IJMPR 2024, 8(10), 77-82

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Original Article
SJIF Impact Factor: 6.669

# A COMPARATIVE EVALUATION OF THE EFFECT OF ESTROGEN AND PROGESTERONE LEVELS ON BONE REMODELLING AROUND DENTAL IMPLANTS

**[*]Dr. Divya Kadali, [1]Annem Venkata Shalmija, [2]Dr. Appari Sonia, [3]Dr. Reehana Pathan, [4]Dr. Vaishnavi Bhattiprolu, [5]Dr. Sri Ramya Komera and [6]Dr. Devika Kolasani**

[*]Associate Professor, Care Dental College and Hospital, Guntur, Andhra Pradesh.
[1]MDS 1st Year, Department of Periodontics and Implantology, DRS. Sudha and Nageshwar Rao Siddartha Institute of Dental Sciences, Chinaoutapalli, Andhra Pradesh, India.
[2]BDS, Kims Dental College Amalapuram, Andhra Pradesh, India.
[3]BDS, Clinical Practitioner, Care Dental College and Hospital, Guntur, Andhra Pradesh, India.
[4]BDS, Clinical Practitioner, Care Dental College and Hospital, Guntur, Andhra Pradesh, India.
[5]BDS, Clinical Practitioner, Gitam Dental College and Hospital, Visakhapatnam, Andhra Pradesh, India.
[6]BDS, Clinical Practitioner, Care Dental College and Hospital, Guntur, Andhra Pradesh, India.

**Article Received on: 22/08/2024**
**Article Revised on: 11/09/2024**
**Article Accepted on: 01/10/2024**

***Corresponding Author**
**Dr. Divya Kadali**
Associate Professor, Care Dental College and Hospital, Guntur, Andhra Pradesh.
divyakadaliperio@gmail.com,
shalmija10@gmail.com,
apparisoniya2@gmail.com,
Pathanreehana84@gmail.com,
vaishnavibhattiprolu02@gmail.com,
komerasriramya20@gmail.com,
kolasani.devika@gmail.com.

## ABSTRACT

**Aim:** The metabolic effect of estrogen and progesterone levels on bone tissue is of concern in the placement of endosseous dental implants. This study was undertaken to evaluate and compare the amount of bone remodelling around implants in patients with high endogenous serum estrogen and patients with low endogenous serum estrogen by assessing the levels of serum alkaline phosphatase, serum acid phosphatase, and serum calcium levels, which are biochemical products used as markers of bone remodelling. **Materials and Methods:** 20 females and 10 male controls were included in the study. In 10 females, implants were placed 10 days after menstruation (high estrogen group) and in 10 females, implants were placed during menses (low estrogen group). Clinical parameters like estrogen, progesterone, alkaline phosphatase and acid phosphatase in the serum were recorded at baseline and after 9 months. **Results:** Laboratory values of estrogen, progesterone, alkaline phosphatase and acid phosphatase in the serum varied greatly by individual. The alkaline phosphatase levels were significantly higher in the high estrogen female group and the acid phosphatase levels were higher in the low estrogen female group. **Conclusion:** The clinical success of dental implant integration was seen regardless of the temporal physiological fluctuations in the ovulatory cycle. There were no differences observed within the confines of the study in the bone remodelling around dental implants. Since it is obvious that the temporary hormonal fluctuation is not the sole factor responsible for the complex process of bone metabolism and bone healing, the dental implant osseointegration was not influenced by the temporary fluctuations in the ovulatory cycle. Hence, within the limitations of this study, bone remodelling around dental implants was not influenced by sex hormones.

## INTRODUCTION

Replacement of missing teeth with implants and implant-supported prosthesis are currently routine procedures for the oral rehabilitation of partially or fully edentulous patients.[1] During the process of osseointegration, an implanted metal element and the living bone fuse.[2] It represents the coupling of the osteoclast and osteoblast activity for bone repair, formation, and adaptation to function. The integration between bone and implant is divided into three mechanisms. The first mechanism is distant osteogenesis. Bone formation takes place from the local bone toward the implant surface in distance osteogenesis. In the second phenomenon, bone formation takes place from the implant surface toward the local bone, which is known as contact osteogenesis. Finally, bone remodelling is the third phenomenon of implant-bone integration.[3]

