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Biomechanical investigation of the effect of Vitamin C supplementation on Osseointegration of titanium implants in rat (Rattus norvegicus) tibia

Investigación biomecánica del efecto de la suplementación con vitamina C sobre la osteointegración de implantes de titanio en tibias de rata (Rattus norvegicus)

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ABSTRACT

In this study, it was aimed to evaluate some possible effects of vitamin C supplementation on the osseointegration process implants placed in rat tibias. Thirty 3-month-old female Spraque Dawley rats (Rattus norvegicus) were divided into 3 groups. In all groups, the corticocancellous part of the the metaphysis of the right tibia bones were surgically reached. Monocortical implant sockets were created by surgical methods under serum cooling, and then titanium implants with 2.5 mm diameter and 4 mm long titanium were integrated on these bone sockets. Group Sham (Control) (n=10): No additional application was made during the experimental process. Group C1 (n=10): 5 mg/kg vitamin C was given to the rats with oral gavage application in three days a week for four weeks of experimental process. Group C2 (n=10): 10 mg/kg vitamin C was given to the rats with oral gavage application in three days a week for four weeks of experimental process. At the end of the four-week experimental setup, all rats were sacrificed and the experimental process was completed. The implants integrated in the tibias of all rats were collected with the surrounding bone tissue after removing the soft tissues for biomechanical analysis. Biomechanical reverse torque analysis was applied to all implants. Statistical analysis of the obtained data; Kruskall-Wallis test, no statistically significant difference was detected between the control and experimental groups (P>0,05). In conclusion, 5 and 10mg/kg vitamin C supplementation has no positive or negative effects on osseointegration. This situaiton can be explained in two ways; the first, the dosages of vitamin C used in this study is not sufficient to create an effect. Second, the endogenous synthesis of this vitamin is enough even though under these stress conditions.

Key words: Vitamin C; osseointegration; rat tibias

RESUMEN

Este estudio, tuvo como objetivo evaluar algunos posibles efectos de la suplementación con vitamina C en el proceso de osteointegración en implantes de ratas. Treinta ratas Sprague Dawley, hembras, de 3 meses de edad, se dividieron aleatoriamente en tres grupos. Todos los ejemplares, fueron abordados quirúrgicamente en la porción corticoesponjosa de la metáfisis tibial derecha. Se perforaron las corticales óseas y se integraron implantes de titanio de 2,5 mm de diámetro y 4 mm de longitud. Grupo control (n=10): no se realizó ninguna aplicación adicional. Grupo C1 (n=10): Se administraron 5 mg/kg de vitamina C por sonda oral tres días a la semana durante cuatro semanas. Grupo C2 (n=10): recibiò 10 mg/kg de vitamina C por sonda oral tres días a la semana durante cuatro semanas. Al final de las cuatro semanas, se sacrificaron todas las rata, dando por finalizado el experimento. Los implantes integrados en las tibias de todas las ratas se recogieron junto con el tejido óseo circundante tras la extracción de los tejidos blandos para su análisis biomecánico. Se aplicó un análisis biomecánico de torque inverso a todos los implantes. El análisis estadístico de los datos obtenidos se realizó mediante la prueba de Kruskall-Wallis. No se detectaron diferencias estadísticamente significativas entre los grupos control y experimental (p > 0,05).En conclusión, la suplementación con 5 y 10 mg/kg de vitamina C no tiene efectos positivos ni negativos sobre la osteointegración. Esto se puede explicar de dos maneras: primero, las dosis de vitamina C utilizadas en este estudio no son suficientes para lograr un efecto; segundo, la síntesis endógena de esta vitamina es suficiente incluso en estas condiciones de estrés.

Palabras clave: Vitamina C; osteointegración; tibias de rata

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INTRODUCTION

Vitamin C, also known as ascorbic acid, is a glucose derivative. In addition to dissolving in water, it shows weak acid properties, it also has a white and crystalline structure. Vitamin C shows a stable structure against heat in acidic solutions, while alkaline can be separated under conditions. When heated, the destruction is increased with daylight [1].

