8%, type 1 error (α) as 0.05 and type 2 error (β) as (power = 0.80), and when the rats were divided into groups, it was calculated that there should be at least seven individuals in each group for the experimental setup.

Implant cavities were created in the corticocancellous bone in the rats' metaphyseal part of the right tibia bones. Machined surfaced titanium implants (Implance Dental Implant Systems; AGS Medical Corporation, Istanbul, Turkey) with a diameter of 2.5 mm and a length of 4 mm were placed in the bone cavities prepared for implants. All rats were randomly divided into four study groups as follows. The experimental design, comprising four distinct groups, was strategically developed to isolate and compare the effects of fasting, a high-fat diet, and their combination, thereby providing a robust analysis of their individual and combined impacts on osseointegration.

Control group (n = 7): After surgical implant placement, this group was fed with a regular diet without additional procedures during the 12-week experimental period.

Fasted group (n = 7): After surgical implant placement, this group was fasted 3 days a week during the 12-week experimental setup. Subjects had free access to water.[25]

High-fatty diet group (n = 7): After surgical implant placement, this group was administered a high-fatty diet without additional procedures during the 12-week experimental period.[24,25]

The fasting group with a high-fatty diet (n = 7): After surgical implant placement, this group was placed on a high-fatty diet and fasted 3 days a week for the 12-week experimental period.[24,25]

Surgical procedure

General anesthesia was achieved by the intramuscular injection of ketamine hydrochloride (50 mg/kg, Ketasol, Richter Pharma AG, Wels, Austria) and xylazine (5 mg/kg, Rompun, Bayer, Germany). After the rats were anesthetized, the surgical area was washed with povidone–iodine and shaved. A 15-mm incision was made in the right tibial crest. The soft tissues were dissected to expose the corticocancellous bone tissue in the metaphyseal part of the tibia bone [Figure 1]. When preparing the implant sockets, a physiodispenser device (NSK Surgic AP; Japan) set to 700 rpm-35 Nm torque and a 20:1 reduction surgical contra-angle (NSK SMax SG20, Japan) were used. The standard drilling protocol determined by the company was followed under physiological cooling during the procedure. Implant slots were created using appropriate drills with sterile saline cooling. Implant cavities with a diameter of 2.5 mm and a length of 4 mm were opened in the bone [Figure 2]. Then, machined surfaced titanium implants (Implance Dental Implant System; AGS Medical Corporation, Istanbul, Turkey), 4 mm long and 2.5 mm in diameter, were placed in the created implant cavities and primary stabilization was achieved[25] [Figure 3]. The selected titanium implants and the surgical protocol followed are based on established standards in dental research, as demonstrated by Yavuz *et al*.,[25] ensuring that our findings are comparable and relevant to clinical settings. After placing the machined surfaced titanium implants, the flap was returned to its original position. Fascia, subcutaneous tissue, and skin were sutured with

4–0 polyglactin sutures. All surgical procedures were performed under sterile conditions.

After the operation, the experimental animals were placed in a heater to maintain their body temperature. Then, the subjects were taken to the recovery room in metal cages, and in the post-operative period, 0.1 mg/kg tramadol hydrochloride was administered subcutaneously to the subjects fed orally once a day for the first 3 days after the operation. Penicillin (50 mg/kg) was administered intramuscularly (IM) for 3 days to control postoperative infection. To ensure standardization, all surgical procedures were performed atraumatically by the same researcher.

Animal feeding procedure

The control and dietary restriction rats were fed with standard diet. Rats in the high-fat and high-fat diet and fasting groups were fed with diets containing 40% fat-based calories.[24,25] Normal diet was consisted of 200 g/kg casein, 615 g/kg starch, 80 g/kg corn oil, and 105 g/kg cellulose. High fat diet was consisted of 200 g/kg casein, 145 g/kg starch, 150 g/kg sucrose, 400 g/kg beef fat, and 105 g/kg cellulose.

