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Investigation of the effect of Arginine Silicate Inositol complex on the osseointegration level of titanium implants

Investigación del efecto del complejo de silicato de arginina inositol en el nivel de oseointegración de implantes de titanio

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ABSTRACT

Arginine silicate inositol complex is a material that increases bone mineral density and the amount of collagen in vascular tissue. The aim of this study was to investigate the effect of the Arginine silicate inositol complex, administered orally via gavage, on the osseointegration level of titanium implants in the tibiae of rats. The experimental animals were divided into four groups a control group, which had no implants or further treatment; a control–implant group, which had implants placed only in the tibia bone but no further treatment; an, Arginine silicate inositol – administered group, which had no implants but was administered Arginine silicate inositol; and an Arginine silicate inositol – implant group, which had both implants placed and Arginine silicate inositol administered. In serum samples obtained from the rats, associated with bone tissue; alkaline phosphatase, osteocalcin, calcium, phosphorus, associated with liver function; alanine aminotransferase, aspartate aminotransferase were analyzed using biochemical methods. Densitometric evaluations were performed on the jaw and femur bones. The titanium screws were removed along with the surrounding bone tissue for histological evaluation. Non Parametric Tests were used the data analysis: Mann–Whitney U (between two groups), Kruskal–Wallis and Dunn test (between four groups), bone–implant connection and thread fill levels did not show a statistically significant difference among the groups (P>0.05). The levels of calcium, alkaline phosphatase, osteocalcin, alanine aminotransferase, aspartate aminotransferase, femur bone mineral density and phosphorus also did not show a statistically significant difference among the groups (P>0.05). The differences in levels of jaw bone mineral density were statistically significant among the groups (P<0.05). Thus, it can be concluded that the Arginine silicate inositol complex may increase jaw bone mineral density, and bone–implant integration.

Key words: Arginine silicate inositol; slicone; arginine; osseointegration; bone implant connection

RESUMEN

El complejo de silicato de arginina inositol es un material que aumenta la densidad mineral ósea y la cantidad de colágeno en el tejido vascular. El objetivo de este estudio fue investigar el efecto del complejo silicato de arginina inositol, administrado por vía oral mediante sonda, en el nivel de osteointegración de implantes de titanio en las tibias de ratas. Los animales experimentales se dividieron en cuatro grupos: un grupo de control, que no tenía implantes ni tratamiento adicional; un grupo de control con implantes, que tenía implantes colocados solo en el hueso de la tibia pero no tratamiento adicional; un grupo administrado con silicato de arginina inositol, que no tenía implantes pero se le administró silicato de arginina inositol; y un grupo con implantes de silicato de arginina inositol, que tenía implantes colocados y silicato de arginina inositol administrado. En muestras de suero obtenidas de las ratas, asociado con el tejido óseo; se analizaron la fosfatasa alcalina, la osteocalcina, el calcio, el fósforo, asociado con la función hepática; la alanina aminotransferasa, la aspartato aminotransferasa y utilizando métodos bioquímicos. Se realizaron evaluaciones densitométricas en los huesos maxilar y fémur. Los tornillos de titanio se retiraron junto con el tejido óseo circundante para la evaluación histológica. Para el análisis de datos se utilizaron pruebas no paramétricas: la prueba U de Mann–Whitney (entre dos grupos), la prueba de Kruskal–Wallis y la prueba de Dunn (entre cuatro grupos). La conexión hueso–implante y los niveles de relleno de la rosca no mostraron una diferencia estadísticamente significativa entre los grupos (P>0,05). Los niveles de calcio, fosfatasa alcalina, osteocalcina, alanina aminotransferasa, aspartato aminotransferasa, de densidad mineral ósea del fémur, y fósforo tampoco mostraron una diferencia estadísticamente significativa entre los grupos (P>0,05). Las diferencias en los niveles de densidad mineral ósea mandibular fueron estadísticamente significativas entre los grupos (P<0,05). Por lo tanto, se puede concluir que el complejo silicato de arginina inositol puede aumentar la densidad mineral ósea de la mandíbula y la integración hueso–implante.