Steroid sex hormones are derived from cholesterol and are believed to play an important role in the maintenance of the skeletal integrity, including the alveolar bone. The hormones estrogen and progesterone are responsible for physiological changes in women at specific phases of their life, starting at puberty.[4] Estrogenic hormones are formed by the ovary, placenta, testes and the adrenal cortex. The major secreted estrogen is 17 B-estradiol which occurs in equilibrium in the systemic circulation with estrone. A deficiency in these hormones has been linked to osteoporosis.[5]

Estrogen receptors are found in osteoblast-like cells and they provide a mechanism for the direct action on bone. These receptors were also located in periosteal fibroblasts, scattered fibroblasts of the lamina propria, and periodontal ligament (PDL) fibroblasts, proving the direct action of sex hormones on different periodontal tissues. Progesterone, similar to estrogen, shows direct effects on the periodontium. Progesterone has a role in bone metabolism which have been demonstrated using experimental, epidemiologic, and clinical data and may play an important role in the coupling of bone resorption and bone formation.[4]

Osteolytic cytokines are expressed throughout the menstrual cycle, but levels of interleukin-1β (IL-β), interleukin-6(IL-6), and tumour necrosis factor alpha (TNF-a) are highest before ovulation when the levels of estrogen and progesterone are low. This temporal fluctuation could effect the early events of alveolar osseous wound healing.[5]

Biochemical markers of bone turnover are broadly divided into two categories: markers of bone resorption, which reflect osteoclast activity and are for the most part degradation products of type I collagen; markers of bone formation, which reflect osteoblast activity and are by products of collagen synthesis, matrix proteins or osteoblastic enzymes. Bone resorption and bone formation are coupled processes and therefore in most situations any of these markers will reflect a change in bone turnover.[6]

Alkaline phosphatase, a membrane-bound glycoprotein catalyses the hydrolysis of phosphate monoesters at a basic pH level. Bone-specific alkaline phosphatase (BALP) is known to be involved in bone calcification which is secreted by osteoblasts to provide a high phosphate concentration at the osteoblast cell surface during bone mineralization.[3]

High amounts of bone resorption markers like acid phosphatase are expressed in bone-resorbing osteoclasts, alveolar macrophages of the lung and dendritic cells. A condition called hypophosphatasia is diagnosed on the basis of bone hypoplasia which has reduced alkaline phosphatase levels. Calcium is also of much biological importance. Calcium plays an indispensable part in mineralisation of the skeletal system and teeth and its deficiency causes osteoporosis which is a painful and crippling disease affecting 1 in 3 women.

The metabolic effect of estrogen and progesterone is of concern in the placement of endosseous dental implants. Hence this study was aimed at evaluating the effect of estrogen and progesterone levels on bone remodelling around dental implants by measuring the amounts of bone markers alkaline phosphatase and acid phosphatase.

The aim of the present study is to compare the amount of bone remodelling around implants in female patients with high endogenous serum estrogen and female patients with low endogenous serum estrogen by assessing the levels of alkaline phosphatase and acid phosphatase in serum.

## MATERIALS AND METHODS

### Study Design

The objective of the study is to compare the amount of bone remodelling around implants in patients with high endogenous serum estrogen and patients with low endogenous serum estrogen by evaluating the levels of alkaline phosphatase and acid phosphatase in serum.

Group A – 10 male controls.

Group B – 10 female patients with high estrogen (had implant placement surgery 10 days after the cessation of their last menstruation).

Group C – 10 female patients with low estrogen (had implant placement surgery during their menstruation).

The estrogen levels, progesterone levels, alkaline phosphatase levels and acid phosphatase will be compared at baseline and 9 months along with the clinical parameters. Approval of the study was obtained from the ethical committee of St. Joseph Dental College and an informed consent was taken from all participants before commencement of the study.

### Study Population

The study population included patients who reported to the department of Periodontics St. Joseph dental college between April 2017 to April 2018.

### Inclusion Criteria

- Patients in the age group of 20 to 45 years
- Partially edentulous patients
- Patients showing a tendency to maintain good oral hygiene
- Good systemic health

### Exclusion Criteria

- Patients with known systemic disease
- Patients on medication and antibiotic therapy
- Patients with psychiatric disorders
- Pregnant or lactating
- Smokers
- Inability or unwillingness to complete the trial
- Teeth with occlusal interferences and restorations
- Poor oral hygiene and mobility

### Collection of blood

The day of implant placement (Phase I surgery), immediately before the surgical procedure and after 9 months, 4mL intravenous blood was drawn from the subject's antecubital vein to determine the serum levels of estrogen, progesterone, alkaline phosphatase, alkaline phosphatase and acid phosphatase levels.