Vitamin C is synthesized from glucose via the uronic pathway in the liver of most mammals (eg., pigs, dogs, cats, ruminants) and both in the liver and kidneys of poultry [2 ,3 ,4]. However in primates, guiana pigs, some species of fish, birds, insects and invertebrates vitamin C cannot be syntesized from glucose due to the lack of the enzyme L-gulonolactone oxidase [5].

When vitamin C is examined chemically, it is seen that it has a strong reducing potential with the ability to stabilize unpaired electrons. By this way vitamin C reduces compounds such as O_2, NO_3, cytochromes A and C. Helps some enzymes metal cofactor to maintain in their reduced state such as Cu^+ in monooxygenase, Fe^{2+} in dioxygenase. Synthesis of hydroxyproline and hydroxylysine in collagen requires vitamin C. This vitamin acts also in oxidation of tyrosine, synthesis of catecholamins from tyrosine, synthesis of bile acid and carnitine. When the metabolic effects of vitamin C are examined, steroidogenesis in the adrenal cortex requires this vitamin. Vitamin C significantly increases iron absorption by preventing nitrosamine formation during digestion. It has also been reported that vitamin C supports endothelial NO synthesis, which is necessary for the regulation of cardiovascular function. Vitamin C provides its function in the synthesis of NO by increasing intracellular tetrahydrobiopterin (BH4) concentrations [6]. Therefore it scavenges free radicals, protect biomolecules from oxidation and maintain metal ions in their reduced forms [1].

The most well-known symptom of vitamin C deficiency is scurvy. Scurvy is directly related to defective collagen synthesis in the connective tissue. Conditions such as bleeding under the skin, soft and swollen gums, excessive bleeding in the gums, loose teeth, cracked capillaries, impaired wound healing, muscle weakness, fatigue, depression, growth retardation, decreased appetite and low resistance to infectious diseases can be seen in both humans and animals due to vitamin C deficiency [7].

Although some organisms can syntesize and the others get vitamin C alimenterally, in some certain cases like stress of surgery, the demand for this vitamin may be greater than endogenous or exogenous sources. In a study on rats it is reported that; ACTH injection caused a 30% decrease in adrenal ascorbic acid level within 20 minutes (min) and this decrease reached the maximum level of 60% within one hour (h) [8].

In the case of bone fractures which are also a big stress factors for the organism; the healing process begins with hypertrophy in chondrocytes and calcification in the matrix of cartilages. A significant increase in alkaline phosphatase levels occurs with the mineralization mechanism. Due to this increase, there is a decrease in the major cartilage protein collagen type II and an increase in type X. It is known that this mechanism in collagens works due to the presence of ascorbate. An *in vitro* study on chondrocytes indicates that, ascorbic acid stimulated the alkaline phosphatase activity [9]. In a study on rats (*Rattus norvegicus*), Xu *et al*. [10], indicated that by the use of zymosan which increases the oxygen free radicals, the fracture healing process is impaired. It has been reported in the literature that vitamin C supplementation increases bone healing in rats [11]. However Giordano *et al*. [12], claimed vitamin C has no positive effect on bone healing in fracture model in rats.

The healing process of implant surgery and osseointegration is the same with the same of fracture healing process. Bone implant fusion; osseointegration is defined as the direct and tight bonding of an alloplastic material with the bone without any connective tissue between it and the bone. Osseointegration is extremely important for the implant material to function clinically and to remain in the mouth for a long time. Therefore we evaluated the osseointegration process similar to fracture healing process. In osseointegration, where direct contact between the implant and the bone is ensured, any connective tissue infiltration between the bone and the implant is not desired [11].

This study aimed to evaluate some possible effects of vitamin C supplementation in rats, on the osseointegration process of implants.