Diets were prepared by mixing all the materials in a mixing machine and turning them into pellets. The high-fat diet composition was modelled as Sahin *et al*.[24] and Yavuz *et al*.[25], who demonstrated its efficacy in inducing hyperlipidemia, a key factor in studying its impact on bone health and osseointegration.

Biomechanical analysis

The experimental setup was completed after 12 weeks. Overall, no fatal or non-fatal complications (such as wound formation or infection) were encountered during the study. At the end of the experimental period, the rats were sacrified and the machined surfaced titanium implants were removed along with the surrounding bone tissue. The excised tissues were fixed in 10% formalin solution. A rapid assessment was performed to prevent possible dehydration of samples. The samples were placed in polymethylmethacrylate blocks before analysis. A Mark-10 (NY, USA) model torque device with calibration and periodic maintenance was used. The implants were fixed in blocks with a reverse torque device. Each implant was fixed on a digital torque tool (Mark-10, NY, USA) for evaluation [Figure 4]. The implant–bone block, made into a single block, was placed in the device chamber to measure the reverse torque. Care was taken to ensure the angle between the lever arm and the implant was 90 degrees. Reverse torque was measured by gradually increasing the forces. The application was completed, and the implants were returned to the bone socket. The highest value (Newton/cm) obtained on the reverse torque meter screen was automatically recorded when the force was balanced.

Statistical analysis

SPSS 23.0 for Windows program (IBM SPSS Statistics for Windows; Armonk, NY, USA) was used for evaluation. Data for each group are expressed as mean ± min–max. Data were evaluated for normality (skiffness and kurtosis–skewness and kurtosis) with Shapiro–Wilks, Kolmogorov–Smirnov tests. It was observed that the data did not show a normal distribution. A non-parametric test-parametric, was used to determine whether there was a statistically significant difference between the groups. Mann–Whittney *U* test was used for pairwise comparisons. Non-parametric tests were chosen due to the non-normal distribution of the data, ensuring a more accurate analysis of the effects of dietary interventions on osseointegration. Significance was evaluated at $P < 0.05$ level.

Results

Biomechanical analysis were performed on implants fixed to the blocks regarding bone–implant connection [Figure 4]. Bone implant connection (BIC) biomechanical analysis results of all groups are shown in Table 1. The *P* value of 0.573 shows that the differences observed between the control and other experimental groups are statistically not significant, suggesting that it was determined that fasting or maintaining a high-fatty diet does not adversely affect bone–implant connection in the tibias of rats ($P > 0.05$). It was observed that the BIC value was numerically lower in the fasting group compared to the control group. It was observed that the BIC value in the groups on a high-fat diet was numerically higher than in the control group. However, it was observed that the BIC value was numerically lower in the starved subjects and later fed a high-fat diet.

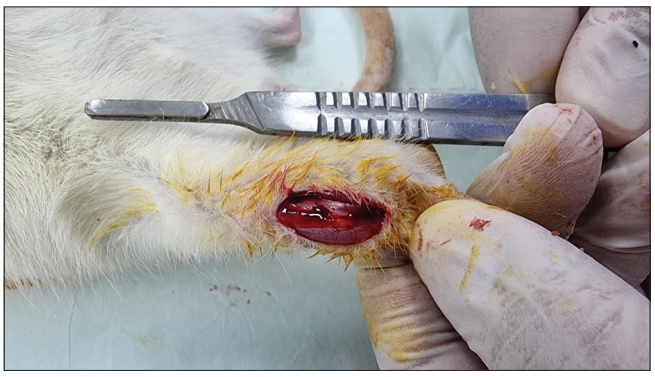

Figure 1: Incision in tibial crest and elevation of the soft tissues for reaching the corticocancellous part of tibial bone

Table 1: Biomechanic Bone implant connection (BIC) levels of the groups; Fasting diet and controls

Parameter	Groups	*n*	Mean (N/cm)	Std. deviation	Min-Max (N/cm)	*P**
BIC	Fasting	7	1,51	0,60	0,80-2,30	>0,05
	Control	7	1,57	0,51	0,90-2,40	(*P*=0,573)
	HFD Fasting	7	1,33	0,44	0,90-2,40	
	HFD	7	1,99	0,93	0,70-3,30	

*Kruskall–Wallis test (non-parametric datas.)

