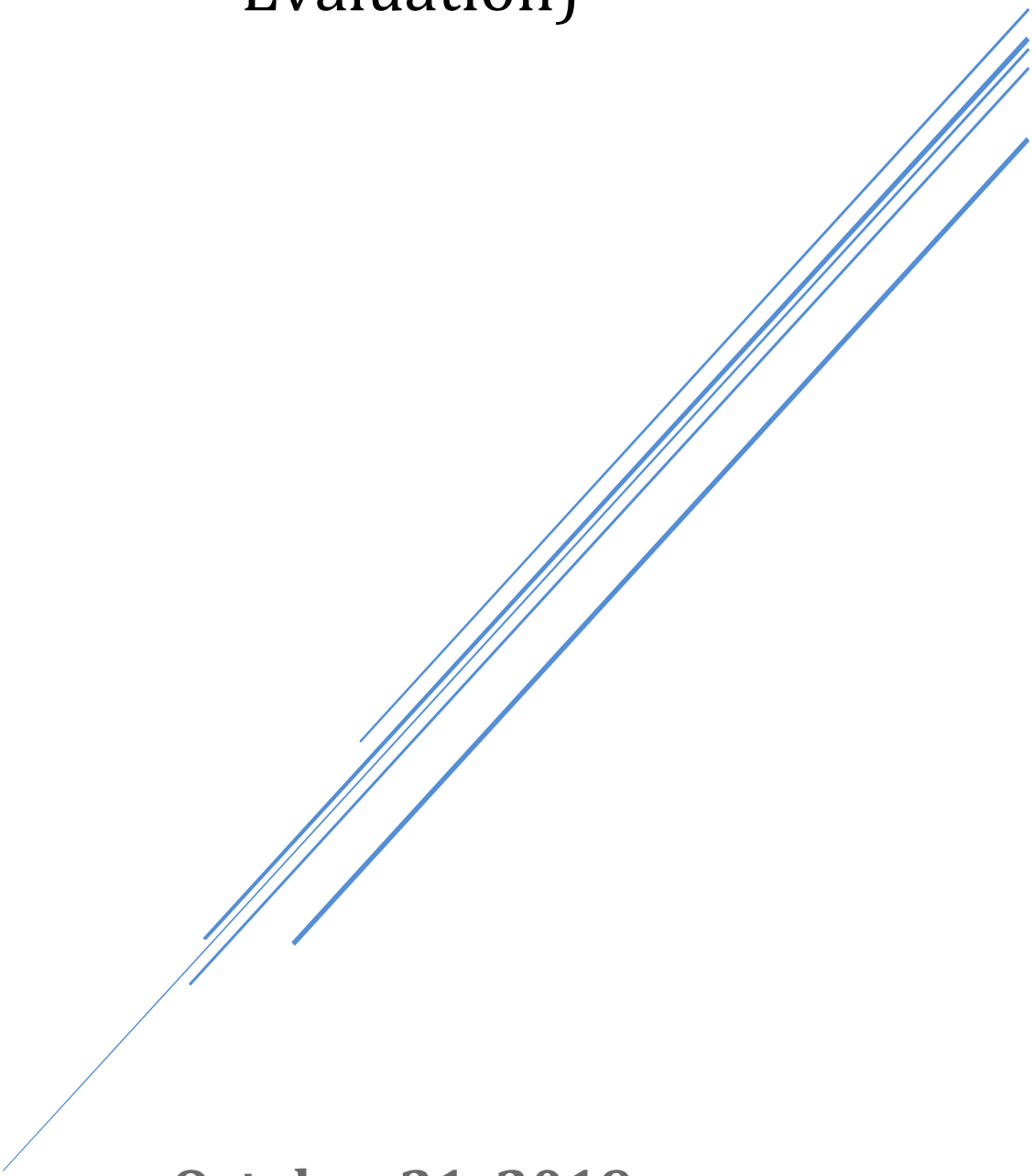
Effect of topical melatonin application on dental implant osseointegration and marginal bone level (Clinical and Radiographic Evaluation)



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Title

Effect of topical melatonin application on dental implant osseointegration and marginal bone level (Clinical and Radiographic Evaluation)

Proposal thesis

Submitted to the Department of Periodontics, College of Dentistry/University of Baghdad in Partial Fulfillment of the Requirements for Master's Degree in Periodontics.

