BULLETIN OF STOMATOLOGY AND MAXILLOFACIAL SURGERY
Volume21, Issue 8

DOI:10.58240/1829006X-2025.21.8-178

ORIGINAL RESEARCH

EVALUATING BONE MARKER LEVELS IN POSTMENOPAUSAL WOMEN WITH DENTAL IMPLANTS

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Received: *Aug.20 2025;* ***Accepted:*** *Sep 20, 2025;* ***Published:*** *Sep 28.2025*

ABSTRACT

Background: Postmenopausal estrogen deficiency accelerates systemic bone loss, potentially compromising the osseointegration and long-term stability of dental implants. In this population, the relationship between systemic bone turnover markers (BTMs), which allow for a non-invasive evaluation of skeletal metabolism, and implant success remains unclear.

Methods: Eighty postmenopausal women, ranging in age from 55 to 75, participated in cross-sectional comparative research. Forty women having titanium implants that had been functional for at least a year and had osseointegration were included in the research. Forty women who were similar in age and body mass index but did not have dental implants made up the control group. Hormone replacement treatment, bisphosphonate usage, and systemic disorders that were not under control were all reasons for exclusion. Utilizing enzyme-linked immunosorbent assays (ELISA), serum samples taken while subjects were fasting were examined for markers of bone formation (BSAP and P1NP) and bone resorption (CTX-I and TRAPP-5b, respectively).

Results: At the outset, there were no statistically significant variations in the demographics of the groups ($p>0.05$). The levels of the resorption marker CTX-I were 0.39 ± 0.07 ng/mL in the implant group and 0.51 ± 0.09 ng/mL in the control group ($p=0.002$). Likewise, at 3.8 ± 0.6 U/L compared to 4.5 ± 0.8 U/L ($p=0.005$), the implant group had reduced TRAP-5b levels. In comparison to the controls (41.3 ± 6.5 ng/mL; $p<0.001$), the implant group exhibited a considerably greater level of the formation marker P1NP (48.5 ± 7.2 ng/mL). The implant group had somewhat higher BSAP levels (14.1 ± 2.5 U/L vs. 13.2 ± 2.9 U/L; $p=0.18$), but the difference was not statistically significant.

Conclusion: A systemic bone turnover profile showing decreased bone resorption and improved bone formation is seen in postmenopausal women who had effective long-term dental implants, in comparison to matched controls.These findings suggest that the functional loading of implants may contribute to a more favorable systemic bone metabolism, and BTMs could serve as potential biomarkers for monitoring skeletal health in this patient population undergoing implant therapy.

Keywords*: Dental Implants, Postmenopause, Bone Turnover Markers, Osseointegration, CTX-I, P1NP, Bone Metabolism.*

INTRODUCTION

The postmenopausal period is characterized by a significant decline in estrogen production, a hormone critical for maintaining skeletal homeostasis. [1] Osteoporosis results from a hormonal change that upsets the delicate equilibrium between osteoblasts' ability to create new bone and osteoclasts' ability to resorb existing bone. This leads to a net loss of bone mass and a degradation of microarchitecture.[2, 3] This systemic condition not only increases the risk of fragility fractures but also poses a considerable challenge to oral and maxillofacial reconstructive procedures, particularly those reliant on bone quality, such as dental implantology. [4]

Because of the many advantages they provide over more conventional prosthetics, dental implants have quickly replaced dentures as the treatment of choice for tooth loss. [5] Orbital fusion, the formation and maintenance of a structural and functional bond between the surface of a load-bearing implant and live bone, is essential for the success of dental implants. [6] It is conceivable that impaired systemic bone metabolism in postmenopausal women might hinder this process, which could result in decreased initial stability, delayed healing, or long-term marginal bone loss around the implant. [7,8] Although there is conflicting evidence, several studies have shown that patients with osteoporosis are more likely to have early implant failure and problems. [9,10]

Bone turnover biomarkers (BTMs) are enzymes or protein fragments secreted during bone production and resorption; they are detectable in urine and serum. [11] In doing so, they provide a dynamic, real-time picture of the body's skeletal activity. Proteins such as bone-specific alkaline phosphatase (BSAP), which is produced by osteoblasts, and procollagen type I N-terminal propeptide (P1NP), which is a peptide that is separated from procollagen when collagen is synthesized, are important indicators of formation.[12] Some indications of resorption include the type I collagen degradation product C-terminal telopeptide (CTX-I) and the tartrate-resistant acid phosphatase 5b (TRAP-5b) enzyme that is released by working osteoclasts**.** [13,14] Metabolic bone illnesses, such as osteoporosis, rely on these markers for a variety of diagnostic and therapeutic purposes, including the evaluation of fracture risk and the tracking of treatment effectiveness. [15]