Palabras clave: Silicato de arginina inositol; slicone; arginina; osteointegración; conexión de implante óseo

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INTRODUCTION

Implant placement is the surgical procedure of inserting alloplastic material of various structures and forms under the oral mucosa or into the bone to support prostheses that replace missing teeth [1]. The aim of this procedure is to eliminate toothlessness using implants that have achieved osseointegration and prostheses placed on these implants [2]. Dental implants are titanium screws or cylinder–shaped material surgically placed into the jawbone through a process called osseointegration [3].

Although observational studies have shown that dental implants have long–term survival, various disruptions and complications are common in this treatment process [4]. Recently, the foundation of implant research has been the development of additional techniques to enhance osseointegration in low–quality bones, a trend that has gained increasing popularity in dental implant procedures. Many new methods are being developed to increase the clinical success of dental implants, shorten the waiting period before loading, and allow for the use of shorter implants in cases where bone volume is insufficient [5, 6].

Arginine (2–amino–5–guanidinovaleric acid) is an amino acid that helps the remineralization effect of fluoride in dental caries by assisting in the nourishment of teeth and providing protection against decay [7, 8]. Arginine can directly influence cell proliferation in bone tissue and increase the production of mediators, such as nitric oxide, type I collagen, alkaline phosphatase (ALP), and insulin–like growth factor, which are involved in the matrix synthesis of bone tissue [9, 10].

Silicon is an essential trace element that is important for collagen in bones, skin, and blood vessels. Epidemiological and clinical studies have indicated that dietary silicon results in increased bone mineral density (BMD) in humans [11]. Research on the effects of silicon on bone tissue has shown increased levels of bone formation markers, such as ALP and osteocalcin, as well as enhanced cell differentiation and type I collagen synthesis [12, 13]. Inositol, which forms hydrogen bonds with arginine and silicon, facilitates the creation of arginine silicate inositol (ASI) complex [14, 15].

The ASI complex, which is composed of arginine (49.47%), silicate (8.2%), and inositol (25%), is thought to be a potential alternative in host modulation based on studies suggesting it can increase BMD and the collagen content of cartilage, connective, and vascular tissues [16]. The ASI complex has also been reported to have a positive effect on hair growth in a rodent model through growth factors [17].

Considering the effect of ASI on biochemical parameters related to bone tissue formation and its properties of increasing bone mineral density and collagen synthesis, it can be thought that it may also have a positive effect on the osseointegration levels of titanium implants. A review of the literature revealed that no studies have examined the effect of ASI on the osseointegration of dental implants. This study aims to investigate through histological and biochemical analyses the effects of the ASI complex on the osseointegration of titanium dental implants in rats.

MATERIAL AND METHODS

Animals and study design

This study was conducted in accordance with the Helsinki Declaration. Ethical approval was obtained from the Firat University Local Ethics Committee for Animal Experiments (approval number 2018/56). The experimental and analysis phases were carried out at the Firat University Experimental Research Center, the Firat University Faculty of Medicine Biochemistry and Nuclear Medicine Laboratories, the Firat University Faculty of Medicine Microbiology Laboratory, and the Erciyes University

In the study, 34 8–week–old female Sprague–Dawley rats (*Rattus norvegicus*) were used. All rats were kept under the same conditions throughout the experiment. During the experiment, the animals were housed in special cages with ventilation. In this study, the amount of ASI used in the diet of rats was determined according to the study of Proctor *et al.* [18].

- **Study groups:** In order to compare the serum samples obtained objectively, the study was conducted by creating control and experimental groups with and without implants.
- **Control group (N = 7):** No additional treatments were applied during the 3–month experimental period. The rats were sacrificed at the end of the period.
- **ASI group (N = 7):** ASI was administered orally via gavage at 3.62 $g \cdot kg^{-1}$ three times a week for 3 months. Blood samples were collected and biochemically analyzed at the end of the period.
- **Control–implant group (N = 10):** Titanium implants (2.5 mm diameter, 4 mm length) were placed in the metaphyseal areas of the right tibiae under general anesthesia. No additional treatments were applied, and the rats were sacrificed at the end of 3 months after the surgical implant placement.
- **ASI–implant Group (N = 10):** ASI was administered as described for the ASI group. Titanium implants were placed in the right tibiae. The rats were sacrificed at the end of 3 months after the surgical implant placement.

