

## **The Effect of Topical Application of Vitamin D on Titanium Dental Implant in Diabetic Patients**

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### **Abstract:**

**Aim:** This study was designed to evaluate the effect of topical application of vitamin D (vit. D) on titanium dental implant in controlled diabetic patients, type 2. **Patients and methods:** Fifteen implant were placed in seven patients. Each patient at least had received one implant in one side of the jaw as control (implant only) and another implant in the other side as study (implant coated with vitamin D3), except one patient was received three implants. Split mouth technique was used in an attempt to limit variables. Clinical examination was made to all patients as: Quality, quantity of the bone and overlying mucosa. Preoperative panoramic radiographs and cone beam computerized tomography (CBCT) were taken for every patient to determine alveolar bone height & width. The change in bone density was measured using (CBCT) a week after surgery, after 3 and 6 months of healing. Primary and secondary stability measured by Osstell device. All readings were recorded and analyzed statistically. **Results:** The results from 0 to 9 months showed statistical significant increase compared to that in control group in bone density all around the implant surfaces ( $p=0.023$  ,  $0.043$  respectively). The mean of vertical bone loss in vit. D group after 3 and after 6 months showed statistical significant decrease compared to that in control group ( $p=0.005$ ). **Conclusion:** The topical application of vit. D on dental implants exhibited less crestal bone loss and slightly enhanced bone density when comparing to control group.

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## Introduction:

Diabetes Mellitus (DM) is the most common systemic disease which is generally considered as a relative and not an absolute contraindication for implant therapy as DM inhibits osteoblastic differentiation. Since tooth loss is greater in diabetic than non-diabetic individuals, the validity of dental implant treatment options for these patients has to be realized and so diabetic patients are eligible candidates for implant therapy (1,2). Chronic hyperglycemia negatively influences osseointegration of dental implants, and implant failure is a common manifestation in such patients (3).

Hyperglycemia inhibits osteoblastic differentiation and alters the response of the parathyroid hormone that regulates the metabolism of phosphorus and calcium (4). In addition, it produces a deleterious effect on the bone matrix and its components and also affects adherence, growth and accumulation of extra-cellular matrix (5). Mineral homeostasis, production of osteoid and "in short" bone formation has been shown to be clearly diminished in various experimental models of diabetes (6). It had been shown that, although the amount of bone formed is similar when comparing diabetes induced animals with controls, there was a reduction in the bone implant contact in diabetics (7,8). This confirms that diabetes inhibits osseointegration and this situation may be reversed by treating the hypoglycemia and maintaining near normal glucose levels (9).

Many researches have focused on improving bone substitutes and implant surfaces to play a role in enhancing bone to implant contact (BIC). This may improve the overall success and survival of dental implants, and achieve faster and better osseointegration by morphologic or biochemical modification (10,11). Biochemical modification consists of the application of biological mediators or biomaterial over the implant surface to induce specific cell and tissue responses, such as vitamin D (12,13).

Human gingival fibroblasts (HGFs) are the most abundant cells in the gingiva and are

responsible for the synthesis of extra cellular matrix (ECM), wound healing, repair and regeneration after dental implant installation (14). HGFs are able to produce the final active metabolite of vitamin D because they express the enzymatic machinery required to synthesize vitamin D<sub>3</sub> (15) as do osteoblastic cells (16).

Vitamin D has been shown to play an essential role in bone mineral homeostasis and in its active form may act as a bioactive protein promoting new bone formation (17). Vitamin D<sub>3</sub> exerted a regulatory effect on osteoblast and osteoclast chemotaxis during increasing vascular tissue infiltration, furthermore it could regulate collagen modification and maturation in an osteoblastic cell culture, which has been proven to be important in early bone formation (18).