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Introduction:-

Melatonin (N-acetyl-5-methoxy-tryptamine) is an indoleamine synthesized and secreted by the pineal gland and other organs, such as the retina, bone marrow, and intestines in a circadian pattern. Extrapineal sites contribute poorly, or only upon specific stimuli to circulating melatonin**(Hardeland et al., 2006)**. Melatonin influences numerous physiological actions that may be mediated by the binding of the indoleamine to membrane receptors in all tissues**(Girgert et al., 2009)**. Because of its lipophilic properties, melatonin passes through cell membranes to gain access to subcellular organelles **(Hevia et al., 2008)**, being capable to bind to some cytosolic proteins like kinase-C **(Macías et al., 2003)**. Currently, melatonin is not considered a hormone in the classical sense of the term, because it is synthesized in several organs and does not exert effects on a specific target **(Tan et al., 2003)**, but it is rather a powerful cell protector against molecular damage. For the synthesis of melatonin, the pineal cells take up tryptophan from the blood and, through hydroxylation and a decarboxylation process, turn it into serotonin. Serotonin is then converted into N-acetylserotonin through N-acetyltransferase and subsequently methylated to the final form of melatonin by the enzyme hydroxy indole-O-methyltransferase **(Reiter, 1991) (Figure 1)**. In healthy individuals, the maximum secretion of melatonin occurs between midnight and 2 a.m., then it decreases to a minimum during the day**(Simonneaux and Ribelayga, 2003)**. Melatonin has numerous physiological functions in different parts of the body, such as the control of circadian rhythms **(McArthur et al., 1997)**, regulation of body temperature**(Dollins et al., 1994)**, and activation of the immune system**(Guerrero and Reiter, 2002)**.In the oral cavity, melatonin has been recognized as an important substance with paracrine effects on nearby cells**(Tresguerres et al., 2002)**, it also acts as an antioxidant and an anti-inflammatory and plays an important role in bone formation and in the reduction of bone resorption**(Peyrot et al., 2008, Hardeland et al., 2009)**.

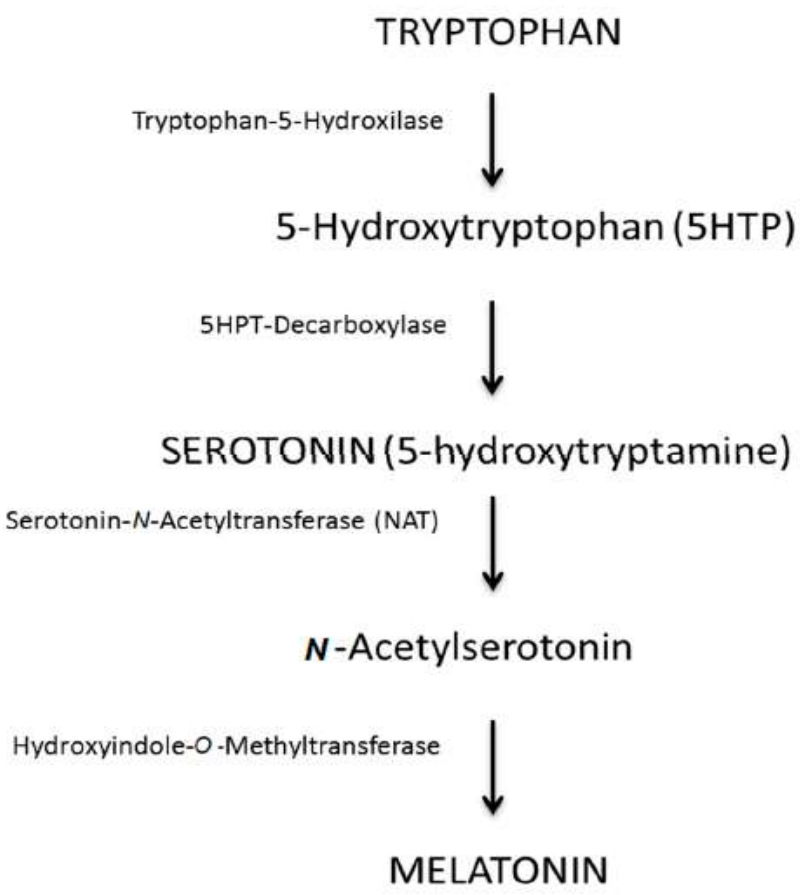

Figure 1. Melatonin synthesis and representation of its molecule (Reiter, 1991)