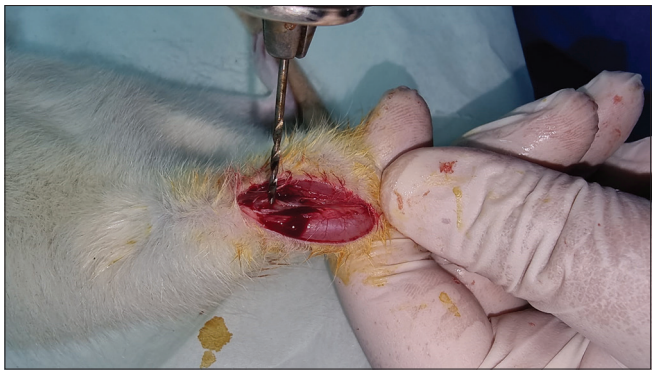

Figure 2: Creation of implant cavities with serum perfusion in corticacancellous part of the metaphysial part of tibia

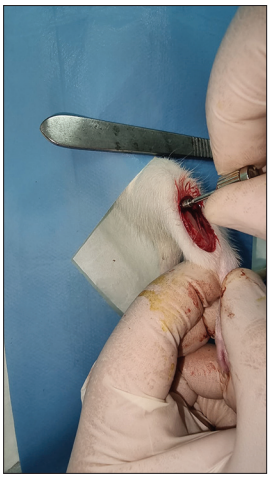

Figure 3: Insertion of the machined surface titanium implants into the bone cavities

Discussion

This study aimed to investigate the effects of a high-fat diet and starvation on the osteointegration of machined surfaced titanium implants in the tibial bones of rats. It was determined that fasting or maintaining a high-fat diet does not adversely affect bone–implant connection in the tibias of rats. The study results were obtained with biomechanical analysis.

The concept of osseointegration was first defined by Branemark *et al*.[26] as "a direct structural and functional connection between living bone tissue and the implant surface under loading, without fibrous tissue." Osseointegration is indispensable for a successful dental implant-supported prosthetic treatment. Most studies in the field of dental implantology have focused on the mechanisms affecting the osseointegration process. The healing mechanism and potential of bone tissue are essential to all bone-related surgical procedures, especially in dental implant surgery, to ensure the quality of peri-implant bone tissue. Infection, dysfunction, and pain are some of the main problems that can disrupt the healing physiology of bone and cause dental implant osseointegration to fail. Lack of osteointegration is a problem, especially in patients where implant placement is difficult, in patients with systemic issues such as diabetes and metabolic bone diseases, in patients with type 4 bone tissue with low bone mineral content and density.[20] In contrast, some known conditions and practices that can positively affect bone healing may contribute to successful dental implant treatment.[27,28]

Fat tissue is not an inert organ whose only function is to store energy. It also has metabolic functions, such as the secretion of proteins that play a role in bone metabolism. In fact, a HFD has a major effect on bone metabolism regardless of a person's weight, and this effect is mainly due to endocrine stimulation rather than mechanical stimulation.[23,29] Many mechanisms have been proposed to explain HFD-induced osteoclastogenesis, including increased expression of RANKL in the bones and decreased expression of the anti-osteoclastogenic cytokine IL-10 and elevated levels of proinflammatory cytokines IL-1 and TNF derived from adipose tissue macrophages in the blood.[25,23,30,31]