Previous studies had reported that vitamin D<sub>3</sub> significantly promoted the expression of osteogenic markers, in addition, vitamin D<sub>3</sub> deficiency negatively impacts osseointegration (19,20). It had been suggested that vitamin D<sub>3</sub> has a direct effect on osseointegration since vitamin D receptor (VDR) are present on osteoblasts and osteoclast precursors(21), So this study was conducted to evaluate the effect of topical application of vitamin D<sub>3</sub> on titanium dental implant in controlled diabetic patients.

## Aim of the study:

The aim of the study was to evaluate the effect of topical application of vitamin D on titanium dental implant in controlled diabetic patients.

## Patients and methods:

This Randomized Controlled Clinical Trial study was conducted on seven controlled diabetic patient (type 2) of both genders. Split mouth technique was used in an attempt to limit variables. Fifteen implant were placed at least as each patient had received one implant

in one side of the jaw as control (implant only) and another implant in the other side as study (implant coated with vit. D3), except one patient was received three implants. The male patients were 5 and female patients were 2. Each patient signed an informed consent form prior to participation in the study. The patients were selected from the Out Patient Clinic of the Oral & Maxillofacial Surgery Department, Faculty of Dentistry, Al-Azhar University.

### **Implants were divided into two groups:**

- Control group: patient received implant without any treatment.
- Vitamin D3 group: patient received implant soaked in vitamin D3 sol. for 30 sec.

The inclusion criteria of this study were; Well-controlled male or female diabetic patients, the site of surgery should be free of acute infection and inflammation. All patient with accepted occlusion and bone height should not be less than 10 mm and ridge width not less than 6 mm.

While the exclusion criteria were; Presence of pathological tissue changes at the site of implant, history of radiotherapy or chemotherapy, pregnancy, hypersensitivity to the proposed medications including anesthesia, inability or unwillingness to maintain a good level of oral hygiene throughout the study period or to return for follow-up visits.

The Implant system: Dentium\*(Dentis Co., Ltd. 951, Woram-Dong, Dalseo-Gu Daegu, South Korea) super line implant system was the implant of choice for this study.

### **Clinical procedures:**

#### **Preoperative clinical evaluation:**

Thorough oral, general examination and investigations were done for each selected patient, radiographic records and complete clinical medical and dental history were taken at first visit, with collection of the following information: patient age and sex; width and height of the ridge at the site of implant insertion. The site of surgery was assessed for

the presence of inflammation or infection.

- **Intra-oral clinical examination was done included:**

Digital examination and inspection of the mucosa covering the edentulous areas for any signs of infection, inflammation, or irritation.

- **Medical history:**

Past medical history was discussed with the patients. Special attention was given to history of diabetes and asked if patients committed to their physician appointments or not to keep their diabetic status controlled.

Investigations: Glycosylated hemoglobin (HbA1c) analysis was done for each selected patient to assess if the patient is diabetic controlled or not.

#### **Preoperative radiographic evaluation:**

1. Peri-apical radiographs using parallel technique to assess bone height.

2. Preoperative panoramic radiographs showing implants site and size.

3. Cone beam computed tomography (CBCT) were taken for every patient to determine alveolar bone thickness, ridge width and length, simulation of implant size and length. CBCT reading for bone quality (bone density).

#### **Disinfection & Anaesthesia:**

The tissue was disinfected by gauze saturated with betadine and left for 3-5 min. Then the patient was instructed to rinse his mouth with sterile normal saline. After testing of the anaesthesia the patient was ready for exposure of the field.

#### **Surgical procedures:**

1. The flap design: A crestal incision was made on the top of alveolar ridge through the mucosa at the site of implant, then surgical area was exposed sufficiently by full-thickness muco-periosteal flap elevation.

2. Drilling for implant fixture: An accurate ridge height was measured by cone beam computed tomography (CBCT) before drilling

sequence with 2 mm safety bone was left intact between the end point of fixture and inferior alveolar nerve canal. The implant position was marked with a round bur. The Standard drilling sequence for the implants was started from the pilot drill, an intermediate drill, and then ended with the final drill. The motion of the drilling was in up and down motion with light intermittent finger pressure under cooling to avoid necrosis of the bone from the heat generation.