MATERIAL AND METHODS

Animals and study design

Animal Ethics Committee confirmed the design of the study with the approval number of (30.11.2020-426281). All experimental procedures were implemented in accordance with the Declaration of Helsinki. 30 female Sprague Dawley rats, 3 months old and weighing 280-300 g (WL, Shimadzu, Japan), obtained from the Firat University Experimental Research Center were used in the study. In order to ensure standardization of the work, vaginal smears were performed and rats in the same estrus period were included in the study. The rats included in the study were kept in plastic cages in rooms with a standard temperature of 24±2°C, with a 12-hour light and 12-hour dark cycle. All of them were fed with a standard diet *ad libitum* and free acces to water. The nutritional values of the diet is shown in TABLE I.

TABLE I
The nutritional values of the diet (%).

Methionine	0,43	Phosphorus	0,74
Crude Protein	24	Sodium	0,04
Crude fat	3,15	Mineral mix	0,1
Crude sellulose	4,96	Crude ash	4,91

The study groups were designed as;

Group Sham (n=10): After the reached the tibial bones with the surgical applications the bone cavities were drilled and titanium implants with the 2,5 mm diameter and 4 mm length were integrated.

Group C1 (n=10): 5 mg/kg of vitamin C was administered three days a week during the 4 weeks period by oral gavage was added to the same surgical procedure [11].

Group C2 (n=10) : 10 mg/kg vitamin C was administered three days a week during the 4 weeks period by oral gavage was added to the same surgical procedure [11].

At the end of the experimental setup; four weeks, all rats were euthanized and the experimental phase was terminated. The implants were gently removed from the soft tissues along with the surrounding bone tissue. All samples were subjected to biomechanical reverse torque analysis in order to evaluate the osseointegration levels.

Surgical procedures

All surgical procedures were performed under general anesthesia. Rats (Rattus norvegicus) were fasted for 8 h before anesthesia. In order to provide anesthesia, 40 mg/kg Ketamine hydrochloride (Ketasol®, Richter Pharma, Austria) and 5 mg/kg Xylazine hydrochloride (Rompun®, Bayer, Germany) were administered intramuscularly using appropriate syringes [11]. Mepivacaine hydrochloride (0,3 ml/kg, scandicaine epinephrine 1:100,000 to 2%; Septodont, France) was infiltrated into the surgical area to reduce bleeding [11]. The surgical area was shaved and washed with povidone iodine to aid sterilization. An approximately 1,5 cm long incision was made by using a number 15 scalpel, taking bone contact from the tibial crest. After the incision, the soft tissues were dissected and the proximal part of the tibial bone was reached using a periosteal elevator (FIG. 1) [11].

FIGURE 1. Skin incision made to reach the tibia bone where the implant will be placed

Implant cavities were formed in the right tibial metaphyseal corticocancellous parts (FIG. 2) by a drill with a diameter of 2,5 mm and a length of 4 mm.

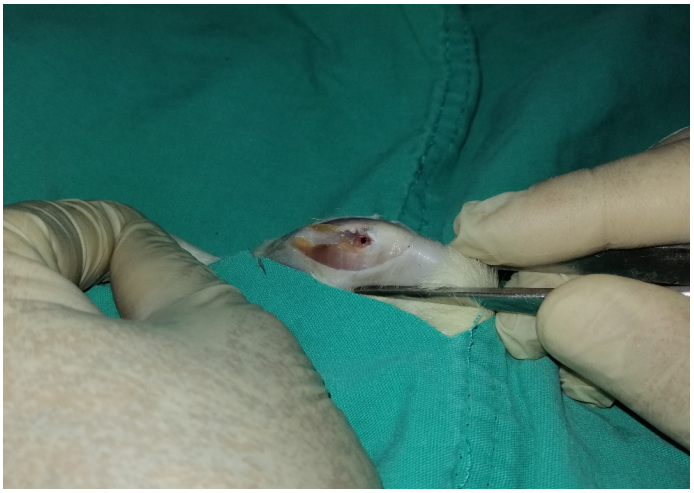

FIGURE 2. The bone socket prepared in the tibia cortico cancellous region where the implant will be applied

While this application, first point drills and then 1,8 mm and 2,5 mm drills were used, respectively. Titanium implants (Implance Dental Implant System, AGS Medical Corporation, Istanbul, Turkiye) with a resorbable blast material (RBM) surface and a diameter of 2,5 mm and a length of 4 mm were placed in the bone sockets created by surgical methods (FIG. 3).