Surgical and Experimental Procedures

All surgical procedures were performed under sterile conditions and general anesthesia. General anesthetics (10 $mg \cdot kg^{-1}$ xylazine (Rompun, Bayer, Germany) and 40 $mg \cdot kg^{-1}$ ketamine (Ketasol, Richter Pharma, Austria) were administered intramuscularly using appropriate syringes. The area for the surgical procedure was shaved and then washed with povidone iodine. During the surgical implant placement, an incision was made over the tibial bone of the rats using a number 15 scalpel to expose the metaphyseal region of the bone. All soft tissues and periosteum were then dissected using a periosteal elevator. To prevent heating while creating the implant sockets, the surgical area was washed with sterile physiological saline. Following dissection, the corticocancellous bone of the metaphyseal portion of the tibia was accessed. Implant holes of 2.5 mm in diameter and 4 mm in length were created in the bone plateau, first with a starting bur, then with 2 mm, 2.2 mm, and 2.5

mm intermediate bur sizes. Titanium implants, 2.5 mm in diameter and 4 mm in length, were inserted into these holes using a special key. After the implants were placed, the soft tissue was sutured with 4-0 absorbable sutures.

To prevent pain and infection after the surgical procedures, antibiotics (cefazolin sodium, 40 mg·kg^{-1}) and analgesics (tramadol hydrochloride, 1 mg·kg^{-1}) were administered intramuscularly for 3 days (d). The rats were sacrificed at the end of a 12–week healing period following the surgical intervention.

For blood sample collection, the rats were first deeply anesthetized. Their abdomens and then their thoracic cavities were opened with surgical scissors to access their hearts. Blood was collected intracardially using 10 mL syringes. The collected blood was placed in 10 mL gel tubes and centrifuged for 10 min at 402 G (Nüve NF 200, Türkiye). After centrifugation, the samples were separated into serum and plasma. The serum portions were transferred to Eppendorf tubes and stored at -80°C (Nüve DF 290, Türkiye) until the day of analysis.

For tissue sampling, the titanium implants applied to the rat tibiae were removed along with the surrounding bone tissue and fixed in 10% formaldehyde. Additionally, the right femur and jaw bones of all the rats were collected for evaluation of BMD. Osteocalcin levels were detected using commercial ELISA kits. The measured values were recorded in ng·mL^{-1}. The sensitivity for osteocalcin was 0.02 ng·mL^{-1}, with an intra–assay coefficient of variation (CV) of < 8% and an inter–assay CV of < 10%. Serum phosphorus (P), calcium (Ca), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and ALP levels were analyzed using an autoanalyzer.

BMD and bone mineral content (BMC) analyses were performed using the DEXA device from the Department of Nuclear Medicine at Firat University, with Version 12.3 software. Ultra–high resolution mode were utilized for the evaluations. The rats' mandibles and right femur bones were assessed, and data on BMC and BMD were recorded.

For nondecalcified histological analysis, the preparation of implant samples was carried out at the Research Laboratory of the Faculty of Dentistry, Erciyes University. In the histological examination, titanium implants placed in the tibiae of the experimental animals were removed along with the surrounding bone and were analyzed according to the preparation method for nondecalcified sections. After removing the implants and surrounding bone from the soft tissue, they were placed in a 4% buffered formalin solution for at least 24 h for fixation. Following fixation, the samples underwent dehydration by being placed in alcohol solutions with increasing concentrations of 70, 80, 90, 96, and 99% for one d each [19].