### 3. Implant installation:

- For control group, the implant with its fixture mount was removed from its sterile package and handled to its position inside the drilled site.

- For study group the implant with its fixture mount was removed from its sterile package and submerged in vitamin D3 solution for 30 seconds (Devarol s 200,000 IU, Memphis co. Egypt) before installation and then slowly threaded using ratchet into the drilled site of the bone in a clockwise direction until all implant was inserted.

The fixture mount was then removed from the top of the implant by the aid of hex instrument, and a smart peg was connected to the fixture to measure implant primary stability by Osstell device. Then the smart peg was removed and the cover screw was driven into the implant. Immediate postoperative periapical X-ray film was done. Closure was done by 3-0 vicryl suture.

### Patient Follow Up:

The 1st visit after the day of surgery was after 3 days for checking the site of surgery and assure that patients were following the instructions.

The second visit was at 7th day after surgery to remove the suture to avoid food debris contamination and request panoramic view and cone beam computed tomography radiograph to evaluate the position of the implant, status of inferior alveolar canal, height, width of ridge and measure bone density around implants of study and control groups.

### Postoperative radiographic evaluation:

1- Post-surgically panoramic radiographs immediately were taken to record the bone height mesial and distal to fixture regarding the length of the implant as a reference point with 1:1 magnification.

2- CBCT were done after a week, 6 and 9 months postoperatively to evaluate bone density & crestal bone loss around dental implants by measuring the gray scale or the Hounsfield units.

Then, the second phase of implant which was the placement of the healing abutment by making a crestal incision and uncover the fixture. The cover screw has been removed by hex and finger driver and the smart peg attached to measure implant secondary stability by Osstell device.

### Statistical analysis:

Data were tabulated, coded then analyzed using the computer program SPSS (Statistical package for social science) version 23.0.

### Results:

#### 1. Pain intensity Periods of visual analog scale (VAS):

The patients complained of pain and discomfort during the first day of implant insertion. Pain was decreased at the second day and began to disappear at the third day. There was no severe pain, large swelling, suppuration or mobility detected during the time of evaluation. Clinical assessment showed good stability without any mobility and no signs of peri-implantitis.

At the 1<sup>st</sup> day, at the 3<sup>rd</sup> day and at the 6<sup>th</sup> day the mean value of pain in vit. D group were (Mean:  $7.38 \pm 0.44$ ; Mean:  $5.06 \pm 0.5$ ; Mean:  $2.63 \pm 0.44$  respectively) showed statistical significant decrease compared to that in control (Mean:  $8.43 \pm 0.45$ ; Mean:  $5.93 \pm 0.67$ ; Mean:  $3.64 \pm 0.38$  respectively) ( $p=0.001$ ,  $0.013$ ,  $<0.001$  respectively). Fig. (1).

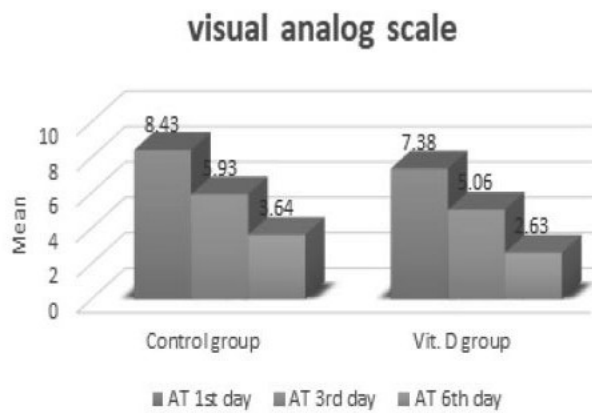


Fig. (1). Bar chart showing the Comparison between different periods of pain.

