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The Effect of local Application of Zoledronate on the level of Interleukin 1Beta Around Orthodontic Miniscrew in Control Diabetic Sample (Experimental Study on Dogs)

Running title: Local Zoledronate around orthodontic miniscrew

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ABSTRACT

The primary aim of the study research is to evaluate the stability of orthodontic (MIs) after treated with Zoledronate (Local Application), and assess the level of interleukin 1 Beta around (MIs) in control Diabetic Samples (Dog).

Material & Method: twenty male beagle dogs weighting (15-20 kg) with average of (16.71kg) and aged between (1.5-2 year)were divided into two groups, Alloxan solution was given intravenously at a dose of 60mg/kg as a single dose This dose was chosen because it was effective in inducing diabetes, The control of Diabetes is done by giving oral anti- diabetic metformin 1700mg/dog /day with average of (101.73mg/kg) alone or in combination with of lente insulin (0.25U /kg- 0.7 U/kg) twice daily. The insertion of (MIs) is proceed by local application of Zoledronate Solution of 16µg of Zoledronate Diluted in 50µL of phosphate buffer saline solution.

Results: The level of interleukin 1 Beta, have been significantly decreased in Zoledronate than control group, beside that the PTV value of secondary stability of Zoledronate was significantly greater than control group at significance level $p<0.05$.

Conclusion the Zoledronate have a great effect on Decrease the level of interleukin 1 Beta in control diabetic sample ,beside that the Zoledronate have a major role on increase the secondary Stability of orthodontic(MIs) in control diabetic sample.

Keywords: Mini-Implant Screw (MIs), Zoledronate (Zol), Interleukin 1 Beta (IL1β), Periotest value (PTV).

INTRODUCTION

The work by Brånemark and others demonstrated the mechanism by which a metal fixture could be integrated in bone without rejection by the body. This phenomenon became known as osseointegration(1).Implant stability plays a critical role for successful osseointegration, which has been viewed as a direct structural and functional connection existing between bone and the surface of a load-carrying implant.(2) Stability can be divided into two types that are vital to the overall success of the (MIs), **primary stability**, a mechanical phenomenon due to initial contact between the implant and bone, and **secondary stability,** associated with the remodeling and deposition of new bone around the implant over time.(3)

As widely known, osseointegration is not assumed for micro-implant as only the mechanical contact between bone and implant interface is necessary to provide stability, this is the reason of immediate loading ability of mini-implants, since no healing period is awaited. However, osseointegration in mini-implants was found to be present in many studies and these investigators recommend a waiting period prior to force application, the theory of osseointegration (the close contact between bone and implant) was established by Branemark and colleagues(4).The bone micro-implant specimens examined after one week of healing an Collagen fibers and granulation tissue were also found at the Peri-implant interface with the beginning of new bone growth, An increased amount of collagen fiber layers and connective

tissue was present around mini screws analyzed after the two-week healing period[5]. Despite the amount of osseointegration that may formed it is thought that removal is not difficult since coherence is relatively low as active remodelling and less mineralized bone formation takes place in the bone around the loaded screw part[6]. The best known drug –induced diabetic model is the alloxan diabetes, It is capable of inducing both type I and type II diabetes mellitus with proper dosage selection, It is a well- known diabetogenic agent widely used to induce Type II diabetes in animals, alloxan is a urea cells, It is used to produce experimental diabetes in animals such as rabbits, rats, mice and dogs, with this agent, it is possible to produce different grades of severity of the disease by varying the dose of Alloxan used [7]. Zoledronate, a third generation bisphosphonate, is 2-(imidazol-l-yl-hydroxyethane- 1, 1 -bisphosphonic acid) in the form of its monohydrate. The compound is characterized by a side chain including an imidazole ring; (Zol) is a more potent inhibitor of osteoclasts than earlier bisphosphonates, beside that it has the largest therapeutic ratio between the desired inhibition of calcium resorption and the unwanted inhibition of mineralization in vitro of all bisphosphonates, A combination of antifracture efficacy, low rate of adverse events, and infrequent dosing make it a desirable agent for the future [8].local application of(ZOL)Acid may resist the negative influence of Experimental osteoporosis that impede bone healing of Bio-oss bone grafts and decrease osseointegration of implants in bone grafts[9].

The combination of systemic and local treatments with(ZOL) can invert negative effect of osteoporosis and promote osseointegration and fixation of dental implants in autologous bone grafts under osteoporotic condition, this type of Combination of systemic and local use of ZOL exerts best effects when compared to their single use[10], (ZOl) like alendronate, may prevent root resorption and facilitates the regeneration of periodontal tissues after replantation[11], The local delivery of a low dose of (ZOL), linked to a fibrinogen matrix, on the surface of titanium bone screws enables early bone regeneration. Beside that it suggests that over the short term local application (ZOL) does not affect osteoblast, immune and macrophage cell populations, the over drilled bone defect model enabled visualization of the early sequence of cellular events close to the implant interface. It also confirmed drug effects in bone that are consistent with those observed in press fit applications [12].