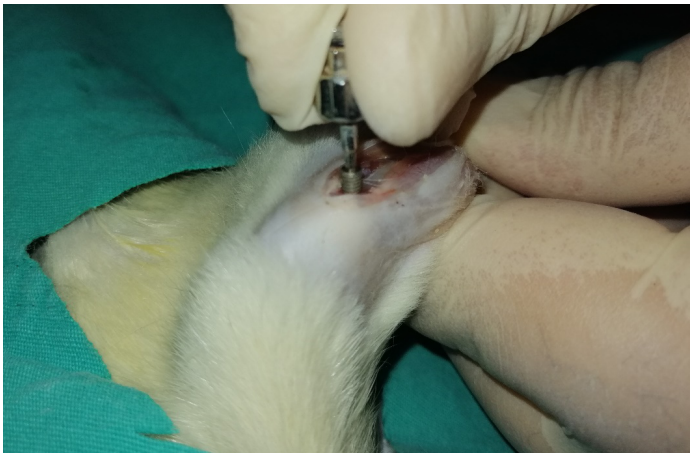

FIGURE 3. Placing the implant into the prepared bone sockets

The surgical procedures were ended by suturing the flaps to their original positions. To avoiding postoperative pain and infection, antibiotics (50 mg/kg Penicillin) and analgesics (0,1 mg/kg Tramadol hydrochloride) were administrated intramuscularly to all rats once a day for three days [11]. No additional procedures were performed during the four-week experimental setup. During the study period, all groups were monitored daily to avoiding the possible complications such as pain, separation of wound edges, infection, immobility and weight loss. At the end of the experiment, all rats were sacrificed after a four-week recovery period. The implants and surrounding tibia bone were taken for biomechanical analysis of the samples (FIG. 4).

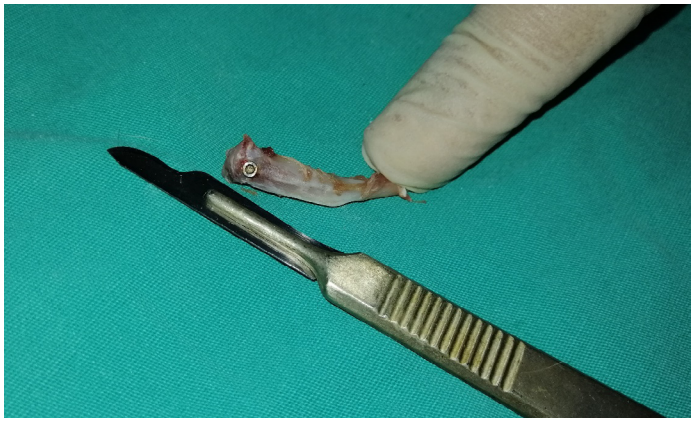

FIGURE 4. Removal of the implant along with the surrounding bone tissues

The samples were stored in 10% buffered formalin solution to preotect from dehydration until the biomechanical reverse torque analysis.

Biomechanical analysis

All samples were subjected to biomechanical analysis after being embedded in polymethyl methacrylate resin. In order to measure the torque of the implants, a ratchet and a hexagonal key were placed in the groove inside the implant. The ratchet was attached to the hexagonal key and manually applied slowly and gradually counterclockwise in a way that would be opposite to the direction of placement of the implant in the socket. (Mark 10, NY, USA) (FIG. 5).

When applying reverse torque analysis, the highest torque force (Ncm) measured during the first rotation of the implant in the socket within the bone was automatically recorded. The data obtained for each implant was recorded as the biomechanical osseointegration value of the implant.

Statistical analysis

For the statistical analysis, SPPS 22.00 software was used. Shapiro Wilks and Kolmogorov-Smirnov tests was first applied to evaluate if the data was distributed normal or not. After determining that the data show not normal distribution, Kruskall Wallis test was applied. The Mann Whitney U test was applied in pairwise comparisons. Data is given as mean minimum-maximum. P-value < 0,05 was considered sufficient to indicate statistical significance.