### Presurgical Procedure

Prior to commencement, the study design was discussed with every selected patient and his / her written consent was taken. Following initial examination and treatment

planning, the selected patients underwent phase 1 therapy. Detailed instructions and plaque control measures were given. Two weeks after phase 1 therapy, only those patients maintaining optimum oral hygiene were subjected to the surgical procedure. All the selected patients underwent routine blood investigations and radiovisiographs of the area of interest were taken. On completion of baseline examination and thorough initial therapy, dental implants were placed at the edentulous sites.

**Technique**

Before surgery, all the patients rinsed their oral cavity with a 0.1% chlorhexidine digluconate solution. A mid-crestal incision was then given at the area of implant placement, and a full-thickness mucoperiosoteal flap was raised to expose the osteotomy site. First the pilot drill was used to establish depth and axis of drilling. The next drill in the sequence is used to drill up to the same depth as established by the pilot drill. The final drill is then placed at the required depth to complete the osteotomy site. The site is flushed with normal saline and isolated before placement of the implant. The implant is removed from the vial and placed in the osteotomy site using the implant carrier. The implant driver engages the internal hexagon of the implant while the other end is inserted into the ratchet to progressively screw the implant to its final seating position. The cover screw is placed into the implant so that a tight seal of the implant is obtained in the osseointegration period and sutures were given with 3-0 silk sutures.

**Postoperative Care**

All patients were prescribed systemic Amoxicillin 500 mg thrice daily for 5 days and a combination of Ibuprofen 400mg and Paracetamol 325mg thrice daily for 3 days. They were also instructed to rinse with 10 ml of Chlorhexidine gluconate (0.2%) mouthwash twice daily for two weeks.

**Prosthodontic Phase**

In both the groups, delayed loading was done. Cover screws were removed and healing abutments were placed after 3 months in the mandibular implants and after 6 months in the maxillary implants. After 15 days of placement of the abutments, abutment level closed tray putty impressions (pick-up impressions) were taken and given for crown fabrication. Each implant was then functionally loaded with metal crowns.