After dehydration, the samples were infiltrated under vacuum for 24 h with methyl methacrylate resin (Kulzer, Wehrheim, Germany). The infiltrated samples were then embedded individually in transparent plastic molds filled with methyl methacrylate, ensuring that no air bubbles were present. Each mold containing one sample (Implance Dental Implant Systems, AGS Medical, Istanbul, Turkiye), was polymerized at 40°C under 450 nm wavelength light for 8 h. After polymerization, the samples were removed from the transparent molds. The flat surfaces of the transparent methyl methacrylate resin blocks containing the samples were adhered to a plexiglass slide under vacuum. The samples on the plexiglass slide were cut into 300 μm thick sections using a diamond saw attached to a precision cutting device. These initial cuts were made longitudinally through the center of the dental implants within the blocks [19].

The sections were then thinned to 50 μm using a micro–grinding system with 1000, 1200, and 2500 grit abrasives. This method produced one histological section from each sample. These sections were stained with toluidine blue for bone–implant connection (BIC) and thread fill (TF) analysis. After staining, the histological preparations were left to dry overnight, and the surfaces of the samples were covered with a coverslip using methyl methacrylate [19].

Bone–implant connection (%) and TF (%) were analyzed using a light microscope (Nikon, Tokyo, Japan) and image analysis program (Nikon, Tokyo, Japan) at the Firat University Faculty of Medicine, Microbiology Laboratory. Twenty nondecalcified preparations were digitally imaged at 2× magnification with high resolution. Evaluations were performed using a blinded and calibrated histomorphometric stereological software system (Nikon, Tokyo, Japan).

Only the lateral surfaces of the implants were evaluated in all samples. The apical regions of the implants were excluded from the evaluation due to the consideration that optimal cavity depth might not be achieved during application. The BIC ratio for each sample was calculated as the ratio of the implant surface directly in contact with the bone to the total length of the implant surface.

For BIC evaluation, first, the total implant circumference (£) was measured as the length at 2x magnification. The non–BIC sections were then measured as the length (a). By subtracting the non–BIC length (a) from the total implant circumference (£), the length of the BIC section was obtained. The total of the BIC sections (b) divided by the implant circumference (£) provided the BIC percentage of an implant [19].

For TF assessment, first, the areas of all threads of the implant were measured at 2× magnification to determine the total thread area. Then, the surface areas not filled with bone in each thread were measured. By subtracting these non–filled areas from the total thread area, the total area filled with bone in the threads was found. The TF percentage of the implant was calculated by dividing the bone–filled area by the total thread area [19, 20].

Statistical analysis

Nonparametric tests were used (after Shapiro–Wilk and Kolmogorov–Smirnov tests indicated nonparametric data). For comparisons between two groups, the Mann–Whitney U test was employed, and for comparisons among four groups, the Kruskal–Wallis test was used. When significant differences were detected with the Kruskal–Wallis test, Dunn's post hoc test was conducted for pairwise comparisons. Statistical significance was set at $P<0.05$.

RESULTS AND DISCUSSION

Bone implant connection levels were close to significance but did not show a statistically significant difference among the groups (*P*>0.05) (FIGS. 1 and 2) (TABLE I).

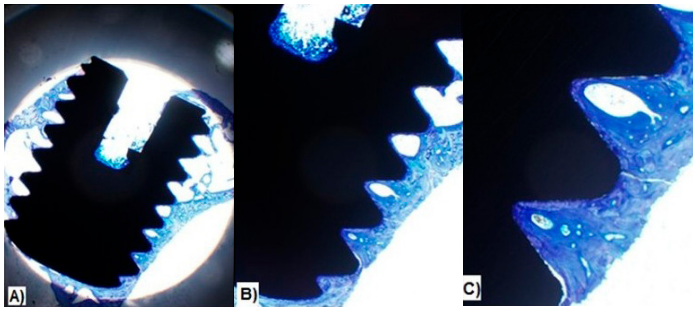

FIGURE 1. A,B,C. Histological sections of the arginine silicate inositol ASI–implant group at 2×, 4× and 10× (×=10 times) magmification, respectively

