



# Effect of melatonin on osseointegration of immediate loading implant supported mandibular over denture: Randomized clinical trial

Doaa Amr A. Heshmat Rostom, Alaa Aboul Ela, Mohamed Farouk Abdalla

Department of Prosthodontics, Faculty of Oral and Dental Medicine, Cairo University, Egypt

## Keywords

Bone density, immediate loading implant, melatonin, osseointegration

## Correspondence

Doaa Amr A. Heshmat Rostom, Department of Prosthodontics, Faculty of Oral and Dental Medicine, Cairo University, Egypt.  
Email: Doaa.heshmat@dentistry.cu.edu.eg

Received: 18 November 2016;

Accepted: 25 December 2016

doi: 10.15713/ins.idmjar.55

## Abstract

**Background:** In the recent years, immediate loading of implant is very demanding to shorten the rehabilitation time. Some authors claimed that Melatonin induces bone formation, increase bone density, and bone implant contact. The aim of this study is to assess the effect of local melatonin administration on bone density around immediate-loaded implant supported over denture.

**Materials and Methods:** Eight completely edentulous patients were selected. The Patient's age ranged between 55 to 65 years old. The study was split-mouth technique, each patient served as his own control, the study group (topical application of melatonin in the implant side), the control group (no melatonin in the other implant side of the same patients). Immediately after the implant placement, implant stability test was performed using the Osstell Monitor, and Digora system was used for assessing the bone density changes. The Radiographic bone density measurements, implant stability assessment, and implant survival were performed at time of loading then at 3, 6 and 12 months after loading.

**Results:** A high statistically significant difference in bone density and implant stability in the immediately loaded implants with local melatonin application ( $P = 0.001$ ).

**Conclusion:** The local melatonin administration increase bone density and improve the osseointegration processes around immediate-loaded implant supported over dentures.

## Introduction

In the recent years, it's very demanding from the patient to shorten the time between implant placement and implant loading. The immediate loading was introduced to shorting the dental rehabilitation time that can be installed in a one-stage procedure with lower cost. The immediate loading of implants has high success rates in the mandible.<sup>[1]</sup>

In immediate loading case a stress-free healing time is essential, immediate implant loading possesses many risks and failure that clinician and patient must be aware of due to implants micro-movement; and the inability to predict final soft and hard tissue outcomes are unpredictable.<sup>[2,3]</sup>

Many biomimetic agents have been developed to induce bone formation to increase bone density and bone-implant contact. Recent researches have been focused in improving process of osseointegration to promote early integration thus to shorten overall treatment time needed and to achieve

faster osseointegration and improve the overall treatment process.<sup>[4]</sup>

Some studies have proved that melatonin is an important stimulator in bone formation. Discovered by Lerner in 1958, melatonin synthesis occurs in the pineal gland and extrapineal tissues as melatonin is secreted during the hours of darkness and with the exposure to artificial light at night (LAN) plasma melatonin levels in the blood decreases.<sup>[5,6]</sup>

Free radicals are increasingly generated with age and are produced in response to oxidative stress due to lifestyle factors (e.g., smoking, alcohol consumption, and high-fat diet), which can lead to excessive bone resorption, Melatonin's actions as a direct free-radical scavenger and as an indirect antioxidant, add yet a third mechanism by which melatonin can protect against bone disease and now, possibly, periodontal disease.<sup>[5]</sup>

Melatonin hormone functions are like cell protector and also as an antioxidant and an anti-inflammatory agent. It has several functions; stimulation of the synthesis of type I collagen fibers,

antioxidant scavenging and detoxifying free radicals thus stop the process of bone resorption through reducing the osteoclast function.<sup>[6-8]</sup>

Topical application of melatonin may act as a biomimetic agent in the placement of endo-osseous dental implants at 5 and 8 weeks after the implantation.<sup>[8]</sup>

Melatonin acts on osteoclasts to reduce resorption of osseous matrix in different forms as melatonin, being an antioxidant, is able to affect the process detoxifying free radicals, which are produced during osteoclastogenesis, leading to an inhibition of resorption of the bone.<sup>[9]</sup>

According to Hosseini *et al.* (2015), they reported that at the end of 4<sup>th</sup> week, after implant placement the main bone adhere along the implant surface and also in the neck, meanwhile. Melatonin stimulates differentiation in preosteoblast lines; thus, melatonin-treated cells matured into osteoblasts after a period of 12-day, instead of 21 days for the preosteoblasts of the control group.<sup>[9,10]</sup>

The aim of this study is to assess the effect of local melatonin administration on bone density around immediate loaded implant supported over denture.