Osseointegration defined as a direct connection between living bone tissues and a titanium implant without any connective tissues. Osteoblasts are bone formative cells, and osteoclasts are bone resorptive cells. When these cells work together physiologically, the formation and resorption processes of bone tissue is known as bone remodelling. The remodeling of bone tissues is regulated by the action of systemic hormones (estradiol, parathyroid, growth, and melatonin) and by the bone marrow and osteoid matrix-derived growth factors**(Tresguerres et al., 2012, Wulandari)**.Insufficient bone quality and quantity can be seen frequently in elderly populations with atrophic and osteoporotic bones, and this situation stems from increased osteoclastic activity due to a reduction in osteoblastogenesis. In addition, local free radical concentrations in all body cells, including osteoblasts, can reduce osteoblastic activity in aged patients. This process could lead to a reduction in bone regeneration capacity**(Cao et al., 2005)**. Melatonin can also suppress osteoclastogenesis, and therefore inhibit bone tissue

resorption**(Cutando et al., 2008, Witt-Enderby et al., 2006)**. In addition to this, *in vitro* research has reported that melatonin can increase osteoblast proliferation and differentiation**(López-Martínez et al., 2012, Muñoz et al., 2012)**. So was proposed that the local application of melatonin during surgical implant placement procedures would be an effective treatment technique for dental implant osseointegration**(Dundar et al., 2016)**. Worthy osseointegration is a prerequisite for dental implants. Optimal osseointegration depends on the formation of new bone around implants, which may be stimulated by the application of biomimetic agents**(Ramazanoglu et al., 2011)**. Considering the bone metabolism, melatonin acts directly on the osteoclast, a multinucleated cell, which resorbs the extracellular matrix through various mechanisms, including the production of free radicals**(Roth et al., 1999)**. Moreover, in pre-osteoblast cultures from rats, melatonin, in a dose-dependent manner, promoted the development of bone sialoprotein and other protein bone markers, including alkaline phosphatase, osteopontin, and osteocalcin, and speeds up their period of differentiation into osteoblasts from the normal rate, which is 21 days, to 12 days, this reaction is mediated by the membrane receptors for the indole**(Roth et al., 1999)**. Also, melatonin, may interfere with the function of the osteoclast and thereby inhibit bone resorption**(Cardinali et al., 2003)**. **(Cutando et al., 2008)** conducted an experimental study using melatonin with dental implants in dogs. Two weeks after implant insertion, melatonin significantly increased all parameters of osteointegration. It has been observed that melatonin, increases bone mass by suppressing resorption through down-regulation of the RANKL-mediated osteoclast formation and activation**(Cutando et al., 2007)**. These data point towards an osteogenic effect of melatonin that may be of clinical importance, as it could be used as a therapeutic agent in situations in which bone formation would be advantageous, such as in the treatment of fractures or of osteoporosis **(Cardinali et al., 2003)**.