## 2. Probing depth:

The mean value of probing depth after 1 month & 3 months of loading in vit. D group (Mean:  $2.35 \pm 0.31$ ; Mean:  $1.44 \pm 0.28$  respectively) statistical non-significant compared to that in control group (Mean:  $2.66 \pm 0.36$ ; Mean:  $1.77 \pm 0.35$  respectively) ( $p=0.096, 0.062$  respectively). Fig. (2).

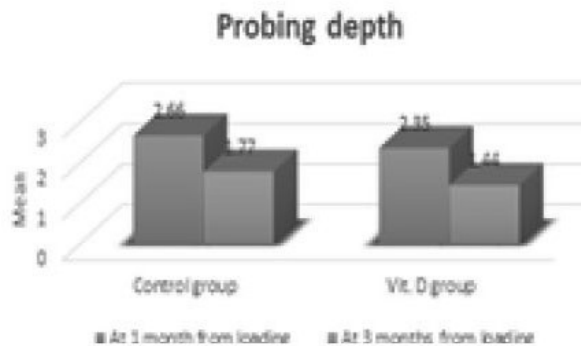


Fig. (2). Bar chart showing the comparison between different periods of probing depth in both groups

## 3. Implant stability quotient (ISQ):

Change & percent of change of ISQ (from 3 months to immediate) in vit. D group ( $14.38 \pm 2.07$ ;  $23.03 \pm 5.36$  respectively) showed statistical significant increase compared to that in control group ( $10.00 \pm 2.71$ ;  $15.28 \pm 3.71$  respectively) ( $p=0.004, 0.007$ ). Fig. (3).

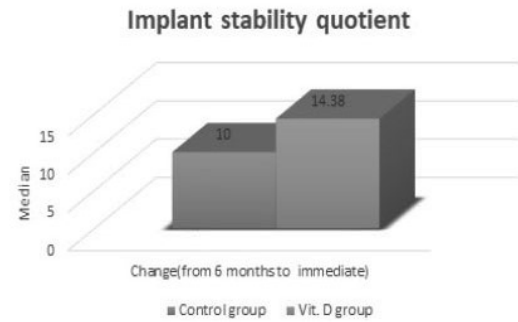


Fig. (3). Bar chart showing the change of (ISQ) from immediate to 6 months.

## 4. Cone Beam CT analysis:

Vertical bone loss in addition to bone density were assessed with CBCT as following:

### A-Vertical bone loss:

After 3 & after 6 months of vit. D group (Median: 0.21, IQR: 0.13-0.26; Median: 0.85, IQR: 0.31-0.94 respectively) showed statistical significant decrease compared to that in control group (Median: 0.90, IQR: 0.80-1.00; Median: 1.30, IQR: 1.20-1.40 respectively) ( $p=0.001, 0.001$  respectively). Fig. (4).

### B-Periods of Bone density:

Change and percent of change (from 9 months to Pre-operative) of vit. D group (Mean:  $92.38 \pm 31.22$ ; Mean:  $18.79 \pm 8.01$  respectively) showed statistical significant increase compared to that in control group (Mean:  $58.14 \pm 17.03$ ; Mean:  $11.54 \pm 3.1$  respectively) ( $p=0.023, 0.043$  respectively).

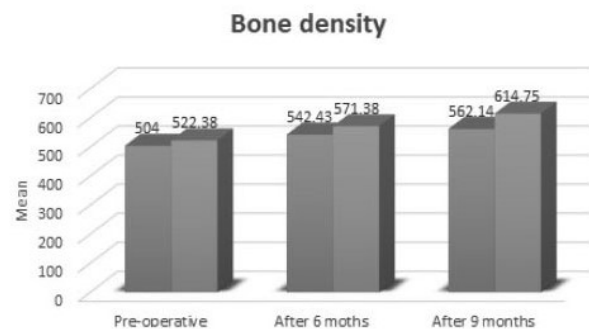


Fig. (51). Bar chart showing the bone density at different periods of in both groups.