## Methodology

This title was registered in PACTR registry, approved by the Ethics Committee, and all participants provided informed written consent. According to sample size calculation eight completely edentulous patients were selected from the outpatient clinic of the department of Prosthodontics, Faculty of Oral and Dental Medicine, Cairo University, to participate in this study. The patient's age ranged between 55 to 65 years old.

Each patient will be allocated a number from sequentially numbered opaque sealed envelopes when they were seen for consent and initial records. They will be then allocated into one of the set-ups using a randomization table.

The study was split-mouth technique, each patient served 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).

Patients were selected according to the following inclusion criteria. The Patients were free of any systemic diseases that might affect bone quality. There should be sufficient inter arch space normal maxillomandibular relationship (Class I Angle classification), the absence of TMJ pathosis. Mandibular intercanine region of sufficient bone thickness and height that is suitable for the proposed implants. Moreover, the patients were physically and psychologically able to tolerate conventional implant surgical protocol.

Cone beam were performed to assure the presence of enough bone to receive 2 implants<sup>1</sup> of 3.7 mm width and 11.5 mm length.

<sup>1</sup> Osteosel dental implant.

After denture construction, the mandibular complete denture was prepared to be used as a surgical template for inserting the implants.

The mandibular denture was duplicated into acrylic resin using rubber base material. This duplicate was used as radiographic and surgical stent.

The radiographic stent was modified to act as a surgical stent. Crestal incisions full thickness mucoperiosteal flaps were reflected using a sharp mucoperiosteal elevator.

Melatonin<sup>[2]</sup> 3 mg is mixed [Figure 1] with one drop of saline, injected in the osteotomy and then the implant was directly inserted into the prepared site without touching any surface. The implant was manually threaded with irrigation until resistance was felt and then slowly threaded into its final position with a torque wrench until the implant top was flush with the ridge crest.

During implant insertion, the tightening torque was 35 Ncm and the implant could be ready for immediate loading. Implant stability was measured through Ostell, if the implant stability quotient (ISQ) is above 65, this meant good primary stability also the bone density was measured around the implants through digora. Both implant stability and bone density were recorded at 3 months, 6 months and 1 year from the baseline.

Ball attachment 2.5 diameter [Figure 2] was screwed on both sides and the mucoperiosteal flap is sutured. For pickup of the ball, a hole was cut in the fitting surface of the lower denture at both canine teeth region. The lower denture was verified for proper seating after insertion of the upper and lower dentures then the lower denture are relined with soft liner and asking the patient to occlude in centric relation over the ball attachment, the soft liner changed every month till 3 months after implant placement after complete osseointegration.

After 3 months from the surgery, the metal caps inserted over the ball attachment, the soft liner was removed from the fitting surface of the lower denture and replaced by auto-polymer acrylic resin for metal cap pick up, a rubber dam placed around the ball attachment for block out, and the patient was asked to occlude in centric relation.

After complete polymerization of the acrylic resin, the denture was removed and examined. The occlusion was checked and re-adjusted.

Immediately after the implant placement, implant stability was performed using the Ostell Monitor. The smart pegs were mounted on the implants and tightened by hand with a screw. The resonance frequency value was measured four times in four directions: Buccal, lingual, mesial, and distal to each implant. RF values were represented by a quantitative unit called the ISQ on a scale from 1 to 100. This procedure was repeated at 3 months, 6 months and 1 year.

The Digora system [Figure 3] was used for assessing the bone density changes mesial and distal to the implant fixtures during the follow-up intervals.

<sup>2</sup> Melatonin puritans pride premium made in USA 3 mg.

Three lines were drawn parallel to the mesial and distal implant surfaces. The first line extended from the first flute of the implant to the implant apex passing tangential to the implant flutes and perpendicular to a tangent drawn to the implant apex. The second line was one millimeter apart, equal, and parallel to the first line. The same procedure was repeated for the third line.

Bone density along each of the three lines was recorded, and then the mean value of the three readings was calculated for each surface. The mean values of the mesial and distal bone density

measurements for each implant during the follow-up intervals were calculated.

**Result**

The mean and standard deviation values were calculated for each group in each test. Data were explored for normality using Kolmogorov-Smirnov and Shapiro-Wilk tests and showed parametric (normal) distribution.

Independent sample *t*-test was used to compare between two groups in independent samples, while repeated measure ANOVA test was used to compare between more than two groups in related samples.