**FIGURES**

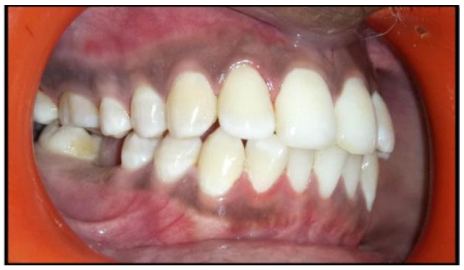

**Figure 1: Pre operative scaling.**

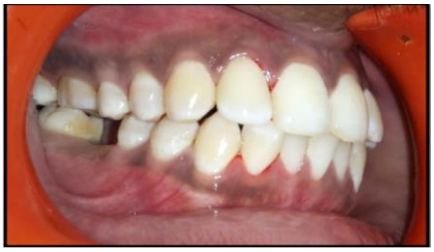

**Figure 2: Post operative scaling.**

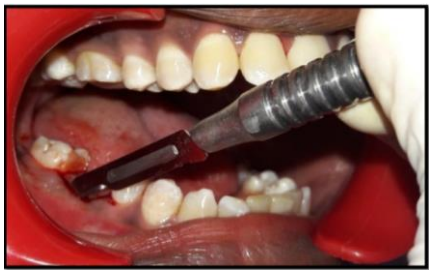

**Figure 3: Mid crestal incision given.**

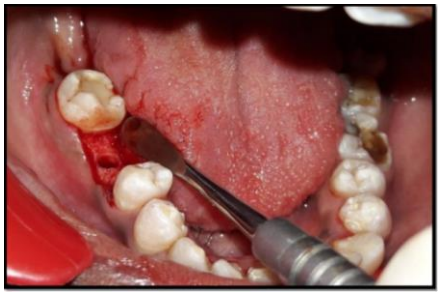

**Figure 4: Full thickness mucoperiosteal flap elevated and osteomy site prepared.**

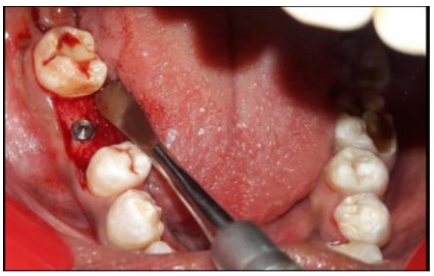

**Figure 5: Implant placement done.**

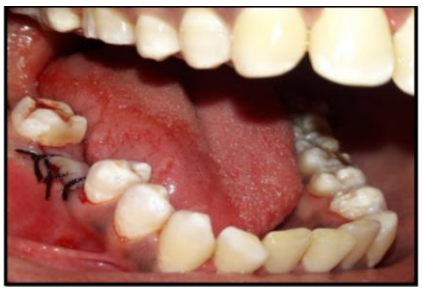

**Figure 6: Mucoperiosteal flap approximation done using silk sutures.**

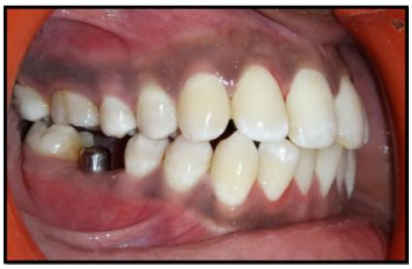

**Figure 7: Gingival former placed.**

**Blood sample collection.**

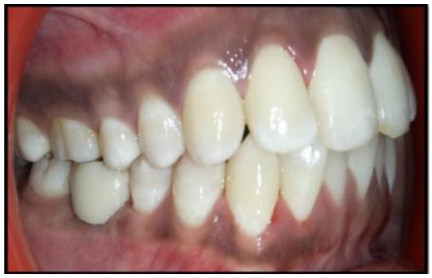

**Figure 8: Prosthesis placed.**

**Table 1: Mean, standard deviation of estrogen levels in each group.**

| Estrogen | Time | N | Minimum | Maximum | Mean | SD | T-Value | P-value |
|---|---|---|---|---|---|---|---|---|
| Group A | Baseline | 10 | 20.25 | 29.20 | 24.85 | 3.06 | 1.88 | 0.09 |
| | 9 months | 10 | 22.50 | 36.50 | 26.86 | 4.41 | | |
| Group B | Baseline | 10 | 39.80 | 50.00 | 44.32 | 3.59 | 0.94 | 0.37 |
| | 9 months | 10 | 40.00 | 54.00 | 45.62 | 3.70 | | |
| Group C | Baseline | 10 | 28.50 | 37.94 | 32.77 | 2.78 | 0.41 | 0.69 |
| | 9 months | 10 | 26.50 | 36.60 | 32.50 | 2.63 | | |

**Table 2: Mean, standard deviation of progesterone levels in each group.**

| Progesterone | Time | N | Minimum | Maximum | Mean | SD | T-Value | P-value |
|---|---|---|---|---|---|---|---|---|
| Group A | Baseline | 10 | 0.10 | 0.25 | 0.17 | 0.04 | 1.16 | 0.28 |
| | 9 months | 10 | 0.10 | 0.23 | 0.15 | 0.05 | | |
| Group B | Baseline | 10 | 3.35 | 6.50 | 4.87 | 0.89 | 0.25 | 0.81 |
| | 9 months | 10 | 3.32 | 7.50 | 4.92 | 1.11 | | |
| Group C | Baseline | 10 | 0.18 | 0.28 | 0.24 | 0.03 | 0.23 | 0.82 |
| | 9 months | 10 | 0.15 | 0.50 | 0.23 | 0.10 | | |

**Table 3: Mean, standard deviation of alkaline phosphatase levels in each group.**

| Alkaline Phosphatase | Time | N | Minimum | Maximum | Mean | SD | P-value |
|---|---|---|---|---|---|---|---|
| Group A | Baseline | 10 | 63.50 | 78.50 | 68.91 | 4.40 | <0.01 |
| | 9 months | 10 | 67.50 | 108.50 | 85.41 | 13.59 | |
| Group B | Baseline | 10 | 62.50 | 75.50 | 68.55 | 3.86 | <0.01 |
| | 9 months | 10 | 78.50 | 103.00 | 87.80 | 7.85 | |
| Group C | Baseline | 10 | 60.25 | 65.50 | 62.48 | 2.24 | <0.01 |
| | 9 months | 10 | 68.50 | 88.50 | 74.80 | 5.93 | |

**Table 4: Mean, standard deviation of acid phosphatase in each group.**

| Acid Phosphatase | Time | N | Minimum | Maximum | Mean | SD | T-value | P-value |
|---|---|---|---|---|---|---|---|---|
| Group A | Baseline | 10 | 1.18 | 3.60 | 2.43 | 0.78 | 2.93 | <0.01 |
| | 9 months | 10 | 1.12 | 2.80 | 1.94 | 0.57 | | |
| Group B | Baseline | 10 | 3.20 | 4.50 | 3.76 | 0.38 | 6.59 | <0.01 |
| | 9 months | 10 | 1.60 | 3.80 | 2.49 | 0.74 | | |
| Group C | Baseline | 10 | 2.00 | 3.80 | 3.31 | 0.78 | 6.12 | 0.02 |
| | 9 months | 10 | 1.80 | 4.7 | 2.70 | 0.66 | | |

## DISCUSSION

The success of dental implants depends mainly upon the stability and osseo integration resulting from the bone remodelling around implants and the bone remodelling is in turn influenced by many systemic factors like sex hormones including estrogen and progesterone.