Interleukin (IL)-1β is one of the most potent cytokine in the inflammatory process in the oral cavity triggered by various stimuli including neurotransmitters, bacterial products, other cytokines and mechanical forces. The action of IL-1β includes attracting leucocytes and stimulating fibroblasts, endothelial cells, osteoclasts, and the mechanism of bone resorption may induce the release of inflammatory mediators, such as interleukin-1, at the biomolecular level. Interleukin-1 exists in two forms: alpha (IL- 1) and beta (IL-1β). Both induce bone resorption, but IL-1β seems to be a more potent inducer of resorption and inhibits bone formation. [13] Levels of IL-1βin the peri-implant crevicular fluid are significantly higher in patients with failing implants than in those healthy one [14]. Most of the studies observed slightly high percentage of early failure of implants in diabetics compared to late failure, beside that the success rates of dental implants in control diabetic patients were in range of 85.5‐100% and were comparable to the non‐diabetic patients, Most of the studies were of opinion that success rate in well/fairly controlled diabetics was either equal or insignificantly lower than normal individuals [15].

Some studies confirmed significantly higher failure of Implant in type I diabetic patients than patients with type II diabetes, and this failure may be due to reduction of insulin in tissues whereas presence of insulin in tissues of type‐2 diabetic individuals may reduce deleterious effect of hyperglycemia [16], the Success of dental implant in well and fairly controlled diabetic patients with proper treatment planning, prophylactic remedies and adequate postsurgical maintenance appears as good as normal individuals[17].The aim of the present study research is evaluation the level of interleukin 1beta cytokinase from the cervical fluid taken round the miniscrew in with the presence of local application of (ZOL) in control diabetic sample.

MATERIAL AND METHOD

A. EXPERIMENTAL ANIMALS

Twenty male beagle dogs weighting (15-20 kg) with average of (16.71kg) and aged between (1.5-2 year)were obtained from the animal house of college of Veterinary Medicine ,Mosul University have been divided into two groups (10 dogs in each group ,first group is the control group that represent the control diabetic without any medical treatment of miniscrew ,other group that represent the miniscrew with local infiltration of (ZOL) All dogs Appeared clinically healthy, with normal periodontal appearance as determined by physical and clinical mouth examination , normal haemogram and clinical chemical profiles, the dogs were housed separately in a controlled environment each of them in single metal cage and fed a home-made diet containing chicken and rice twice a day with sufficient tap of water all the period of study , the animal selection ,management and surgery protocol were approved by the animal care center in the college of veterinary Medicine of Mosul university, the experimental segment of the study started after an adaptation period of 2 months.

B. INDUCTION AND CONTROL OF DIABETES

The Dogs were fasted for 24 h prior to the induction, the Blood was collected for determination of biochemistry profile including: glucose, and serum alanine transaminase (ALT), alkaline phosphatase (ALP)Triglyceride (TG), cholesterol, electrolytes).Catheters were placed in the cephalic vein, Fresh solution of alloxan monohydrate (Sigma, USA) for diabetes mellitus induction was primed just prior to injection.[17] Alloxan solution was made by dissolving it in normal saline at a concentration of (100 mg/ml), this prepared solution was given intravenously at a dose of 60mg/kg as a single dose This dose was chosen because it was effective in inducing diabetes as stated in preceding readings[18], Six hours after alloxan injection, the blood glucose levels were measured every 4 h until the improvement of the hyperglycemia. After giving the alloxan solution, the blood glucose levels must be checked regularly twice a day, one at the morning and the other at the evening using the blood glucose monitoring system, once the hyperglycemia developed the fasting blood glucose levels were measured at 10: 00 a.m. every morning.

Diabetes was confirmed at one week after the alloxan injection by the presence of continuous fasting hyperglycemia>180mg/dl and persistent glycosuria, were considered diabetic and introduced into the study. The control of Diabetes is done in Some diabetic dogs by giving oral anti- diabetic metformin 1700mg/dog /day with average of (101.73mg/kg) that have been divided into two equal parts (two tablets of 500mg at the morning and one tablet & half of 500mg at the evening that given with the meal, But in other cases the metformin will not adjusting enough to control the diabetes induced by alloxan, that need to use a combination of metformin 1700mg with use of lente insulin(Mixture of 30% semi-lente and 70% ultralente insulin)(0.25U /kg- 0.7 U/kg) twice daily.