The significance level was set at  $P \leq 0.05$ . Statistical analysis was performed with IBM® SPSS® Statistics Version 20 for Windows.

The result shows the bone density change by time in Melatonin group. There was a statistically significant difference between (0 Months), (3 Months), (6 Months) and (Year) where ( $P = 0.0001$ ) [Table 1].

A statistically significant difference was found between 3 months ( $121.48 \pm 28.96$ ), 6 months ( $171.97 \pm 17.29$ ), and 1 year ( $185.25 \pm 25.07$ ), where  $P = 0.001$  and  $P = 0.0001$ , respectively. The percentage of change of bone density from 0 month (the baseline) to 1 year in the melatonin group is 84.64%, in the control group is 39.53%.

Implant stability change by time in melatonin and control group a statistically significant difference was found between 3 months ( $69.68 \pm 0.91$ ), 6 months ( $75.21 \pm 2.81$ ), and 1 year ( $75.34 \pm 2.94$ ), where  $P = 0.001$  and  $P = 0.0001$ , respectively.

The percentage of change of implant stability from 0 month (the baseline) to 1 year in the melatonin group is 8.46% while in the control group is 3.75% and the implant in both groups are survived.

**Discussion**

The problem of immediate loading is the micro movement that would endanger the osseointegration process, so to increase the implants resistance to movement, the implant is placed in regions with high bone density and the insertion torque values over 32 Ncm is a prerequisite for immediate loading.<sup>[11]</sup>

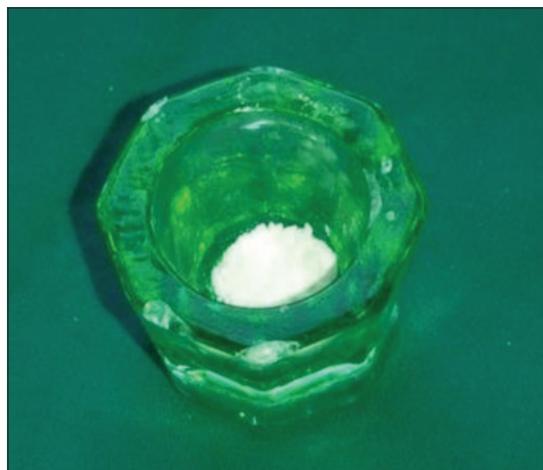


Figure 1: Melatonin tablet



Figure 2: Ball attachment screwd immediately post-operative

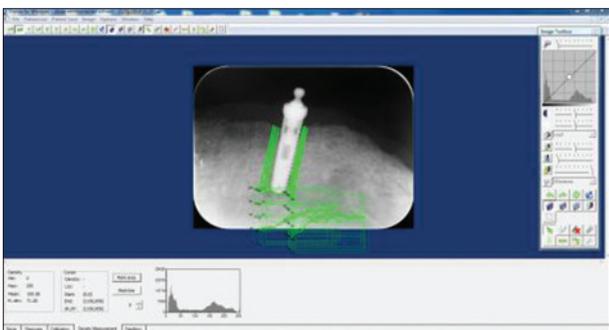


Figure 3: Digora bone density assessment

**Table 1:** The mean, SD values of bone density for all groups

Variables	Mean±SD	
	Control group	Melatonin group
0 months	109.79±24.83 <sup>a</sup>	100.33±17.69 <sup>a</sup>
3 months	103.48±15.13 <sup>a</sup>	121.48±28.96 <sup>a</sup>
6 months	143.32±25.35 <sup>b</sup>	171.97±17.29 <sup>b</sup>
Year	153.20±28.77 <sup>b</sup>	185.25±25.07 <sup>b</sup>
<i>P</i>	0.0001*	0.0001*

SD: Standard deviation. \*High statistical significance (0.0001), <sup>a,b</sup>Statistical significant if  $P > 0.05$

In this context, it has been hypothesized that melatonin may increase bone density in shorter time and reduce micromotion to improve osseointegration.<sup>[5,12]</sup>

Melatonin was used in this study because it was found that melatonin acts on osteoclasts, reducing the formation of free radicals. It has antioxidant activities, through detoxifying the free radicals produced during osteoclastogenesis. This leads to reduction of bone resorption.<sup>[13]</sup>

The actions of melatonin on bone tissue are of interest because it may be possible to apply melatonin during endosseous dental implant surgery as a biomimetic agent. As a result, the healing process could enjoy greater precision and a reduced period of implant osseointegration and settling, improving patient's quality of life. It could be used as a therapeutic agent in situations in which it is necessary to increase bone formation.<sup>[14]</sup>