RESULTS AND DISCUSSION

Five rats (two rats from sham and C2 groups, one rat from the C1 group) were excluded from the study because their implants did not fit properly and were not osteointegrated. The biomechanic bone implant connection (BIC) data of the groups are shown in TABLE II.

FIGURE 5. Performing the torque analysis with a digital torqmeter (Mark 10, NY, USA).

TABLE II
Biomechanic bone implant connection (BIC) (Newton/cm) levels of the groups

Groups	N	Mean	Minimum	Maximum	P*
Sham (Control)	8	5,74	3,7	7	0,12
C vit dosage 1	9	4,27	2,5	6	
C vit dosage 2	8	4,93	2,8	9	

* Kruskall Wallis test. Differences were not statistically significant (P>0,05).

The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to evaluate whether the data showed normal distribution. Since it was understood that the data did not show normal distribution, nonparametric tests were used in the analyses, and the data were presented with mean and minimum-maximum values. The mean BIC ratios of groups sham (control animals), C1 and C2 are determined as 5,74N, 4,27N and 4,93N, respectively. Although there is numarical difference between the groups, it is not found statistically significant (P>0.05). From these results, it was observed that the doses of vitamin C used in this study did not have any effect on the osseointegration levels of the implants.

In this experimental study, we investigated the effects of vitamin C supplementation with two different doses on implant

osteointegration in rat tibia by biomechanical method. Although some numerical variations were found among the groups, the differences were not statistically significant which agrees with the results of Bozoglan *et al* and Giardiano *et al* [11 , 12].

Long *et al*. [13], claims that plasma ascorbic acid levels decreases to extremely low levels in the case of trauma or infections due to increased catabolism and turnover rate. In the light of these data we supplemented our subjects with higher doses than the turnover amount.

Researchers [9 , 14 , 15 , 16] worked on osteoblast cell cultures and established that ascorbic acid treatment induced matrix mineralisation and collagen synthesis. Although we did not study on molecular detections, the possibility of not observing any positive effect like them may be due to circadian rhtym difference between *in vitro* and *in vivo* studies.

Yilmaz *et al.* [17], supplemented bone fractured rats with 0,5 mg/kg vitamin C. However, although they observed beneficial effects of vitamin C supplementation, the difference may be due to the difference between the statistical evaluation in this study and their light microscopic observation results. The other possibility of the difference may be the way of supplementation. In this study, subjects were given c vitamin supplement via oral gavage. Also farmacokinetics differences may occur between intraperitoneal and oral supplementation. Similar to this study, in the study by Bozoglan et al., which was performed with oral gavage, it was reported that bone healing and osseointegration values did not create a statistical difference [11].

Deyhim *et al.* [18], study on rats which developed osteoporosis after ovariectomy, oral vitamin C was administered 22 mg. While the researchers found an increase in bone density in the femoral bones of the rats after the experimental setup, they also found an increase in both bone density and bone mineral content in the lumbar bones. They reported that oral vitamin C supplementation can treat the negative effects of osteoporosis and increase the antioxidant capacity, which has an important place in the osseointegration mechanism. The possitive effect differences than our study can be explained by the supplementation amount.

In another study that we can evaluate in terms of osseointegration and bone metabolism Zhu *et al.* [19], reported that vitamin C intake following ovariectomy in rats prevented low-cycle bone loss. The researchers stated that the positive effects on bone mineral density and micro-computed tomography parameters obtained from the subjects were due to the stimulation of bone formation with vitamin C supplementation. They claimed that bone formation parameters were obtained 8 weeks after ovariectomy, similar to controls, and that vitamin C could be a skeletal anabolic agent. The different results from our study may be explained by the rats used in this study were ovariectomised and their possible metabolic alternations.

Sarısözen *et al.* [20], determined statisticaly significant increase (P<0,05) in fracture healing process of rats. The difference from this study may be due to the their high supplementation of vitamin C (200 mg/kg) than ours (5 and 10mg/kg) and analysis method.