C. SURGICAL PROCEDURE

The dogs must be fastened overnight before anesthesia, but access to water continues till the anesthesia given, each group was treated in separated days in the morning, before (MIs) placement, all animals were sedated with ketamine 10% (2.2 mg/kg intramuscularly)and Xylazine 2% (0.22 mg/kg intramuscularly).this dose of sedation keep the dog anesthetized for one hour. Before doing the implant insertion, we applied the 0.2% Chlorhexidinegluconate as disinfectant to the implant area by the gauge, then determined the exact location of implant insertion using well sterile wood landmarks that measured the distance from the cusp tip of second, third, and fourth premolars downward till 18mm, and the first molars till 20mm in the Mandibule, were placed in the furcation and between the teeth, depending on space availability in each dog, all the inserted (MIs) (Dentos, Korea,1.3mm in diameter ,7mm length)was done in the non-keratinized gingiva, after punching of the non-keratinized Gingiva, the drilling of the bone is done by using 1.1mm drilling bur, with Surgical hand piece connected to implant Surgical engine at 1600(rpm) speed with 35 newton /cm torque, clockwise rotation with profuse sterile normal saline solution at room temperature (25ºc) was used to irrigate the site and maintained continuously throughout the drilling by sterile disposable syringe. The Preparation of (ZOL) solution must be proceed the insertion of (MIs) in (ZOL) experimental Group, the protocol of solution preparation reported that 50µg of phosphate buffer solution (pH 7.1) contain 16µg of (ZOL) according to Cuairan et al. in (2014)[19]. Zometa dose is equivalent 4mg/5ml,so that 0.8mg/1ml and this equal to 800µg/ml, beside that 16µg/50µL is equal to 320µg/ml so in order to prepare 1ml of 320µg/ml of Zometa we need to add 600ml of phosphate buffer saline solution to 400ml of Zometa (Fig.1).

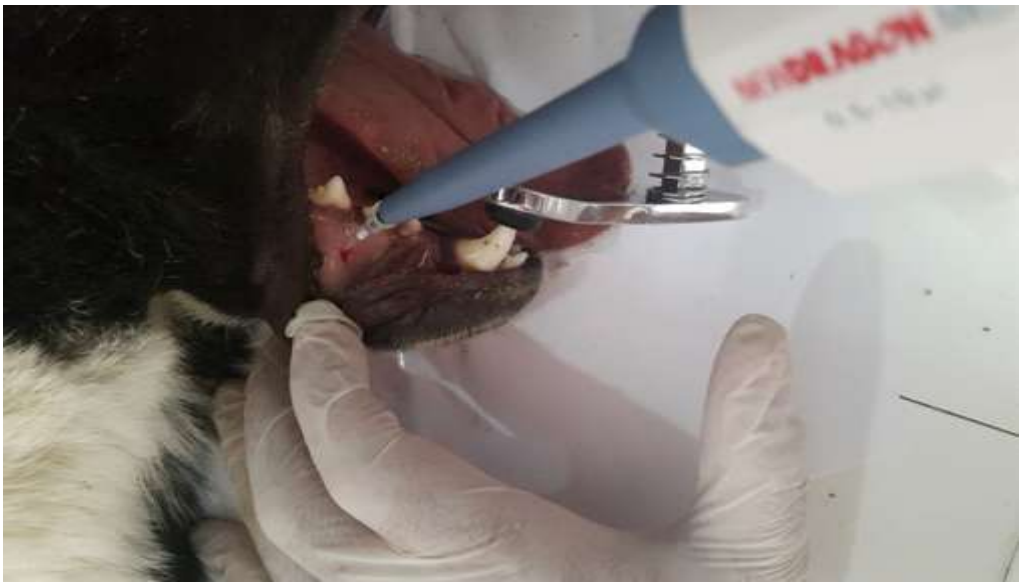

Figure (1) shows the dropping of (ZOL) using graduated micropipette before (MIs) insertion.

D. IMPLANT STABILITY TESTS

The stability test was done at the time of insertion, and then at the end of fourth week.

E. BIOCHEMICAL TESTING (ELISA)

1. Specimen collection and storage have been done after isolating the (MIs) with gauze; the site was dried gently with an air syringe to eliminate the possibility of contamination with saliva.
2. Sampling was achieved in the clinic at approximately 20C degree at room temperature and 40% relative humidity between 9:00 and 10:00 AM.
3. Filter Papers were used to collect (MIs) cervical fluid (the amount was collected by this paper about 2µl) and placed in Eppendorf tube, all filter papers were autoclaved and weighed on a digital scale before used.
4. Two filter papers for (MIs) cervical fluid were inserted into the base of the pocket in both sides until slight resistance was felt; these papers were left in place for 3 minutes. Samples containing blood were thrown away (Fig.2).
5. Acceptable filter Papers were put in the Eppendorf tubes and weighed again to determine the volume of fluid collected.
6. Sterilized saline solution (250µL) was added to the Eppendorf tubes and samples were centrifuged for 1 minute, all cytokines were recovered from the paper strips by 5 minutes of centrifugal elution.
7. The papers were then removed and the solutions were stored at (-20C) until the immunoassay was performed.