Evaluation of the data obtained from this study did not show statistical significance. It was determined that the biomechanical data, especially in the HFD-applied groups, were numerically higher than those in the control group. However, in the study by Dündar *et al*.[32] in which the effects of a HFD and restraint stress on osteointegration were examined, it was reported that the HFD had histologically negatively effects BIC levels compared to controls, whereas Dündar *et al*.[32] examined the data histopathologically in their experimental studies, we analyzed the data biomechanically. We attribute the difference in study results to the use of different methods. It has been reported in experimental studies that exposure to starvation may have positive effects on the treatment of cancer (melanoma, glioma, breast

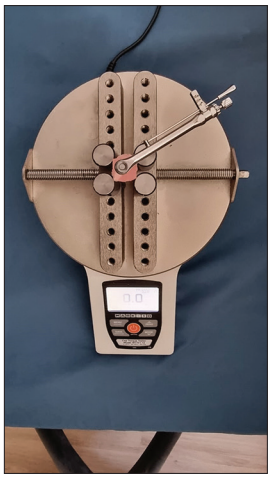

Figure 4: Biomechanical analysis of the osseointegration of the implants with reverse torque after experimental protocols (Mark 10, NY, USA)

cancer, prostate cancer, lung cancer, and leukaemia).[20] The body responds to food deprivation by increasing the breakdown of proteins. Proteolytic pathways release amino acids during fasting and use them for energy, which is compensated by forming new protein molecules in the body. As a result, the body is given a new opportunity for regeneration.[20] The relationship between longer life expectancy and short-term starvation involves changes in energy production and utilization, suppression of oxidative stress, decreased insulin resistance, inflammatory response, and changes in communication between cells and organs.[20,21] Hisatomi *et al*.[33] examined the effect of 96-h fasting on bone mechanism. As a result, they reported that fasting did not cause any major changes in the macroscopic morphology of the bone but caused a significant decrease in bone density. Although our findings indicate that fasting does not adversely affect osseointegration, this contrasts with the results of Hisatomi *et al*.,[33] (2019), who reported reduced bone density under similar dietary restrictions. This discrepancy may be attributed to differences in the duration of fasting or the specific parameters used to measure osseointegration and bone density. Contrary to the expected outcomes that suggested a detrimental effect of fasting on bone health, in this study, our findings demonstrate the fact that the biomechanical data obtained from the fasting group was numerically lower than the control group; however, there was no difference at the statistical level, may suggest that intermittent fasting does not negatively affect bone metabolism.

In previous studies, rats fed an atherogenic HFD became hyperlipidemic and showed significantly reduced bone mineral content and decreased bone volume in both femoral and tibial bones. For example, Lac *et al*.[34] reported that during the early growth period (35 days), HFD-fed rats had lower bone mineral density. They exhibited a negative correlation between visceral fat and bone mineral density compared to the regular diet-fed control group. In an experimental study, Lu *et al*.[35] reported that bone mineral content levels and trabecular bone area were significantly reduced in the HFD group compared to the control groups in young male rats. Contrary to the expected outcomes that suggested a detrimental effect of high-fat diets on bone health, in this study, our findings demonstrate. However, there was no statistically significant difference between the BIC levels of the groups, it was found that the HFD group showed a numerical increase in BIC levels compared to the control group. The unexpectedly higher osseointegration rates in the high-fat diet group could be attributed to the methodological variations (animal models, diet compositions, duration of dietary interventions, and methods of assessing osseointegration. The methodological variations (animal models, diet compositions, duration of dietary interventions, and methods of assessing osseointegration) particularly in the composition of the high-fat diet used in our study compared to that of Lac *et al*.,[34] and Lu *et al*.[35] could explain the variations in bone density and osseointegration outcomes observed; we believe that this will be important for the standardization of future studies. In our study; the lack of significant differences in osseointegration between the diet groups suggests that neither fasting nor a high-fat diet adversely impacts the bone–implant interface, contrary to what was hypothesised in previous studies.