In the context of dental implantology, the utility of BTMs is an area of growing interest. Recent studies have explored their potential to predict implant stability and identify patients at higher risk for osseointegration failure. [16] One example is the correlation between high levels of resorption markers before surgery and an increased likelihood of early implant failure in certain groups of patients. [17] However, much of the existing research has focused on heterogeneous populations or has not specifically isolated the postmenopausal demographic, where the underlying physiology of bone turnover is fundamentally altered. It remains unclear whether the successful, long-term functional loading of dental implants in postmenopausal women influences systemic bone metabolism, or if a pre-existing favorable bone marker profile is a prerequisite for success. This represents a significant research gap. Understanding this relationship could lead to improved patient selection, personalized treatment planning, and the development of non-invasive monitoring strategies for this at-risk population.

In light of this, the current study set out to compare serum levels of critical markers for bone formation and resorption (CTX-I and TRAP-5b) in postmenopausal women who had long-term dental implants (i.e., those who had successful procedures) with those of a control group of postmenopausal women who did not have dental implants.Our hypothesis was that the implant group would exhibit a bone marker profile indicative of a more balanced or anabolic state compared to the control group.

MATERIALS AND METHODS

Study Design and Ethical Approval

Taking place from January to December 2024, this comparative cross-sectional research was carried out at the Center for Oral Health of the University Hospital.

Study Population and Sample Size

Eighty women who had gone through menopause were enrolled, with forty women split evenly between the two groups. An effect size of 0.65, an alpha of 0.05, and a power of 80% were used to estimate the minimum need of 38 participants per group when calculating the sample size using G*Power 3.1 software, which was based on prior data on CTX-I levels.

- **Implant Group (n=40):** This group consisted of postmenopausal women with at least one endosseous titanium dental implant (various systems) that had been in functional loading for a minimum of 12 months.
- **Control Group (n=40):** This group comprised age- and Body Mass Index (BMI)-matched postmenopausal women who were partially or fully edentulous but had no dental implants.

Inclusion and Exclusion Criteria

Every participant had to meet these requirements: she had to be a female, between the ages of 55 and 75, and she had to be willing to provide a blood sample in addition to having to be postmenopausal (defined as no menstruation for at least 12 months in a row for reasons other than menstruation). Additional criteria for the implant group included: implants that were clinically and radiographically effective without mobility, peri-implantitis (defined as a probing depth of less than 5 mm, absence of blood during probing, and absence of

suppuration), or increasing marginal bone loss (defined as less than 0.2 mm per year after the first year).

In both groups, participants were not allowed to participate if they had the following conditions: a history of cancer or radiation therapy to the head and neck area; chronic kidney or liver disease; current smoking or heavy alcohol consumption (>2 units/day); active, untreated periodontal disease; or a current or previous use of hormone replacement therapy (HRT) or drugs known to affect bone metabolism (e.g., bisphosphonates, selective estrogen receptor modulators, corticosteroids).

Clinical and Radiographic Assessment

A comprehensive medical history was obtained from all participants. For the implant group, a detailed dental history was recorded, including implant type, location, and time since placement. Clinical implant stability was confirmed using a combination of manual testing (absence of perceptible movement) and resonance frequency analysis (Osstell ISQ), with an Implant Stability Quotient (ISQ) >65 considered stable. To ensure that there was no radiolucency around the implants, periapical radiographs were performed to measure the amounts of crestal bone.

Biochemical Analysis

The subjects' venous blood samples (5 mL) were taken between 8:00 and 10:00 AM after an overnight fast in order to reduce the impact of circadian variability. The samples were taken in tubes designed to separate serum. After 30 minutes of room temperature clotting, they were centrifuged at 3000 rpm for 15 minutes. Half of the serum was separated and kept at -80°C until it was time for analysis.