In addition, Dethlefs-Canto *et al.* [21], reported in their review that vitamin C application after tooth extraction reduces postoperative pain, inflammation, probing pocket depth at the extraction site, and mesiodistal length of the socket, and has the potential to accelerate alveolar bone healing after tooth extraction. Abdulhameed and his colleagues reported in an in vitro study that vitamin C may have a positive effect on ossification by increasing mineralization in cells [22].

CONCLUSION

In the light of all these data, our study results indicate that; 5 and 10mg/kg vitamin C supplementation has no positive or negative effects on osseointegration. We can explain this in two ways; the first, the dosages of vitamin C used in this study is not sufficient to create an effect. Second, the endogenous synthesis of this vitamin is enough even though under these stress conditions. Further studies need to be performed to determine these two aspects.

Conflicts of Interest

The authors declare that there are no known conflicts of interest.

Acknowledgement

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BIBLIOGRAPHIC REFERENCES

[1] Barrios-Garay K, Toledano-Serrabona J, Gay-Escoda C, Sánchez-Garcés MÁ. Clinical effect of vitamin C supplementation on bone healing: A systematic review. Med. Oral Patol. Oral Cir. Bucal. [Internet]. 2022; 27(3):e205-e215. doi:https://doi.org/pxjz

[2] Olsen E, Wagenhoffer Z, Hetényi N. Nutrition, health and welfare of Norwegian pet guinea pigs. Acta Vet. Hung. [Internet]. 2025; 73(2):73-80. doi:https://doi.org/pxj2

[3] Akinmoladun OF. Stress amelioration potential of vitamin C in ruminants: a review. Trop. Anim. Health Prod. [Internet]. 2022; 54(1):24. doi:https://doi.org/pxj3

[4] Ranjan R, Ranjan A, Dhaliwal GS, Patra RC. l-Ascorbic acid (vitamin C) supplementation to optimize health and reproduction in cattle. Vet. Q. [Internet]. 2012; 32(3-4):145-150. doi: https://doi.org/pxj4

[5] Saha, S.K., Pathak, N.N. Digestion, Absorption and Metabolism of Nutrients. In: Fundamentals of Animal Nutrition. 1st edition. Singapore: Springer. 2021; p. 219–246. doi: https://doi.org/pxj5

[6] Li R, Guan L, Liu Y, Hu Z, Liu J, Li C, Min H. The roles of vitamin C in infectious diseases: A comprehensive review. Nutrition. [Internet]. 2025; 134:112733. doi: https://doi.org/pxj6

[7] Lombardi AA, Sammon M, Schreyer KE. Vitamin C and D Deficiency in Urban America: A Case Report. Clin. Pract. Cases Emerg. Med. [Internet]. 2024; 8(1):38-41. doi: https://doi.org/pxj7

[8] Briggs FN, Briggs W. The effect of ACTH on the ascorbic acid concentration of adrenal venous plasma of the rat. Endocrinol. [Internet]. 1958; 62(1):24-29. doi: https://doi.org/fcm8rn

[9] Theruvath AJ, Mahmoud EE, Wu W, Nejadnik H, Kiru L, Liang T, Felt S, Daldrup-Link HE. Ascorbic Acid and Iron Supplement Treatment Improves Stem Cell-Mediated Cartilage Regeneration in a Minipig Model. Am. J. Sports Med. [Internet]. 2021; 49(7):1861-1870. doi: https://doi.org/pxj8

[10] Xu Z, Zhang Y, Lu D, Zhang G, Li Y, Lu Z, Wang F, Wang G. Antisenescence ZIF-8/Resveratrol Nanoformulation with Potential for Enhancement of Bone Fracture Healing in the Elderly. ACS Biomater. Sci. Eng. [Internet]. 2023; 9(5):2636-2646. doi: https://doi.org/pxj9