Osteolytic cytokines are expressed throughout the menstrual cycle, but are known to be highest before ovulation when the levels of estrogen and progesterone are low. This temporary fluctuation could effect the early events of alveolar osseous wound healing.

Estrogen and progesterone hormones are formed by the ovary, placenta, testes and the adrenal cortex. A deficiency in these hormones has been related to osteoporosis. Supplemental estrogen has been shown to decrease vertebral and hip fractures in postmenopausal women and therefore estrogen hormones can be said to inhibit bone resorption in the balance of bone mass regulation.

Menstruation is the cyclic, orderly sloughing of the uterine lining which may be divided into two phases: 1) follicular or proliferative phase, and 2) the luteal or secretory phase. The first day of menses until ovulation is the follicular phase. During the follicular phase, serum estradiol levels rise in parallel to the growth of follicle size as well as to the increasing number of granulosa cells. The rise and fall of estrogen levels occurs twice during the menstrual cycle. The estrogen levels rise during the mid-follicular phase and are dropped after ovulation. A secondary rise in estrogen level occurs during the mid-luteal phase, i. e 10 days after menstruation, with a decrease at the end of the menstrual cycle. This secondary rise in serum estrogen parallels the rise of serum progesterone. This is in accordance to the studies by Shannon M. Hawkins *et al*. (2008), M. Mihm *et al*. (2011) and Reed et al (2015).

Since the metabolic effect of estrogen and progesterone levels on bone tissue is of concern in the placement of endosseous dental implants, this study was undertaken to evaluate and compare the amount of bone remodelling around implants in patients with high endogenous serum estrogen and patients with low endogenous serum estrogen by assessing the levels of serum alkaline phosphatase, serum acid phosphatase, and serum calcium levels, which are biochemical products used as the markers of bone remodeling.[15]

In group B (high estrogen females) implants were placed when the estrogen levels were high, i.e during the mid-follicular phase and the mid-luteal phase and in group C (low estrogen females), implants were placed during the menstrual phase when the estrogen levels were low, i.e during the first few days of follicular phase. The progesterone levels also were comparatively high in the high estrogen group, as the rise in progesterone parallels the rise of serum estrogen during the mid-luteal phase. This rise and fall of etsrogen and progesterone is in accordance to the studies conducted by Shannon M. Hawkins *et al*. (2008), M. Mihm *et al*. (2011), and Reed *et al*. (2015).

In this study, the alkaline phosphatase enzyme was higher in males. The enzyme activity also varies in the same age with respect to gender and is slightly higher in men than women because of the increased circulating dimeric isoforms of bone ALP in males. This is accordance to the studies done by Van Hoof et al (1994) and Masrour Roudsari J *et al*. (2012).

In this study, among females the alkaline phosphatase levels were significantly higher in the high estrogen females which could be attributed to the role of estrogen on alkaline phosphatase expression. 17β-estradiol had a direct action on the growth and expression of alkaline phosphatase, an osteoblastic differentiation marker, in strains of normal human bone marrow stromal cells. This is in accordance to the studies conducted by P. J. A Rombout *et al*. (1978), Holzer et al (2002) and Bashu Dev Pardhe *et al*. (2017).

The females with low estrogen levels in this study had reduced expression of alkaline phosphatase. The immediate suppression of alkaline phosphatase, at even the low dose estradiol, indicates an inhibition of osteoblasts at or before the stage of extracellular matrix synthesis associated with alkaline phosphatase production and that estradiol administration resulted in a transient increase in trabecular bone volume and trabecular number. This is in accordance to the studies done by Sims *et al*. (1996) and B. Lawrence Riggs *et al*. (1997).