## 5. Bleeding index:

After 1 month & 3 months from loading in vit. D group (Mean:  $2.31 \pm 0.37$ ; Mean:  $1.13 \pm 0.23$  respectively) showed statistical non-significance compared to that in control group (Mean:  $2.36 \pm 0.38$ ; Mean:  $1.29 \pm 0.27$  respectively) ( $p=0.82, 0.23$  respectively).

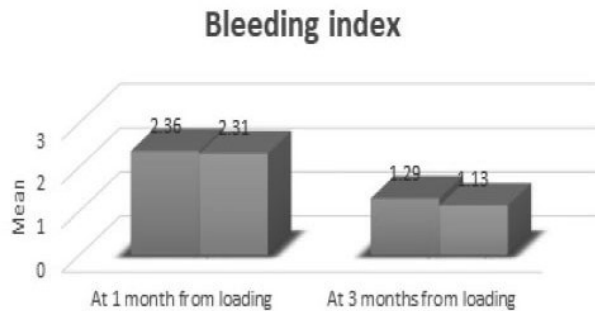


Fig. (55). Bar chart showing the comparison between different periods of bleeding index in both groups

## Discussion:

The use of biocompatible materials to improve bone formation around dental implants has been widely documented in the literature. A wide variety of substances have been studied to improve bone regeneration and peri-implant bone response such as vitamin D (22). Links between vit. D and bone metabolism have been reported in the literature and its effect on stimulating osteoblast proliferation and differentiation (23).

In the present study, Split mouth technique was used in an attempt to limit variables. Fifteen implant were placed in seven patients. Each patient at least had received one implant in one side of the jaw as control (implant only) and another implant in the other side as study (implant coated with vit. D3), except one patient was received three implants. The male patients were 5 and female patients were 2. However there was no statistical significant effects of sex, age on the obtained results in both groups. This may be due to decreasing number of cases in the present study.

Clinical and radiographic evaluations were done to assess success of implants. Clinically,

pain and probing depth were followed in order to differentiate between the effect of topical application of vit. D on titanium dental implant and implant placement without application of vit. D. Resonance frequency analysis was done to determine implant stability (24). CBCT was used to assess vertical bone loss and CBCT reading (bone density) (25).

In the present study, pain was evaluated with VAS which slightly decreased in study group than in control group. As regard Percent of change (from the 1st to 3rd day) of vit. D group (Mean:  $31.44 \pm 3.81$ ) were non-significant compared to that in control group (Mean:  $-29.78 \pm 5.42$ ) ( $p=0.002$ ) while percent of change (from the 1st to 6th day) of vit. D group (Mean:  $64.49 \pm 5.11$ ) showed significant decrease compared to that in control group (Mean:  $56.79 \pm 3.88$ ) ( $p=0.006$ ).

In the present study also, probing depth was decreased in all patient of both groups at 3 months from loading particularly in the study group. This improvement and the reduction of peri-implant probing depth indicated improvement of the collagen fibers arrangement and density around dental implant that preventing peri-implantitis and increasing of osseointegration. Also bleeding index showed significant decrease of both vit. D and control groups.

All implants in the present study were evaluated for primary and secondary stability by osstell device. The primary implant stability was  $64.25 \pm 11.78$  ISQ, in the study group and  $65.43 \pm 5.47$  in the control group. ISQ in the study and control group were increased to  $78.63 \pm 11.93$  and  $75.43 \pm 6.9$  respectively. In Degidi's et al study in 2010(26), all the implants were with an initial stability (ISQ) below 46 ISQ failed, while in those with ISQ over 60 were successful.