Pirih *et al*.[4] reported that oxidized lipids and/or hyperlipidemia negatively affect the mechanical strength of bone and impair bone regeneration. Micro-computed tomography and histological results showed that bone regeneration was significantly impaired in men with a HFD. In addition, it was determined that the cortical bone volume fraction (bone volume/tissue volume) in the femur bones of the subjects in the HFD group was significantly reduced compared to the control group. Keuroghlian *et al*.[12] reported that atherosclerosis-susceptible C57BL/6J male rats fed a HFD showed a decrease in the amount and strength of bone–implant fusion in their femurs and a significant increase in implant loss. These results support the hypothesis that a HFD may reduce osteointegration and cause negative consequences in dental implant treatments. Contrary to the literature, although there was no statistically significant difference between the BIC levels of the groups in this study, a numerically significant difference was found in the BIC levels of the HFD group. The lack of statistical difference may be due to the number of subjects. Hirasawa *et al*.[36] stated that a HFD also increased osteoblast apoptosis.

In rats, the low-density lipoprotein level increases directly proportional to the rise in Type 1 collagen C-terminal telopeptide (CTX), a marker of osteoclastic bone resorption. Parhami *et al*.[37] found that oxidized lipids inhibited the differentiation of osteoblasts. Sage *et al*.[38] reported that lipid oxidation products potentiated the adverse effects of a HFD on bone tissue. Contrary to these studies, Dundar *et al*.[10] reported in their study on rats that feeding a high-fat diet does not cause any difference in osseointegration, bone mineral content-bone mineral density and biochemical bone data compared to controls. Similary; Yavuz *et al*.[25] reported that feeding a high-fatty diet and fasting does not cause any difference in osseointegration, bone mineral content-bone mineral density, and biochemical bone data compared to controls.[25] In 2016, Dündar *et al*.[7] evaluated the effect of a high-fat diet on the bone–implant connection in their study on rabbits. As a result, they found that HFD did not decrease the BIC in rabbit tibias. Our results support the growing body of literature that suggests high-fat diets do not significantly impair bone health at the cellular level, aligning with findings from Dundar *et al*.,[10] (2020) and Yavuz *et al*.,[25] (2024), thereby reinforcing the notion that fat diets is not effective in implant osteointegration.

Although implant osseointegration is negatively affected by many factors (smoking, systemic conditions, and oral hygiene), a high-fat diet and fasting do not significantly affect the implant–bone connection. Given the lack of adverse effects from fasting and high-fat diets on osseointegration observed in our study, clinicians might consider more flexible dietary guidelines for patients post-implant surgery, which could enhance patient compliance without compromising implant success. We believe this is important regarding the postoperative recommendations we will give patients.

The present study has several limitations. First, long bones such as the tibia and femur have different osteogenic properties compared to jaw bones (mandible–maxilla) and may respond differently to HFD and fasting. Second, we could not evaluate titanium implants' survival rate or long-term bone-implant connections' success in this study. Third, although *in vivo* studies are crucial to understanding the effects of HFD and fasting on bone, the results of these studies can only be used to extrapolate the corresponding pathways in humans. Fourth, biomechanical analysis evaluated the degree of osteointegration between the bone and the implant. Lastly, although the findings are promising, using a single animal model restricts the generalizability of the results to human populations. Further research on clinical, histopathological and immunohistochemical is needed to explore the long-term effects of combined fasting and high-fat diets on osseointegration, particularly in diverse populations and using varied implant materials to fully understand our findings' clinical relevance.

Conclusion

This study concluded that hyperlipidemia and intermittent fasting did not affect bone–implant osteointegration in the tibia bone of rats. Further clinical and experimental studies are required to understand the effects of hyperlipidemia and intermittent fasting on dental implants' survival rate and success. It can be stated that this study, which aims to determine medical risk factors associated with implant success, including bone formation around the implant and bone–implant fusion, can contribute to the literature.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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