Toxicology of Melatonin:-

The physiological functions of the pineal hormone melatonin are extremely diverse. The functions include direct and indirect modulations of anti-oxidative defense, blood pressure, body temperature, cortisol rhythm, reproduction and immune function **(Claustrat and Leston, 2015)**. Correspondingly, exogenous melatonin has been investigated as a treatment for a number of medical and surgical diseases, demonstrating encouraging results **(Andersen et al., 2014, Gitto et al., 2011)**. In the USA, melatonin is available as an over-the-counter non-prescription drug. In most European countries, however, melatonin remains a prescription drug (Circadin) and has only been approved as a treatment for primary insomnia in people over 55 years of age. However, a recent Norwegian register study documented a 3- to 5-times increase in off-label use among children and adolescents in the time period 2004 to 2012 **(Hartz et al., 2015)**. Melatonin is generally considered safe **(Yousaf et al., 2010)**, but the increasing clinical use with potentially increasing doses necessitates further investigations of the risks of both mild and serious adverse effects. In experimental animal studies, exogenously administered melatonin has been given in doses up to 800 mg/kg without any acute toxic effects **(Barchas et al., 1967)**. A number of studies in preterm infants have investigated the anti-oxidative/anti-inflammatory and clinical effects of exogenous melatonin in different conditions, such as pain during tracheal intubation (10 mg/kg x 10 doses, randomized)**(Gitto et al., 2012)**, asphyxia (10 mg x 8 doses, randomized) **(Fulia et al., 2001)**, respiratory distress (10 mg/kg x 10 doses, randomized)**(Gitto et al., 2004b)**. Despite repeated high doses of intravenous melatonin, no signs of adverse effects were observed **(Gitto et al., 2004c, Gitto et al., 2004a)**. Oral melatonin in doses of 0.5–10 mg was administered daily from 10 days to 12 weeks to improve sleep quality **(Wright et al., 2011, Cortesi et al., 2012)**. The studies performed detailed registration of possible adverse effects, demonstrating a number of mild adverse effects, such as agitation, dizziness, headache, nausea, and sleepiness **(Wasdell et al., 2008, Jain et al., 2015)**. Another study was to assess the toxicology of melatonin (10 mg), administered for 28 days to 40 volunteers randomly assigned to groups receiving either melatonin (N_30) or placebo (N_10) in a double-blind fashion, according to

the parameters analyzed, there is no toxicological effect that might compromise the use of melatonin at a dose of 10 mg for the period of time utilized in this study**(Seabra et al., 2000)**. A randomized, double-blind, placebo-controlled study including 54 female patients undergoing breast cancer surgery were given 6 mg of oral melatonin or placebo to improve depressive symptoms and anxiety during a three month investigational period **(Hansen et al., 2014)**. Finally, a randomized, double-blind, placebo-controlled study was conducted in elderly patients suffering from Alzheimer's disease who were administered 2 mg of melatonin or placebo for a 24-week period **(Wade et al., 2014)**. A substantial number of both animal and human studies document that short-term use of melatonin is safe, even in extreme doses. No studies indicate that exogenous melatonin possesses any serious adverse effects. Also, randomized clinical studies indicate that long-term administration only induces mild adverse effects comparable to placebo treatment. **(Andersen et al., 2016).**

Periotest M device:-

Periotest device was developed to measure the damping characteristics of natural teeth and has been used to evaluate implant **(Cehreli et al., 2009)**. It was developed by Schulte in 1983 to quantify TM **(Shulte et al., 1983)**, and then utilized by **Teerlinck et al. (1991),** to measure implant stability and to overcome destructive methods in measuring the implant stability like histologic analysis, tensional test, push-out/pull-out test and removal torque analysis. The (Classic/Wired) Periotest device has been the subject of several studies with generally favorable results. These results showed that the Periotest device generally demonstrated a high degree of repeatability and reliability**.** A wireless version of the Periotest (Periotest "M") has been introduced to the profession. According to information provided by the electronic page of the Periotest M /wireless device manufacturer (Medizintechnik Gulden, Modautal, Germany), Periotest M is simpler to perform an objective evaluation of an implant's stability compared to classic Periotest. In Periotest M wireless design, the user can benefit from maximum freedom of movement. The device can be used for taking measurements on a wide variety of implants, without the need for any special accessories, such as a smart peg **(Pang et al., 2014)**. The Periotest has an

important advantage against the others like the Osstell device: it can be applied directly to the implant superstructure **(Geckili et al., 2009)**.

The limitations of Periotest are the inability of the instrument to measure the mesiodistal mobility, the possible effect of position and angle of the rods on the measured value **(Satwalekar et al., 2015)**. The readings of PTV are from (−8 to +50) according to information provided by the device manufacturer (Medizintechnik Gulden, Modautal, Germany) **(Pang et al., 2014), (Table 1)**. These readings are displayed digitally on a monitor as (PTVs), **(Aparicio et al., 2006)**.

(Table 1): Interpretation of readings of implant stability in periotest **(Pang et al., 2014)**.

Reading	Interpretation
−8 to 0.0	Good osseointegration, the implant can be loaded.
+0.1 to +9.9	Clinical examination is required, in most cases, loading is not possible.
+10 to +50	Osseointegration is not sufficient, the implant cannot be loaded.