Melatonin increases pre-osteoblast/osteoblast/osteoblast-like cell proliferation, promotes the expression of type I collagen and bone marker proteins interthread bone is an intermediate situation of new bone in with the implant by stimulation of osteoblasts and the old bone in the total peri implant area by osteoclast inhibition, and melatonin continues its activity passing on from the 2<sup>nd</sup> to the 5<sup>th</sup> week and to the 8<sup>th</sup> week.<sup>[14-16]</sup>

Arat Bilhan *et al.* (2015) they said that use of a splinted attachment can be preferred to reduce forces emerging around the implants. The use of 2 solitary attachments in cases with good bone quality and ideal sized implants are safe with the bilateral loading on over dentures.<sup>[17]</sup>

The resilient liner for ball pick-up of implant ball attachment acts as progressive loading of force over the implant. Elmasry *et al.* (2013) used soft liner pick up at the day of surgery and replace it every month till complete osseointegration. Ehab *et al.* (2015) stated that the resilient liner was used to reduce the functional forces on early loaded implants.<sup>[18,19]</sup>

Around the immediately loaded implants the bone becomes more mineralized, where the loading affects healing and remodeling around implants, which in turn influences the mechanical properties of the supporting bone. These findings were in accordance with Turkyilmaz *et al.* (2006).<sup>[20]</sup>

Another explanation can be that the significant increase in the mean bone density indicates favorable bone reaction to the applied forces that were within the physiologic limit tolerated by the bone. Moreover, the proper distribution of the load might have enhanced the structural orientation of bone trabeculae and hence increase bone density around the implants.<sup>[6,21]</sup>

In this study, the results of bone density showed a higher statistically significant ( $P = 0.0001$ ) from the 0 month to 12 months of function in the immediately loaded implant over denture; these results are consistent with other previous studies.<sup>[22,23]</sup>

The increase in the bone density owing to melatonin addition may be due to the effects of melatonin on bone formation that accelerate bone formation within 2 months. This was in agreement with Calvo-Guirado *et al.* (2009) where they reported that melatonin increased new cortical bone width and length

during the early stages (15 and 30 days) and also promoted early cell differentiation.<sup>[24]</sup>

The previous results were consistent with previous animal histological studies; that melatonin increased bone density and bone implant contact, accordingly it increased implant stability.<sup>[25,26]</sup>

As well most of the previous studies that were done on animals, so the use of melatonin is still a controversial aspect in the dental field. More detailed studies are necessary to extend the therapeutic possibilities of melatonin in dentistry.

## Conclusion

The local melatonin administration increase bone density and improve the osseointegration processes around immediate-loaded implant supported over dentures.

It's recommended to do further radiographical studies on humans and to prepare a suitable pharmaceutical form of melatonin with precalculated to be introduced well in the implant hole.

## References

- Zancope K, Simamoto Júnior PC, Davi LR, Prado CJ, Neves FD. Immediate loading implants with mandibular overdenture: A 48-month prospective follow-up study. *Braz Oral Res* 2014;28. pii: S1806-83242014000100241.
- Avila G, Galindo P, Rios H, Wang HL. Immediate implant loading: Current status from available literature. *Implant Dent* 2007;16:235-45.
- Suzuki JB, Misch CE, Sharawy M, Sarnachiaro OJ, Sarnachian GO, Mota L, *et al.* Clinical and histological evaluation of immediate-loaded posterior implants in nonhuman primates. *Implant Dent* 2007;16:176-86.
- Schenk RK, Buser D. Osseointegration: A reality. *Periodontol* 2000 1998;17:22-35.
- Maria S, Witt-Enderby PA. Melatonin effects on bone: Potential use for the prevention and treatment for osteopenia, osteoporosis, and periodontal disease and for use in bone-grafting procedures. *J Pineal Res* 2014;56(2):115-25.
- El-Dayem MA, Assad AS, Sanad ME, Abdel-Dayem HM, Abdel-Alim H, Banasr F. Topical application of melatonin around immediate implants. *J Res Commun* 2014;2:1-12. Available from: <http://www.usa-journals.com>.
- Gómez-Moreno G, Guardia J, Ferrera MJ, Cutando A, Reiter RJ. Melatonin in diseases of the oral cavity. *Oral Dis* 2010;16:242-7.
- Guardia J, Gómez-Moreno G, Ferrera MJ, Cutando A. Evaluation of effects of topic melatonin on implant surface at 5 and 8 weeks in Beagle dogs. *Clin Implant Dent Relat Res* 2009;13:262-8.
- Cutando A, Arana C, Gómez-Moreno G, Escames G, López A, Ferrera MJ, *et al.* Local application of melatonin into alveolar sockets of beagle dogs reduces tooth removal-induced oxidative stress. *J Periodontol* 2007;78:576-83.
- Hosseini SH, Kazemian M, Ghorbanzadeh S. A brief overview of cellular and molecular mechanisms of osseointegration. *Int J Contemp Dent Med Rev* 2015;2015:Article ID: 010415.
- Jaffin RA, Kumar A, Berman CL. Immediate loading of dental