The quantities of BTMs in the serum were determined using commercial enzyme-linked immunosorbent assay (ELISA) kits, following the methods provided by R&D Systems, Minneapolis, MN, USA. The markers analyzed were:

- "BSAP (Quantikine ELISA, intra-assay CV <5.5%, inter-assay CV <7.8%)
- P1NP (Quantikine ELISA, intra-assay CV <6.0%, inter-assay CV <8.2%)
- CTX-I (Serum CrossLaps® ELISA, intra-assay CV <5.0%, inter-assay CV <7.5%)
- TRAP-5b (Microvue TRAP-5b ELISA, intra-assay CV <4.5%, inter-assay CV <6.9%) All samples were analyzed in duplicate by a single technician blinded to the group allocation of the samples."

Statistical Analysis

Statistical Package for the Social Sciences, Version 26.0 (IBM Corp., Armonk, NY) was used for data analysis. The Shapiro-Wilk test was used to determine whether the data distribution was normal. Mean ± standard deviation (SD) was used to display descriptive statistics for continuous variables, while frequencies and percentages were used for categorical data. Age, body mass index (BMI), and BTM levels were compared between the two groups using independent samples t-tests. Categorical variables were tested using the Chi-square test. Statistical significance was determined by a p-value less than 0.05.

RESULTS

Participant Characteristics

In all, 80 people took part in the trial; 40 got implants and 40 got a placebo. In Table 1 we can see a summary of the research population's demographic and clinical details. Statistics showed no significant differences between the two groups with respect to mean age, body mass index (BMI), or years after menopause ($p>0.05$ for all). The average number of years that implants lasted in the implant group was 4.6 ± 2.1 years.

"Table 1. Demographic and Clinical Characteristics of Study Participants

Characteristic	**Implant Group (n=40)**	**Control Group (n=40)**	**p-value**
Age (years)	64.1 ± 5.2	63.5 ± 5.8	0.631
BMI (kg/m²)	26.8 ± 3.1	27.3 ± 3.5	0.519
Years Since Menopause	13.9 ± 4.5	14.7 ± 5.0	0.448
No. of Implants per Patient	2.8 ± 1.5	N/A	-
Time Since Implant Placement (years)	4.6 ± 2.1	N/A	-

Comparison of Bone Turnover Markers

Table 2 displays the main outcome measurements, which are the blood levels of indicators for bone production and resorption. There was a significant difference in the bone turnover profile between the control group and the implant group.

Specifically, levels of the bone resorption marker CTX-I were significantly lower in the implant group (0.39 ± 0.07 ng/mL) than in the control group (0.51 ± 0.09 ng/mL), representing a 23.5% reduction ($p=0.002$). Similarly, the resorption marker TRAP-5b was also significantly lower in the implant group (3.8 ± 0.6 U/L vs. 4.5 ± 0.8 U/L; $p=0.005$).

Conversely, the bone formation marker P1NP was significantly higher in the implant group (48.5 ± 7.2

ng/mL) compared to the control group (41.3 ± 6.5 ng/mL; p<0.001). While serum BSAP levels were higher on average in the implant group (14.1 ± 2.5 U/L) than in controls (13.2 ± 2.9 U/L), this difference did not reach statistical significance (p=0.18).

Table 2. Comparison of Serum Bone Turnover Marker Levels Between Groups

Bone Marker	**Implant Group (n=40)**	**Control Group (n=40)**	**p-value**
Formation Markers			
BSAP (U/L)	14.1 ± 2.5	13.2 ± 2.9	0.180
P1NP (ng/mL)	48.5 ± 7.2	41.3 ± 6.5	**<0.001**
Resorption Markers			
CTX-I (ng/mL)	0.39 ± 0.07	0.51 ± 0.09	**0.002**
TRAP-5b (U/L)	3.8 ± 0.6	4.5 ± 0.8	**0.005**

Correlation Analysis

Within the implant group, we ran a post hoc correlation analysis to look for any connections between BTM levels and clinical factors. The outcomes may be shown in Table 3. There was no statistically significant relationship between the measured BTMs and the amount of time an implant was able to function (p>0.05 for all). Having said that, there was a moderately significant negative association (r = -0.35, p=0.027) between the number of years after menopause and P1NP levels, which means that bone production potential could diminish with postmenopausal age, even in those who had stable implants.