Cone-beam computed tomography (CBCT):-

Cone-beam computed tomography (CBCT) is an imaging modality that offers significant advantages for the evaluation of implant patients **(Hatcher et al., 2003, Schulze et al., 2005)**. The field of view (FOV) is an important feature that describes the extent of the imaged volume from large FOV (greater than 15 cm) to medium FOV (8 to 15 cm) and limited FOV (less than 8 cm). Limited FOV units image a small area, delivering less radiation and producing a higher-resolution image **(Newman et al., 2018)**. CBCT allows for defining with elevated accuracy the quality (cortical/medullar ratio) and the quantity (height and thickness) of bone available for the implant, providing the essential information of performing or not a preimplant bony graft **(Garlaschi et al., 2014)**. when compared to medical CT, CBCT can be recommended as a dose reducing technique for dental

implant applications**(Okano et al., 2009, Qu et al., 2010)**. The effective dose from CBCT examinations ranges from 13 μ Sv with the 3D Accuitomo CBCT machine using the 4 x4 cm FOV to 479 μ Sv with the CB Mercury CBCT machine **(Table 2)**. For comparison, the effective dose from one panoramic radiograph is approximately 10 to 14μSv**(Ludlow et al., 2006).** Furthermore, the exposure from a maxillomandibular medical CT ranges from 474 to 1160 μSv**(Loubele et al., 2009)**. The average background radiation in the United States is 3000 μSv (3 mSv) per year or 8 μSv per day **(Table 2)**. It is important to understand that every effort must be made to reduce the effective radiation dose to the patient. By using the smallest possible FOV, the lowest mA setting, the shortest exposure time, and a pulsed exposure mode of acquisition, it is possible to accomplish effective dose reduction to the patient**(Sur et al., 2010)**.

Table 2. CBCT Machines

CBCT Scanner	FOV (cm)	Effective Dose (μSv)	Digital Panoramic Equivalent (14 μSv)	No. of Days of Annual per Capita Background (3 μSv = 3000 μSv)	References
i-CAT classic	22/13 (40 s)/13 (10 s)	82/77/48	5.9/5.5/3.4	10/9.4/5.8	Loubele et al[19]
	6 min. (low resolution/ high resolution)	96.2/118.5	6.9/8.5	11.7/14.4	Hatcher[20]
	6 max. (low resolution/ high resolution)	58.9/93.3	4.2/6.6	7.2/11	Hatcher[20]
	22/13	206.2/133.9	14.7/9.6	25/16	Hatcher[20]
	13	61.1	4.4	7.4	Silva et al[21]
i-CAT next generation	23 × 17	74	5.3	9	Ludlow and Ivanovic[15]
	16 × 13 (19 mAs)	87	6.2	10.6	Ludlow and Ivanovic[15]
	16 × 13 (18.5 mAs)	83	5.9	10.2	Pauwels et al[22]
	16 × 6	45	3.2	5.5	Pauwels et al[22]
Newtom 9000	23	56.2	4	6.9	Silva et al[21]
	12 in (male/female)	93/95	6.6/6.8	11.3/11.6	Coppenrath et al[23]
Newtom 3G	19	68	4.9	8.3	Ludlow and Ivanovic[15] Ivanovic[16]
ProMax 3D	8 × 8 (72 mAs/96 mAs)	488/652	35/47	59/79	Ludlow and Ivanovic[15]
	8 × 8 (169 mAs/19.9 mAs)	122/28	8.7/2	15/1.7	Pauwels et al[22]
Picasso-Trio	12 × 7 (127 mAs/91 mAs)	123/81	8.8/5.8	15.1/10	Pauwels et al[22]
PaX-Uni3D	5 × 5 max.	44	3.1	5.4	Pauwels et al[22]
Kodak 9000 3D	Max. ant./min. post.	19/40	1.4/2.9	2.3/4.9	Pauwels et al[22]
Kodak 9500 3D	20 × 18	92			Pauwels et al[22]
	15 × 9	136			Pauwels et al[22]
	20 × 18 (small/medium/ large adult)	76/98/166	5.4/7.0/11.9	9.3/12.1/20.4	Ludlow et al[24]
	15 × 9 (small/medium/ large adult)	93/163/260	6.6/11.6/18.6	11.4/20.1/32.0	Ludlow et al[24]
	28 mAs	84	6	10.3	Pauwels et al[22]
SCANORA 3D	14.5 × 13	68	4.9	8.4	Pauwels et al[22]
	10 × 7.5	46	3.3	5.7	Pauwels et al[22]
SkyView	17 × 17	87	6.2	10.7	Pauwels et al[22]
ILUMA	19 × 19 (20 mAs/152 mAs)	98/498	7/35.6	11.9/60.6	Ludlow and Ivanovic[15]
	20.5 × 14 (76 mAs)	368	26.3	45.3	Pauwels et al[22]

Aim and objectives:-

Aim: - To evaluate the osseointegration following the application of melatonin around dental implants.