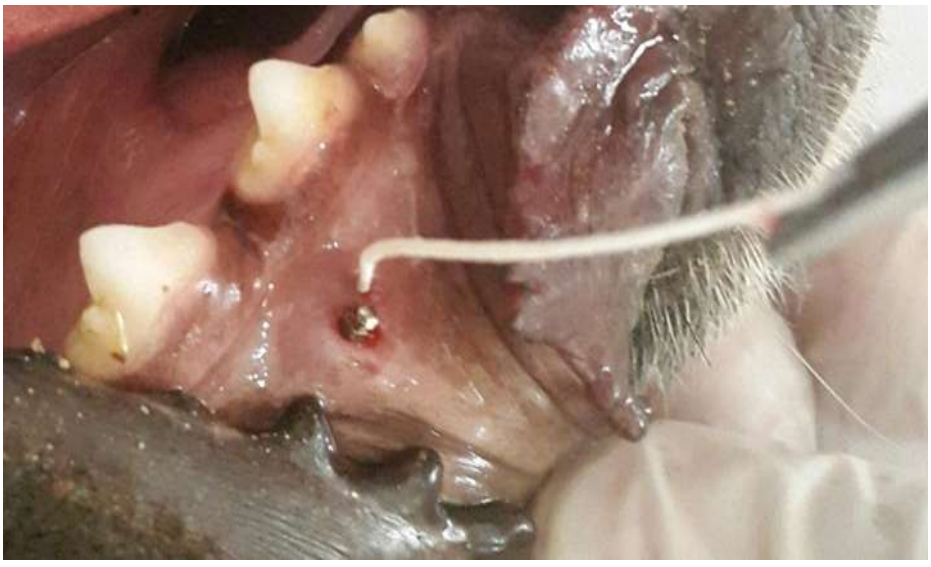

Figure (2) Sample Collection around the (MIs) using Sterile Filter Paper.

Dog Interleukin 1β (IL-1β) ELISA Kit has been used For the quantitative determination of dog interleukin 1β (IL-1β) catalogue number: MBS 704429, San Diego, California, USA, concentrations in serum, plasma, cell culture supernates, tissue homogenates, For research purposes only, all reagents provided are stored at 2 - 8°C. And do not uses past kit expiration date.

RESULTS

In the insertion stage, primary stability, the mean values of Periotest stability `measurement were -2.48±0.10 in control group, -3.72±0.036 in (ZOL) group, all the micro implant begin again checked for secondary stability after one mouth, the secondary stability decreased to a mean of -1.37±0.077 for the control group and increased in (ZOL) experimental study group -4.97±0.175, (Fig.3) simplified the primary stability differences between the entire study groups and (Fig.4)simplified secondary stability differences between all of the study groups.