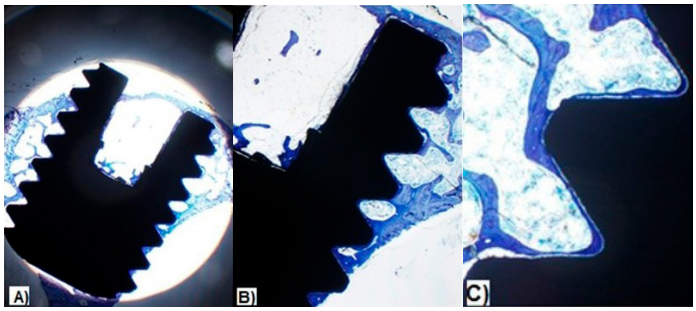

FIGURE 2. A, B, C. Histological sections of the control implant group at 2×, 4× and 10× (×=10 times) magmification, respectively

TABLE I
Bone implant connection ratios (%) of the groups

Group	N	X̄	SD	Min	Max	Skewness	Kurtosis	*P*
Control–Implant	10	38.97	7.29	28.74	49.51	-0.01	-0.91	0.08
ASI–Implant	10	48.21	12.65	32.19	69.21	0.12	-1.22	

SD = Standard deviation, Min: Minimum, Max: Maximum

According to the results, the group with the highest average TF and BIC level was the ASI–implant group. However, TF levels did not show a statistically significant difference among the groups (*P*>0.05) (FIGS. 1 and 2), (TABLE II).

TABLE I
Therad filling (%) of the groups

Group	N	X̄	SD	Min	Max	Skewness	Kurtosis
Control–Implant	10	38.20	8.06	24.40	49.40	-0.40	0.82
ASI–Implant	10	44.01	5.61	31.80	52.63	-0.77	-1.22

SD = Standard deviation, Min: Minimum, Max: Maximum

According to the biochemical results obtained, no statistically significant differences were found among the groups in terms of Ca, P, osteocalcin, ALT, AST, and ALP values (*P*>0.05) (TABLE III).

When considering the average jaw BMD (JBMD) of the groups, a statistically significant difference was found among the groups (TABLE III). The average JBMD values of the ASI–implant and control–implant groups were higher than those of the other groups (*P*<0.05). The average JBMD value of the control–implant group was found to be higher than that of the ASI group. However, no statistically significant differences were detected among the groups for jaw BMC, femoral BMD, and femoral BMC levels (*P*>0.05) (TABLE III).

Nowadays, high clinical success rates have been reported in dental implantology. However, despite this, one topic that still attracts the most attention in implantology research is the improvement of osseointegration quality. The most important reasons for this are the length of time between application and loading and the persistent question marks regarding clinical success in cases where bone quality is insufficient.

In addition to features such as the shape and thread character of the implant, studies on this topic have focused on ensuring that bone–derived healing cells move faster to the implant surface [21, 22]. In this study, we aimed to evaluate the effects of the ASI complex on both bone tissue and osseointegration using biochemical, histopathological, and radiological methods. Previous research related to the osseointegration of implants has generally involved different animal models, especially in the tibia regions [23].

The stability biologically provided by osseointegration varies depending on the surface characteristics of the implant and the healing capacity of the bone in which it is placed, and it is achieved as a result of the regeneration and remodeling of the bone around the implant [24]. Other studies aimed at achieving good and faster osseointegration despite inadequate bone quality have usually involved biological products and biochemicals applied systemically or topically.

For this purpose, materials such as platelet–rich plasma, simvastatin, recombinant human bone morphogenetic protein–2, and recombinant fibroblast growth factor–2 with melatonin have been used in the literature [25, 26, 27]. Various studies have shown that the ASI composition can increase the osteoblastic activity of bone tissue and the mineral content of Ca and P [28]. Additionally, the ASI complex can enhance bone tissue healing in rats [29]. In our literature review, we could not find any studies examining the effect of ASI on osseointegration.

Seaborn and Nielsen [30] examined the absorption and effects on bone mineralization when arginine and silicon were used together. In a study conducted on four groups of 21–d–old rats, Group I was fed a standard diet (2.3 $\mu g \cdot g^{-1}$ silicon and sufficient arginine) as the control group, Group II was given 5 $mg \cdot g^{-1}$ arginine in the standard diet, Group III was given 35 $\mu g \cdot g^{-1}$ silicon, and Group IV was given 35 $\mu g \cdot g^{-1}$ silicon and 5 $mg \cdot g^{-1}$ arginine for 8 weeks.