The present study also determines the changes in bone density around implants in this study vit. D group and control groups from baseline to 9 months using CBCT scan. Multislice and cone beam CT images are frequently used to determine mineral density of craniofacial bone structures. Radiographic

evaluation with CBCT has an advantages over CT include, low radiation dose, lower cost, potentially better access, and high special resolution (27). Yet, there is no consensus regarding the accuracy of CBCT for this type of analysis. While some studies advocate its use, others advocate that CBCT is not an adequate tool for this type of evaluation because the intensity values of CBCT are influenced by the characteristics of the system and by the scanned object (28). The density changes in radiographic techniques is based on the darkness and brightness of images, expressed with Hounsfield Unit in CT scan and with gray scale in CBCT. Gray scale has many applications in determining the origin of lesions and tissues and density changes, but gray scales are not the same in various devices. So far, CBCT manufacturers have not introduced a standard system for displaying gray scale. HU is a standard scheme for measuring CT values in CT scan. Some studies have shown a strong linear relationship between HU and gray scale. However, gray scale is different due to higher noise levels, more scattered radiation, high heel effect and beam hardening artifacts(28). There is a close linear correlation consented to determine the conversion ratio to transform the gray density values of CBCT to that of CT (HU). In particular, in the present study, the conversion ratio was approximately 0.7 ( $0.7 \times$  values of CBCT = values of CT)(29). The parameters for production of the image were constant for all images; this was in full agreement with Ribeiro-Rotta RF et al (2010) (30) who advocate that CBCT scan can become a reliable tool for bone density assessment. In the present study preoperative CBCT was done to assess implant site and nerve position. A week after implant installation CBCT was done to make it a reference point for bone dimensions, density and was compared them with the result at 6 months and 9 months.

The results of bone density changes in current study were:

After a week, after 6 months and after 9 months vit. D group showed non-significant compared to that in control group ( $p=0.64$ ,  $0.47$ ,  $0.14$  respectively). As regard Change

and percent of change (from 6 months to Pre-operative) vit. D showed non-significant compared to that in control group ( $p=0.12$ ,  $0.14$  respectively).

The results from 0 to 9 months showed significant increase compared to that in control group in bone density all around the implant surfaces ( $p=0.023$ ,  $0.043$  respectively). Regarding the mean of vertical bone loss, In the present study, After 3 and after 6 months of vit. D group showed significant decrease compared to that in control group.

Cho et al (31) (2011) inserted implants with vit. D coating in the rabbit's tibiae . At 4 and 12 weeks, osseointegration level was determined through bone implant contact BIC values. At 4 weeks, test implants showed higher total BIC values ( $37.08 \pm 10.18$ ) compared to control implants ( $28.01 \pm 8.70$ ). At 12 weeks statistically significant differences were found between the two groups.

In an experimental study performed by Hong et al(32) (2012) in healthy beagle dogs and created a surgical defects and supplemented the dogs with high dose of vit. D and calcium during 4 weeks. At 4 weeks, animals were sacrificed and authors found that vit. D/Ca supplementation increased new bone formation and bone density, and reduced crestal bone loss when compared to non supplemented groups.

The main problem during performing this study was there were very few reports about the local application of vitamin D in clinical trials to promoting osseointegration around dental implant. The degree of concentration of vitamin D was also a matter of debate in the previous literatures.

From the result of the present study it was obvious that vitamin D had an effect on bone density and osseointegration enhancement. Further investigations and more reserchs are needed using adifferent concentration to confirm and support its effect.

## Conclusions:

Within the limitation of the present study the following conclusions can be drawn:

The topical application of vit. D on dental implants exhibited less crestal bone loss and slightly enhanced bone density when comparing to control group.

### Recommendations:

It seems appropriate to determine blood levels of vitamin D3 before implantation and apply possible supplementation. There is a need for further research on the correlation between the osseointegration of implants and the concentration levels of vitamin D3. The efficacy of topical application of vit. D on titanium dental implant remains controversial and require further investigation. Also systemic supplementation of vitamin D3 may has better effect on osseointegration of dental implant.

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