[11] Bozoglan MY, Dundar S, Bozoglan A, Yildirim TT, Ozcan EC, Kirtay M, Kaya CA, Habek O. Evaluation of the Effects of the Systemic Vitamin C Supplementation on Peri-Implant Bone Regeneration and Osseointegration: An Experimental Study. F.U. Med. J. Health Sci. [Internet]. 2023 [cited Feb 13, 2025]; 37(3):243–248. Available in: https://goo.su/3FFyx

[12] Giordano V, Albuquerque RP, do Amaral NP, Chame CC, de Souza F, Rodrigues Apfel MÍ. Supplementary vitamin C does not accelerate bone healing in a rat tibia fracture model. Acta Ortop. Bras. [Internet]. 2012; 20(1):10-12. doi: https://doi.org/gb9t5m

[13] Long CL, Maull KI, Krishnan RS, Laws HL, Geiger JW, Borghesi L, Franks W, Lawson TC, Sauberlich HE. Ascorbic acid dynamics in the seriously ill and injured. J. Surg. Res. [Internet]. 2003; 109(2):144-148. doi: _ https://doi.org/bnd3d9

[14] Li W, Huang Y, Gu D, Peng S, Zhang B, Peng F, Zhang D, Li M, Xiao J, Jia Z, Qiu L. Ascorbate-loaded MgFe layered double hydroxide for osteomyelitis treatment. J. Control. Release. [Internet]. 2025; 378:1045-1060. doi: https://doi.org/pxkc

[15] Zhang H, Zhang Y, Zhang Y, Wei H, Jin S, Huo T, Qin L. Combination of inorganic nitrate and vitamin C prevents collagen-induced arthritis in rats by inhibiting pyroptosis. Food Funct. [Internet]. 2025; 16(2):673-690. doi: https://doi.org/pxkd

[16] Metzger W, Ammo T, Sossong D, Bubel M, Mattes C, Stumpf H, Später T, Laschke MW, Pohlemann T. Establishing a simple protocol to induce the osteogenic differentiation of MC3T3-E1 cells in 2D and its transfer to 3D spheroid cultures. Biotech. Histochem. [Internet]. 2025; 100(4):179-192. doi: https://doi.org/pxkf

[17] Yilmaz C, Erdemli E, Selek H, Kinik H, Arikan M, Erdemli B. The contribution of vitamin C to healing of experimental fractures. Arch. Orthop. Trauma Surg. [Internet]. 2001; 121(7):426-428. doi: https://doi.org/fbvpw8

[18] Deyhim F, Strong K, Deyhim N, Vandyousefi S, Stamatikos A, Faraji B. Vitamin C reverses bone loss in an osteopenic rat model of osteoporosis. Int. J. Vitam. Nutr. Res. [Internet]. 2018; 88(1-2):58-64. doi: https://doi.org/pxkg

[19] Zhu LL, Cao J, Sun M, Yuen T, Zhou R, Li J, Peng Y, Moonga SS, Guo L, Mechanick JI, Iqbal J, Peng L, Blair HC, Bian Z, Zaidi M. Vitamin C prevents hypogonadal bone loss. PLoS One. [Internet]. 2012; 7(10):e47058. doi: https://doi.org/f4hmqf

[20] Sarisözen B, Durak K, Dinçer G, Bilgen OF. The effects of vitamins E and C on fracture healing in rats. J. Int. Med. Res. [Internet]. 2002; 30(3):309-313. doi:https://doi.org/pxkh

[21] Dethlefs-Canto J, Osses-Barría F, Vergara-Zenteno R, Bustos-Ponce A, Villavicencio-Duarte J. The effectiveness of vitamin C in dental alveolus healing after dental extraction: A scoping review. Med. Oral Patol. Oral Cir. Bucal. [Internet]. 2025; 30(1):e124-e128. doi:https://doi.org/pxkj

[22] Abdulhameed EA, Rani KGA, AlGhalban FM, Abou Neel EA, Khalifa N, Khalil KA, Omar M, Samsudin AR. Managing Oxidative Stress Using Vitamin C to Improve Biocompatibility of Polycaprolactone for Bone Regeneration *In Vitro*. ACS Omega. [Internet]. 2024; 9(29):31776-31788. doi: https://doi.org/pxkk