- implants in the completely edentulous maxilla: A clinical report. *Int J Oral Maxillofac Implants* 2004;19:721-30.
12. Calvo-Guirado JL, Gómez-Moreno G, Maté-Sánchez JE, López-Marí L, Delgado-Ruiz R, Romanos GE. New bone formation in bone defects after melatonin and porcine bone grafts: Experimental study in rabbits. *Clin Oral Implants Res* 2015;26:399-406.
  13. Reiter RJ, Rosales-Corral SA, Liu XY, Acuna-Castroviejo D, Escames G, Tan DX. Melatonin in the oral cavity: Physiological and pathological implications. *J Periodontol Res* 2015;50:9-17.
  14. Gómez-Moreno G, Aguilar-Salvatierra A, Boquete-Castro A, Guardia J, Piattelli A, Perrotti V, *et al.* Outcomes of topical applications of melatonin in implant dentistry a systematic review. *Implant Dent* 2015;24:25-30.
  15. Roth JA, Kim B, Lin W, Cho M. Melatonin promotes osteoblast differentiation and bone formation. *Int J Oral Biol* 1999;274:22041-7.
  16. Sethi S, Radio NM, Kotlarczyk MP, Chen CT, Wei YH, Jockers R, *et al.* Determination of the minimal melatonin exposure required to induce osteoblast differentiation from human mesenchymal stem cells and these effects on downstream signaling pathways. *J Pineal Res* 2010;49:222-38.
  17. Arat Bilhan S, Baykasoglu C, Bilhan H, Kutay O, Mungan A. Effect of attachment types and number of implants supporting mandibular overdentures on stress distribution: A computed tomography-based 3D finite element analysis. *J Biomech* 2015;48:130-7.
  18. Elmasry M, Ibrahim S, Emil A. Comparative study between the effect of computer guided implant insertion technique versus conventional flap technique on immediately loaded implant supported overdenture prostheses. *J Cairo Univ* 2013;59:3545-50.
  19. Elsaih EA, Gebreel AA, Elsayed ME. Early progressive versus delayed loading of two implants retained mandibular overdentures. *J Egypt Dent* 2015;58:3597-609.
  20. Turkyilmaz I, Sennerby L, Tumer C, Yenigul M, Avci M. Stability and marginal bone level measurements of unsplinted implants used for mandibular overdentures: A 1-year randomized prospective clinical study comparing early and conventional loading protocols. *Clin Oral Implants Res* 2006;17:501-5.
  21. May D, Romanos GE. Immediate implant supported mandibular overdentures retained by conical crowns: A new treatment concept. *Quintessence Int* 2002;33:5-12.
  22. Misch CE. Bone density: A key determinant for clinical success. *Contemporary Implant Dentistry*. 2<sup>nd</sup> ed. St. Louis, MO: Mosby; 1999. p. 318.
  23. El-Khatib M. Immediate Versus Delayed Loading of Mandibular Bar Retained Implant Overdenture, Ph.D Thesis. Faculty of Oral and Dental Medicine, Cairo University; 2010. p. 33.
  24. Calvo-Guirado JL, Gómez-Moreno G, Barone A, Cutando A, Alcaraz-Baños M, Chiva F. Melatonin plus porcine bone on discrete calcium deposit implant surface stimulates osteointegration in dental implants. *J Pineal Res* 2009;47:164-72.
  25. Cutando A, Mun F. Melatonin stimulates osteointegration of dental implants. *J Pineal Res* 2008;45:174-9.
  26. Turkyilmaz I, Tumer C, Avci M, Hersek N, Celik-Bagci E. A short-term clinical trial on selected outcomes for immediately loaded implant-supported mandibular overdentures. *Int J Prosthodont* 2006;19:515-9.

**How to cite this article:** Rostom DA, Ela AA, Abdalla MF. Effect of melatonin on osseointegration of immediate loading implant supported mandibular overdenture: Randomized clinical trial. *Int Dent Med J Adv Res* 2016;2:1-5