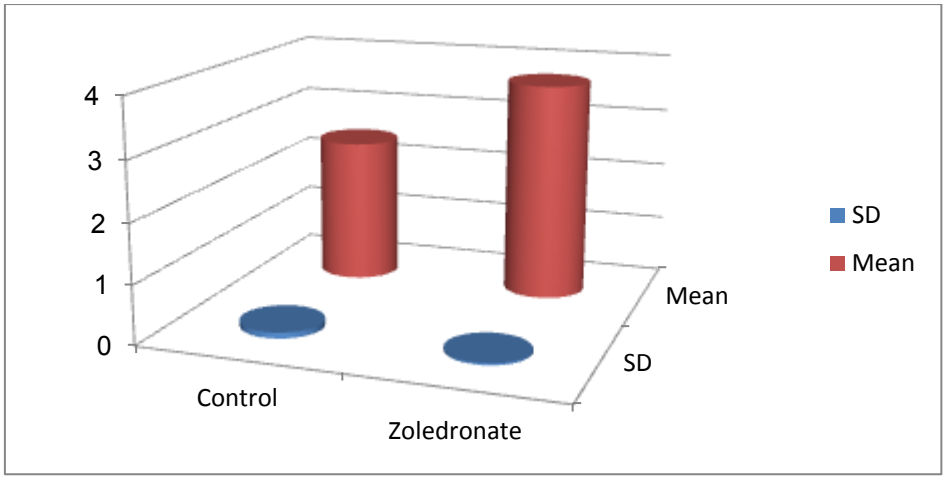

Figure (3) shows descriptive statistic of primary stability for all Groups

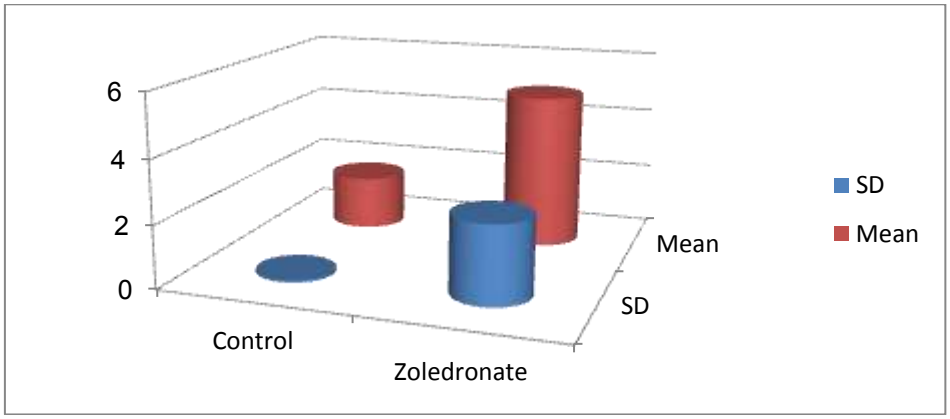

Figure (4) shows descriptive statistic of secondary stability for all Groups

For the statistical test, the result of comparing the primary and secondary stability for each group using t-test and significance at $p<0.05$, showed a significant increase in the stability value after four weeks healing period as represented by secondary stability in the (ZOL) group, while significant decrease in stability value as represented by secondary stability for control group table (1), While on comparing the secondary stability between control group and (ZOL) group there is a significant changes observed in the comparison between them at significant level $p<0.05$ as shown in table (2).

Table (1) shows Comparison between the primary and secondary stability of all groups.

Study Groups	Stability Comparison	Primary Stability		Secondary Stability		t-value	p-value
		Mean	SD	Mean	SD		
Control	Primary vs Secondary	2.48	0.109	1.37	0.077	64.527	<0.001*
Zoledronate	Primary vs Secondary	3.72	0.366	4.97	0.175	58.06	<0.001*

*significance at $p< 0.05$, all measurements in Periotest

Table (2) the comparison of secondary stability between control group and Zoledronate group

Groups	Mean±SD	t-value	p-value
Control	1.37±0.077	-133.949	<0.001*
Zoledronate	4.97±0.175		

*significance at $p< 0.05$, all measurements in Periotest

The descriptive statistics of the of interleukin 1 Beta showed that the serum interleukin 1 beta of the control group is 53.04+3.06 (pg/mL) which is the highest mean value, the zelodronate group showed the lowest mean value 30.55+0.283 (pg/mL), as shown in the figure(5), for the statistical test on comparing the interleukin 1 Beta between

the control group and the experimental study group using the paired t-test and significance level at $p<0.05$, showed a significant decrease in interleukin 1 Beta level for the zelodronate group when compared with control group, as shown in table (3).

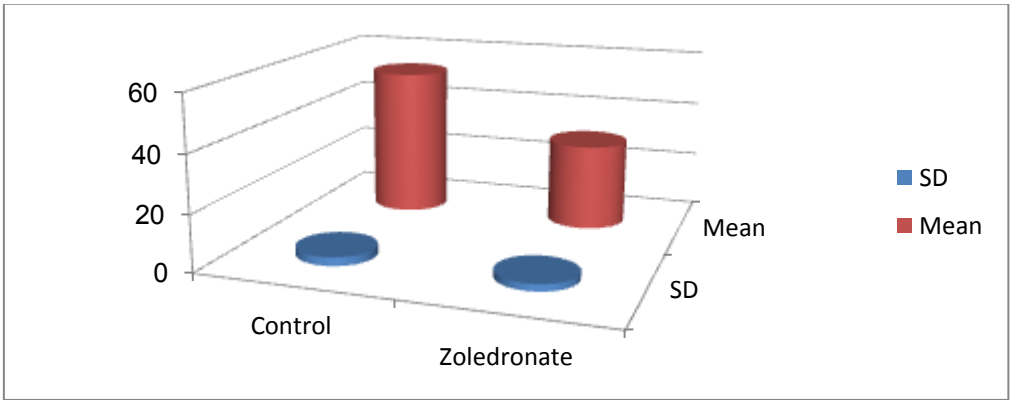

Figure (5) shows descriptive statistics of interleukin 1 Beta in all Groups.

Table (3) the comparison of interleukin 1 Beta between control group and Zoledronate group

Groups Comparison	Control Group		Zoledronate Group		t-value	p-value
	Mean	SD	Mean	SD		
Control vsZoledronate	53.04	3.06	30.55	2.19	42.95	<0.001*

* Significance at $p<0.05$, all measurements are in (pg/mL)

DISCUSSION

The stability of orthodontic implant have been previously evaluated using different approaches as insertion torque, torque of removal and pullout tests, while the most noninvasive method to measure the stability is the Periotest and the resonance frequency analysis ,the benefit of using Periotest is to measure the stability that reflect the amount of bone surrounded the implant ,so that this device giving the picture whether there is restraining the amount of bone surrounded the implant or not.[20] In this study primary and secondary stability formed , many Different factors may contribute to initial implant stability, the degree of primary stability after the implant placement has been related to local factors, implant factors, patient characteristic and surgical technique, so that Initial stability of implants can be significantly less in bones of low density or insufficient volume ,also Larger bone-to-implant contact fractions have been reported in bone sites of higher density, beside that the length of the dental implant, its diameter, its design, as well as the micro-morphology and the type of implant surface are considered key factors inducing primary stability[21].