Objectives: -

1- Measuring primary and secondary stability of the dental implant by Periotest M device.

2- Measuring marginal bone level around the dental implant in baseline and after 6 months follow up using a cone-beam computed tomography (CBCT).

Research Hypothesis:-

The topical application of melatonin powder in the osteotomy site has an effect on osseointegration around the dental implant and minimize marginal bone loss.

Null hypothesis:-

The topical application of melatonin powder in the osteotomy site has no effect on osseointegration around the dental implants and in minimizing marginal bone loss.

Methodology:-

Study design: - a split-mouth clinical trial.

Setting & Subjects:

The study will be conducted in a split-mouth design on patients male with missing teeth in the upper or lower jaw (canine to 1st molar area), the subjects will be selected depending on bone density and from those attending to the department of periodontics.

Inclusion criteria:

1. Patients male have good oral hygiene.

2. Patients were periodontally healthy.

3. Patients had at least two missing teeth in the upper or lower jaw (canine to 1st molar area) indicated for the dental implant.

Exclusion criteria:

1-Patients with any systemic diseases that influence bone healing such as osteoporosis and diabetes mellitus.

2-Fully edentulous.

3-Patients who had parafunctional habits.

4-Smokers.

5-Patients who were not able to follow the treatment protocol.

Sample Size:

Twenty single-piece endosseous implants use for patients with at least two missing teeth in the upper or lower jaw (canine to 1st molars area).

Materials:-

1-Melatonin powder (*N-Acetyl-5-methoxytryptamine)* from (Sigma-Aldrich/Germany).

2-Periotest M device (Medizintechnik Gulden, Germany).

3-Dentium implant surgical kit system and DI fixtures (Dentium Co., Korea).

Procedure:

Twenty single-piece endosseous implants (Dentium Co, Korea) will use to restore missing teeth in the upper or lower jaw (canine to 1st molars area) from both sides. The study will be split-mouth technique, each patient serves as his own control (served into 2 groups), the study side (topical application of melatonin in the implant side), and the control side (no melatonin in the other implant side of the same patients). According to the study reported by **(Cutando et al., 2008)** the estimated dose of melatonin required to enhance osseointegration of dental implant and minimize the marginal bone resorption is 1.2 mg of melatonin powder for each implant. CBCT for all patients before implant placement to determine bone density, dimension, and anatomical landmarks. Prior to surgery, all patients will instruct to use chlorhexidine 0.12% mouthwash as antiseptic. After local anesthesia, a mucoperiosteal flap will reflect. The manufacturer's instructions should be followed for the preparation of the implant osteotomy site. For the study

side, 1.2 mg of melatonin powder will place in the osteotomy site before the insertion of the implant. For the control side, no melatonin powder will be used and implants will be inserted directly in the prepared implant site. After dental implant installation, the gingival former will insert into the body of the fixture, then the Periotest M device will use to measure the primary stability of the DI fixture. After that, the gingival former will be removed and cover screw place and tightened into the fixture. Sutures will place after flap replacement. Patients should be instructed to use antibiotics amoxicillin 500mg and metronidazole 500mg 3 times/day for 5 days after surgical procedure, soft diet and proper oral hygiene measures. Also, CBCT immediately after implant placement to record baseline bone level, CBCT after 6 months follow up to measure marginal bone level around implant comparing with baseline measurement, and measure the secondary stability using periotest M device.

Stopping rules

The occurrence of an unexpected include implant failure...

Budget and funding

This study is self-funded.

Justification for ethical approval:-

According to the college of the dentistry/university of Baghdad following the Declaration of Helsinki / Tokyo on medical protocol and ethics.

Dissemination

Postgraduate Thesis.

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