In the group given arginine and silicon, the Ca mineral density in the femur and vertebrae was found to be higher than in the other groups. The researchers also reported that silicon absorption was higher in the group given arginine and silicon together compared to the other groups.

TABLE III
Biochemical and DEXA values of the groups. [a]Statistically different compared with control. (*P*=0.03; *P*<0.05)

GROUPS PARAMETERS	CONTROL (N = 7)	ASI (N = 7)	IMPLANT CONTROL (N = 10)	ASI IMPLANT (N = 10)	*P*
Ca (mg·dL^{-1})	10.29 (10.12–10.58)	10.34 (9.82–11.06)	10.34 (9.94–11)	10.43 (9.67–11.15)	0.64
P (mg·dL^{-1})	5.60 (4.9–7.6)	5.69 (5.0–6.2)	5.70 (5.2–6.1)	5.82 (4.7–6.8)	0.21
Osteocalcin (ng·mL^{-1})	8.67 (4.24–12.71)	6.63 (3.84–11.74)	7.60 (4.54–10.62)	6.56 (4.41–8.91)	0.36
AST (IU·L^{-1})	236.71 (141–391)	213.14 (160–291)	200.5 (148–266)	216.20 (169–274)	0.93
ALT (IU·L^{-1})	85.43 (59–157)	93.14 (79–108)	82.2 (71–97)	83.0 (70–107)	0.15
ALP (U·L^{-1})	135.43 (56–342)	114.14 (79–156)	103.5 (58–114)	81.6 (22–153)	0.25
JBMD (g·cm^{-2})	0.30 (0.27–0.33)	0.31 (0.29–0.33)	0.33 (0.31–0.34) [a]	0.33 (0.39–0.36)[a]	0.03
JBMC (g)	0.62 (0.57–0.74)	0.61 (0.52–0.69)	0.60 (0.49–0.76)	0.54 (0.41–0.73)	0.25
FBMD (g·cm^{-2})	0.26 (0.23–0.29)	0.24 (0.23–0.26)	0.23 (0.19–0.26)	0.23 (0.20–0.25)	0.05
FBMC (g)	0.38 (0.29–0.50)	0.44 (0.38–0.59)	0.40 (0.26–0.56)	0.36 (0.23–0.48)	0.25

Previous studies have reported that the main effective materials of the ASI complex (arginine and silicon) increase BMD and the amount of connective tissue collagen [11]. In a study by Yaman *et al*. [29], the potential effects of the ASI complex on the healing of critical–sized bone defects in rats were evaluated. The results showed that ASI supplementation significantly improved critical–sized bone defects. Yaman *et al.* [29] study demonstrated that ASI could enhance bone repair and has the potential to be used as a therapeutic regimen in humans. The higher numerical levels of BIC and TF data in ASI–treated subjects compared to controls can also be evaluated in this context.

Another study reported better bone bonding in silicone–supported implants and ceramics compared to control groups without silicon. In the study, sintered hydroxyapatite surfaces and silicon–hydroxyapatite surfaces were implanted in sheep models for 6 and 12 weeks. Samples containing the bone–implant interface were prepared for ultramicrotomy and transmission electron microscopy using a dehydration sample preparation procedure. The results showed that the morphology of hydroxyapatite deposits and the sequence of events at the bone interfaces with pure hydroxyapatite and silicon–hydroxyapatite implants differed.

Organized collagen fibrils were found at the bone– silicon–hydroxyapatite interface after 6 weeks, while they were found around pure hydroxyapatite implants only after 12 weeks. Around silicon–hydroxyapatite, significantly more nodular aggregates of plate–like apatite crystallites were observed 12 weeks later compared to around pure hydroxyapatite.

These findings suggest that the inclusion of silicate ions in hydroxyapatite supports the process of bone remodeling at the bone– hydroxyapatite interface. Transmission electron microscopy observations showed that trabecular bone covered the silicon–hydroxyapatite implants, and collagen fibrils formed a mechanical lock with the silicon–hydroxyapatite ceramic implants. In this study, silicon, which dissolves and forms an amorphous layer in implants and ceramics, was found to increase the proliferation and differentiation of osteoblasts, type I collagen synthesis, and bone mineralization [31].