Secondary stability is the result of the formation of new woven and lamellar bone onto the implant surface, Micro-motion beyond a certain degree has been shown to prevent secondary implant stability to occur, beside that Sufficient primary stability prevents micro-motions between the surface of the implant and the surrounding bone also the Secondary stability, which is associated with healing and increases in total (MIs) stability, first becomes apparent three weeks after miniscrew placement and can be tested at the beginning of fourth weeks[22].In regarding the comparison between primary and secondary stability, in the present study results showed a significant higher PTV of secondary over primary stability in zelodronate group, but higher primary over secondary stability in control group, further the statistical comparison of secondary stability between the control and Zoledronate study group showed a significant higher PTV of secondary stability in Zoledronate group over control group, the result of the current study disagree with the result obtained by Massey et al., (2012)[23],The fact that the micro implant were not loaded could also have decreased their stability in 3-dimensional micro- computed tomography study have shown greater amounts of cortical and non-cortical bone surrounding moderately loaded than unloaded micro implant .

The present study results agreed with Mahesh et al., (2014)[24], who study the local effect of implant hole grafting with calcium phosphor –silicon putty on secondary stability that increased over the primary stability if compared with control group (non-grafted).There is an agreement of the study results with Back et al., (2012) [25] Where strong bone implant integration of intramedullary implants is done by local application of Zoledronate to stimulate fracture healing, beside that Cuairan et al., (2014)[19] found that the local application of small amount of Zoledronate 16µg diluted in 50µg of buffered phosphate saline solution in miniscrew implant hole increase the secondary stability through

increasing the trabecular bone formation around the implant when comparing with the primary stability ,they detect that the stability increase slightly at the end of test period (8 weeks) in dogs in experimental group with slightly decrease in stability at the same period in control group.

The current study explain that, the primary bone that formed after the implant insertion is weak bone not fulfill the complete integration of bone with implant, and that weak bone had replaced after the 4th week or between the 5th and 6th by more strong lamellar bone and this explain why the secondary stability in experimental group is larger than primary stability when comparing with control group and this agree with the study conducted by Turner & Nentwing, (2014) [20], Interleukin 1 Beta is one the most important cytokines that stimulates bone resorption and inhibits bone formation; this mediator also stimulates the prostaglandin synthesis and protease production[26] IL-1beta in co-operation with other inflammatory mediators has an important role in regulating and amplifying the inflammatory response in periodontal and Peri-implant tissues beside that A high level of IL-1beta in the gingival crevicular fluid and the gingival tissue have been associated with chronic periodontitis[27], Low concentration of IL-1β stimulates insulin release and proliferation in rat and human islets [28] beside that the Increased IL-1β levels is accompanied with impaired insulin secretion, decreased cell proliferation and apoptosis of pancreatic beta cells [29]

There is inverse relationship between serum levels of IL-1β and beta cell function one way or another supports the role of increased IL-1β in pancreatic beta-cell dysfunction and further confirms the hypothesis that increased secretion of this cytokine reduces the amount of secretion of insulin from beta cells, In contrast, the positive and significant relationship between IL-1β and blood glucose concentration in diabetic patients that describe the role of this inflammatory cytokine in prevalence of diabetes and the determining parameters of type II diabetes[30] . The result of the present research showed that a significant decrease of interleukin 1 Beta(IL-1ß) level of the Zelodronate group over the control groups , and this result agree with the result obtained by Kao et al., (1994),[31] he stated that the Inflammation correlates with elevated levels of interleukin-1 beta in gingival crevicular fluid, the analysis of interleukin-1 beta levels in diseased implants compared to Those in matching healthy implants in 12 patients indicates that the level of interleukin-1 beta was approximately three times that at healthy sites, Interleukin 1 Beta (IL-1ß) levels correlated with probing depths at teeth and implants while being elevated at inflamed peri-implant tissue, most studies reported about increased levels of IL-1b in mucositis and peri-implantitis[32]and the result of the current study agree with this study. Other authors did not find a significant difference in the level of IL-1 Beta between the healthy sites of implants and the implant with peri-implantitis[33],

The result of the current study research regard the interleukin 1ß agreed with the Kelly et al.,(2015) [34] they found that The pro-inflammatory cytokine interleukin (IL)-1β induces apoptosis in pancreatic β cells Likewise, Jun N-terminal kinase (JNK), which can be activated in response to IL-1β, plays a role in insulin resistance in obesity ,Blockade of IL-1β using a neutralizing antibody beside that Metformin directly inhibits complex I (NADH: ubiquinoneoxidoreductase) of the mitochondrial electron transport chain (ETC) Complex I is the first of four complexes that comprise the ETC, located in the inner mitochondrial membrane, Metformin has been proposed to inhibit this process so that reduce the level of interleukin 1 Beta., The result of the current study agree with the study conducted by Monga et al., (2014)[35] they stated that IL-1β levels in peri-implantic cervical fluid around the miniscrew show a significant rise during miniscrew insertion and on immediate load in.