In this study, there was higher alkaline phosphatase activity in patients with higher progesterone levels due to better osseointegration. This is because progesterone appears to act directly on bone by engaging an osteoblast receptor or indirectly through competition for a glucocorticoid osteoblast receptor and progesterone seems to promote bone formation and/or increase bone turnover. Progesterone plays a role in the coupling of bone resorption with bone formation through estrogen-stimulated increased progesterone binding to the osteoblast receptor. This is in accordance to the studies by J. C. Prior *et al*. (1990) and Gillian R. Snow *et al*. (1986).

The increased alkaline phosphatase (ALP) levels indicates bone remodelling around the dental implants and hence better osseo-integration. ALP plays a role in mineralization process, which is to prepare alkaline atmosphere (basic) in osteoid tissue formed so that calcium can be deposited on the tissue. Increased ALP expression then indicates osteogenic differentiation. This is in accordance to studies conducted by Ujjawal Sharma *et al*. (2014) and Sherman *et al*. (2016).

The acid phosphatase levels were higher in the low estrogen females which indicated that there was poorer bone formation around the implants placed in that group. The acid phosphatase level describes the number of osteoclasts in addition to their activity, appears to be a highly specific and sensitive marker of bone resorption. This is in accordance to the studies conducted by Nihal Thomas *et al*. (2016), H Bull *et al*. (2001) and Halleen *et al*. (2006).

In this study, the bone integration was seen regardless of fluctuations in the sex hormone levels. However, further clinical trials with larger sample size and longer durations are required to determine whether estrogen and progesterone levels have a role on bone remodelling around dental implants.

**SUMMARY**

This study has been designed to decide whether endogenous estrogen and progesterone hormones have a role in bone remodelling around dental implants. 20 females and 10 male controls were included in the study. In 10 females, implants were placed 10 days after menstruation (high estrogen group) and in 10 females, implants were placed during menses (low estrogen group).

Clinical parameters like estrogen, progesterone, alkaline phosphatase and acid phosphatase in the serum were recorded at baseline and after 9 months. The alkaline phosphatase and acid phosphatase levels increased in both the female experimental groups. The alkaline phosphatase levels were significantly higher in the high estrogen female group which was due to the direct action of estrogen on alkaline phosphatase activity.

The clinical success of dental implant integration was seen regardless of the temporal physiological fluctuations in the ovulatory cycle. There were no differences observed within the confines of the study in the bone remodelling around dental implants. Laboratory values varied greatly by individual, but since it is obvious that the temporary hormonal fluctuation is not the only factor in charge the complex process of bone metabolism and bone healing, the dental implant osseointegration was not influenced by the temporary fluctuations in the ovulatory cycle. Hence, within the limitations of this study, bone remodelling around dental implants was not influenced by sex hormones. However, further clinical trials with larger sample size and longer durations are required to determine whether an association exists between sex hormones and dental implant osseointegration.

**STUDIES**

1. LTC Michael F. Cuenin, COL Benjamin S. Hanson, COL Michael A. Billman, LTC Val L. Kudryk The Effects of Estrogen and Progesteron Levels on Osseointegration of Dental Implants. International journal of AMSUS, Military medicine, 1997 Sep; 162(9): 582-5.
2. Gabriela Giro, Celso Eduardo Sakakura, Daniela Goncalves, Rosa M. R. Pereira, Elcio Marcantonio Junior and Silvana R. P. Orrico Effect of 17b-Estradiol and Alendronate on the Removal Torque of Osseointegrated Titanium Implants in Ovarietomized Rats J Periodontal, 2007; 78: 1316-1321.
3. Gabriela Giro, Danila Goncalves, Celso Eduardo Sakakura, Rosa Maria Rodrigues Pereira, Elcio Marcantonio Junior and Silvana Regina Perez OrricoInfluence of estrogen deficiency and it's treatment with alendronate and estrogen on bone density around osseointegrated implants: radiographic study in female rats. Oral surg Oral Med Oral Pathol Oral Radiod Endod; 2008; 105: 162-7.
4. Daniel Van Steenberghe, Mare Quirynen, Liene Molly and Reinhelde Jacobs Impact of systemic diseases and medication on osseointegration. Periodontology, 2000; 33: 2003, 163-171.
5. Jussi Halleen Tartarate resistant Acid phosphatase 5 (TRACP) as a marker of bone resorption Immuno diagnostic systems (IDS); Review Series, April 06; 3.
6. Hisashi Watanabe, Makoto Umeda, Tomoko Seki, and Isao Ishikawa Clinical and Laboratory Studies of Severe Periodontal Disease in an Adolescent Associated With Hypophosphatasia Department of Periodontology, Faculty of Dentistry, Tokyo Medical and Dental University, Tokyo Japan, 64.