Dündar *et al*. [32] previously created experimental periodontitis in rats fed diets containing the ASI complex and examined the biochemical, immunological, and radiological effects of the ASI complex. In the study, the tissue destruction parameters (CRP, alveolar bone destruction, RANK, RANKL, MMP–8, IL–1β, MPO, PMNL infiltration) of the periodontitis group were found to be higher than those of the control group, while the construction parameter was found to be lower. No significant effect of the ASI complex on BMD was observed. Moreover, the results obtained regarding MPO levels in Dündar et al.'s study suggest that ASI may prevent and/or reduce periodontal tissue destruction by reducing oxidative stress.

In this study, BMD values in the jaw and femur were examined, and the BMD value in the ASI–implant group in the jaw was found to be significant compared to the control–implant group. An examination of the BIC and TF values obtained from this study showed no statistical differences between the groups. However, both values, especially BIC, were found to be numerically higher in the ASI–treated group than in the control group. In this study, similar to the study by Dündar *et al*. [32], no significant differences were observed between the groups in terms of serum bone formation markers, such as ALP, Ca, and P levels. The lack of significant differences in these serum bone formations in our study contradicts the results of studies by Şahin *et al*., Önderci *et al*., and Küçükbay *et al*., which reported that ASI increased serum bone formation markers [28, 33, 34].

This difference may be due to the study model we used. Therefore, further studies need to alter the application dose, duration, and method of ASI complex administration. Moreover, the lack of significant differences in serum ALP, Ca, and P levels among the groups in our study is similar to the results obtained in the study by Yilmaz *et al*. [35], evaluated the bone formation–resorption cycle in 77 osteoporotic and nonosteoporotic women and did not find statistically significant levels of serum ALP, Ca, and P, reporting that resorption markers are more effective than formation markers in the evaluation of the bone formation–resorption cycle . Thus, the lack of statistical significance in serum ALP, Ca, and P levels among the groups may be explained by these findings.

Şahin *et al*. [28] compared the effects of ASI and ASI components (A + S + I) on inflammation markers and joint health in rats with collagen–induced arthritis. In the group in which the ASI complex was applied, ALT, AST, creatinine, total cholesterol, total triglycerides, and low–density lipoprotein levels were found to be significantly lower than in the arthritic control group. The normal levels of AST, ALT, urea, and creatinine in the treatment groups showed that the ASI complex and A + S + I separately do not have toxic effects on the liver and kidneys [36].

Similarly, in a study conducted by Bakir *et al.* [37] with arginine, glutamine, and a combination of glutamine and arginine, no significant differences were found in ALT and AST levels. In this study, similar to Bakir et al.'s study, it was observed that the ASI complex did not cause a significant change in the ALT and AST values of the ASI–implant and ASI–control groups.

The current study does have some limitations. First, the molecular mechanisms underlying the relationship between the ASI complex and bone tissue metabolism were not fully explained due to the method used in this study. Second, in vivo studies can only be used to predict corresponding pathways in humans. Third, in this study, we could not evaluate the survival rate of titanium implants or the long–term success of BIC. Fourth, long bones, such as the tibia and femur, have different osteogenic properties compared to jawbones (mandible–maxilla) and therefore may respond differently to ASI complex feeding [19].

This study is the first to histologically and biochemically examine the effects of ASI complex on the osseointegration of titanium dental implants. However, only the ASI complex was evaluated; the effects of arginine and silicon were not separately evaluated. Therefore, the fact that the unique effects of the materials and the synergistic interaction created by their combined use were not examined in our study creates limitations in evaluating the findings [29, 32].

CONCLUSION

Based on the limited results of this study, it can be stated that, although not statistically significantly but higher BIC and TF ratios were detected in rats using the ASI complex. These results may be indicated that ASI complex may increase the osseointegration level of titanium implants. Further studies with different working and application methods are needed for more advanced research on the subject.

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Conflict of Interest

The authors declare no conflicts of interest.

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