The tendency toward gradually reducing IL-1β levels around the mini-screw over the period after loading towards the baseline is suggestive of adaptive bone response to stimulus.,Regarding the level of interleukin 1 Beta, that reflect the degree of inflammation in the area of miniscrew insertion in the group of Zoledronate, the result agree with the result obtained by Choi et al., (2010) [11] they stated that topical application of alendronate and zoledronate, both nitrogen containing Bisphosphonates, prevented inflammatory root resorption and inflammatory cell response in the delayed replantation model. Also Surface modification of implants with hydroxyapatite-Zoledronate improves periprosthetic bone quality and osseous integration [36]. The local delivery of a low dose of Zoledronate, linked to a fibrinogen matrix, on the surface of titanium bone screws enables early bone regeneration, Moreover, it suggests that over the short term local application Zoledronate does not affect osteoblast immune and macrophage cell populations[12].

REFERENCES

[1] Kanomi, R. (1997). Mini-implant for orthodontic anchorage. J ClinOrthod 31(11): 763-767.
[2] Gulsahi, A. (2011). Bone quality assessment for dental implants, INTECH Open Access Publisher.
[3] Raghavendra, S.; M. C. Wood&T. D. Taylor (2005). "Early wound healing around endosseous implants: a review of the literature." Int J Oral Maxillofac Implants 20(3): 425-431.
[4] Albrektsson, T.; P. I. Branemark;H. A. Hansson&J. Lindstrom (1981). "Osseointegrated titanium implants. Requirements for ensuring a long-lasting, direct bone-to-implant anchorage in man." ActaOrthopScand 52(2): 155-170.
[5] Wu, J.; Y. X. Bai&B. K. Wang (2009). "Biomechanical and histomorphometric characterizations of osseointegration during mini-screw healing in rabbit tibiae." Angle Orthod 79(3): 558-563.
[6] Serra, G.;L. S. Morais;C. N. Elias;M. A. Meyers;L. Andrade;C. Muller&M. Muller (2008). "Sequential bone healing of immediately loaded mini-implants." Am J OrthodDentofacialOrthop 134(1): 44-52.
[7] Etuk, E. (2010). "Animal models for studying diabetes mellitus." AgricBiol JN Am 1(2): 130-134.

[8] Silverman, S. L. (2011). "Defining zoledronate's duration of action and optimal dosing interval for an effective therapy." CurrOsteoporos Rep 9(1): 4-5.
[9] Deng, J.;M. Qi;J. Li;M. Zhang;J. Li;Y. Liang&W. Dong (2011). Effect of local treatment with Zoledronate Acid on bone healing of Bio-oss bone graft and osseointegration of dental implants in osteoporotic rats. Human Health and Biomedical Engineering (HHBE), 2011 International Conference on.
[10] Qi, M.;J. Hu;J. Li;J. Li;W. Dong;X. Feng&J. Yu (2012). "Effect of zoledronate acid treatment on osseointegration and fixation of implants in autologous iliac bone grafts in ovariectomized rabbits." Bone 50(1): 119-127.
[11] Choi, S. C.; Y. D. Kwon;K. C. Kim&G. T. Kim (2010). "The effects of topical application of bisphosphonates on replanted rat molars." Dent Traumatol 26(6): 476-480.
[12] Arnoldi, J.;A. Alves&P. Procter (2014). "Early tissue responses to zoledronate, locally delivered by bone screw, into a compromised cancellous bone site: a pilot study." BMC MusculoskeletDisord 15: 97.
[13] Rossi, M.; S. Whitcomb&R. Lindemann (1996). "Interleukin-1 beta and tumor necrosis factor-alpha production by human monocytes cultured with L-thyroxine and thyrocalcitonin: relation to severe root shortening." Am J OrthodDentofacialOrthop 110(4): 399-404.
[14] Sari, E. &C. Ucar (2007). "Interleukin 1beta levels around microscrew implants during orthodontic tooth movement." Angle Orthod 77(6): 1073-1078.
[15] Turkyilmaz, I. (2010). "One-year clinical outcome of dental implants placed in patients with type 2 diabetes mellitus: a case series." Implant Dent 19(4): 323-329.
[16] Alsaadi, G.; M. Quirynen;A. Komarek&D. van Steenberghe (2007). "Impact of local and systemic factors on the incidence of oral implant failures, up to abutment connection." J ClinPeriodontol 34(7): 610-617.
[17] Dubey, R. K.; D. K. Gupta&A. K. Singh (2013). "Dental implant survival in diabetic patients; review and recommendations." Natl J MaxillofacSurg 4(2): 142-150.
[18] Anderson, H. R.;A. W. Stitt;T. A. Gardiner;S. J. Lloyd&D. B. Archer (1993). "Induction of alloxan/streptozotocin diabetes in dogs: a revised experimental technique." Lab Anim 27(3): 281-285.
[19] Sheweita, S. A.; A. A. Newairy;H. A. Mansour&M. I. Yousef (2002). "Effect of some hypoglycemic herbs on the activity of phase I and II drug-metabolizing enzymes in alloxan-induced diabetic rats." Toxicology 174(2): 131-139.
[20] Turner, P. S. &G. H. Nentwig (2014). "Evaluation of the value of bone training (progressive bone loading) by using the Periotest: A clinical study." Contemporary clinical dentistry 5(4): 461.
[21] Barikani, H.;S. Rashtak;S. Akbari;S. Badri;N. Daneshparvar&A. Rokn (2013). "The effect of implant length and diameter on the primary stability in different bone types." J Dent (Tehran) 10(5): 449-455.
[22] Shadid, R. M.; N. R. Sadaqah&S. A. Othman (2014). "Does the Implant Surgical Technique Affect the Primary and/or Secondary Stability of Dental Implants? A Systematic Review." Int J Dent 2014: 204838.
[23] Massey, C. C.;E. Kontogiorgos;R. Taylor;L. Opperman;P. Dechow&P. H. Buschang (2012). "Effect of force on alveolar bone surrounding miniscrew implants: a 3-dimensional microcomputed tomography study." Am J OrthodDentofacialOrthop 142(1): 32-44.
[24] Mahesh, L.; T. Narayan;G. Kostakis&S. Shukla (2014). "Periotest values of implants placed in sockets augmented with calcium phosphosilicate putty graft: a comparative analysis against implants placed in naturally healed sockets." J Contemp Dent Pract 15(2): 181-185.
[25] Back, D. A.;S. Pauly;L. Rommel;N. P. Haas;G. Schmidmaier;B. Wildemann&S. H. Greiner (2012). "Effect of local zoledronate on implant osseointegration in a rat model." BMC MusculoskeletDisord 13: 42.
[26] Yaghobee, S.; A. Khorsand&M. Paknejad (2013). "Comparison of interleukin-1beta levels in gingival crevicular fluid and peri-implant crevicular fluid and its relationship with clinical indexes." J Dent (Tehran) 10(1): 1-9.
[27] Engebretson, S. P.; J. T. Grbic;R. Singer&I. B. Lamster (2002). "GCF IL-1beta profiles in periodontal disease." J ClinPeriodontol 29(1): 48-53.
[28] Schumann, D. M.; K. Maedler;I. Franklin;D. Konrad;J. Storling;M. Boni-Schnetzler;A. Gjinovci;M. O. Kurrer;B. R. Gauthier;D. Bosco;A. Andres;T. Berney;M. Greter;B. Becher;A. V. Chervonsky;P. A. Halban;T. Mandrup-Poulsen;C. B. Wollheim&M. Y. Donath (2007). "The Fas pathway is involved in pancreatic beta cell secretory function." ProcNatlAcadSci U S A 104(8): 2861-2866.
[29] Osborn, O.;S. E. Brownell;M. Sanchez-Alavez;D. Salomon;H. Gram&T. Bartfai (2008). "Treatment with an Interleukin 1 beta antibody improves glycemic control in diet-induced obesity." Cytokine 44(1): 141-148.
[30] Wang, C.; Y. Guan&J. Yang (2010). "Cytokines in the Progression of Pancreatic beta-Cell Dysfunction." Int J Endocrinol 2010: 515136.
[31] Kao, R. T.; D. A. Curtis;D. W. Richards&J. Preble (1994). "Increased interleukin-1 beta in the crevicular fluid of diseased implants." The International journal of oral & maxillofacial implants 10(6): 696-701.
[32] Guncu, G. N.;A. C. Akman;S. Gunday;N. Yamalik&E. Berker (2012). "Effect of inflammation on cytokine levels and bone remodelling markers in peri-implant sulcus fluid: a preliminary report." Cytokine 59(2): 313-316.
[33] Rams, T. E.; B. E. Balkin;T. W. Roberts&A. K. Molzan (2013). "Microbiological aspects of human mandibular subperiosteal dental implants." J Oral Implantol 39(6): 714-722.
[34] Kelly, B.; G. M. Tannahill;M. P. Murphy&L. A. O'Neill (2015). "Metformin Inhibits the Production of Reactive Oxygen Species from NADH:UbiquinoneOxidoreductase to Limit Induction of Interleukin-1beta (IL-1beta) and Boosts Interleukin-10 (IL-10) in Lipopolysaccharide (LPS)-activated Macrophages." J BiolChem 290(33): 20348-20359.
[35] Monga, N.; S. Chaurasia;O. P. Kharbanda;R. Duggal&R. Moganty (2014). "A study of interleukin 1β levels in peri-miniscrew crevicular fluid (PMCF)." ProgOrthod 15(1): 30-36.
[36] Suratwala, S. J.;S. K. Cho;J. J. van Raalte;S. H. Park;S. W. Seo;S. S. Chang;T. R. Gardner&F. Y. Lee (2008). "Enhancement of periprosthetic bone quality with topical hydroxyapatite-bisphosphonate composite." J Bone Joint Surg Am 90(10): 2189-2196.