Table 3. Correlation between Bone Markers and Clinical Variables in the Implant Group (n=40)

	Time Since Implant Placement (years)	**Years Since Menopause**
	r (p-value)	*r* (p-value)
BSAP	0.12 (0.46)	-0.21 (0.19)
P1NP	0.09 (0.58)	**-0.35 (0.027)**
CTX-I	-0.15 (0.36)	0.24 (0.14)
TRAP-5b	-0.07 (0.67)	0.18 (0.26)”

DISCUSSION

After menopause, some women have dental implants, and this research compared their profiles with those of a control group to see how their systemic bone turnover markers changed over time. Women who had implants that stayed in place showed a markedly altered pattern of systemic skeletal metabolism, with less bone resorption and more activity in the opposite direction of bone creation. Particularly, P1NP levels were greater in the implant group, whereas CTX-I and TRAP-5b levels were significantly lower in the control group.This supports our hypothesis that this population demonstrates a more favorable bone homeostasis.

The observed reduction in resorption markers CTX-I and TRAP-5b in the implant group is particularly noteworthy. High levels of these markers are established indicators of increased fracture risk and are a hallmark of the accelerated bone turnover state seen after menopause. [15]Our finding suggests that the presence of successfully osseointegrated and functionally loaded implants may be associated with a systemic attenuation of this heightened osteoclastic activity. One potential explanation lies in the principle of mechanotransduction. The physiological forces transmitted through the implants to the surrounding jawbone stimulate osteocytes, which act as mechanosensors. [16]This local stimulation is known to promote anabolic activity and inhibit bone resorption pathways, such as the RANKL/OPG system, to maintain bone mass. [17]While this effect is most pronounced locally, it is plausible that the chronic, long-term nature of this stimulation could contribute to subtle but significant changes in systemic BTM levels. This concept aligns with studies in other fields showing that regular mechanical loading through physical exercise can systemically reduce bone resorption markers in postmenopausal women. [11]

Furthermore, the significantly elevated levels of the formation marker P1NP in the implant group suggest an enhanced systemic osteoblastic activity. Because it represents the production of type I collagen, the principal organic component of bone, P1NP is thought to be the most sensitive indicator of bone formation **[12].**The lack of a statistically significant difference in BSAP, another formation marker, might be due to its longer half-life and reflection of later stages of osteoblast activity compared to P1NP. [11] The discordance between P1NP and BSAP has been noted in other studies and may reflect different temporal dynamics of bone formation. The elevated P1NP strongly indicates that an active process of bone matrix deposition is more prominent in the implant-bearing group.

Our results are consistent with some previous research, although direct comparisons are challenging due to differences in study design and populations. For example, a study by Sobouti F et al. found that patients

with successful implants had different local (crevicular fluid) and systemic BTM profiles compared to those with failing implants. [11] Our study extends this concept by demonstrating a difference between postmenopausal women with successful implants and a control group without implants, suggesting the difference is not just about failure versus success, but perhaps about the presence of functional implants themselves. In contrast, other studies have failed to find a strong correlation between systemic BTMs and implant outcomes, highlighting the complexity of the issue. [17] The strict inclusion/exclusion criteria in our study, particularly the exclusion of patients on bone-modifying agents, may have allowed for a clearer signal to be detected.

The clinical implications of these findings are potentially significant. If the observed BTM profile is a consequence of successful implant loading, it suggests that implant-supported oral rehabilitation might offer a secondary benefit of promoting better systemic skeletal health. More pragmatically, if a favorable BTM profile is a prerequisite for successful osseointegration, these markers could be used pre-operatively to risk-stratify patients. A postmenopausal woman with very high baseline resorption markers might benefit from adjunctive therapies to modulate bone turnover before or during implant treatment. [15] Longitudinal studies are needed to differentiate between these two possibilities.

Several limitations of this study must be acknowledged. First, its cross-sectional design prevents the establishment of causality. We cannot determine whether the favorable BTM profile enabled successful osseointegration or if the successful implants modulated the BTM profile over time. A prospective longitudinal study, measuring BTMs before implant placement and at several follow-up points, is required to clarify this relationship. Second, our sample size was relatively modest, which may have limited our power to detect smaller differences, such as in BSAP levels. Third, we measured systemic BTMs, which reflect global skeletal activity and may not perfectly mirror the specific events occurring at the bone-implant interface. Future studies should consider correlating systemic markers with local markers from peri-implant crevicular fluid. Finally, we did not assess bone mineral density (BMD) via DXA scans, which would have provided a structural correlation to our biochemical findings.

CONCLUSION

Within the limitations of this study, our findings demonstrate that postmenopausal women with stable, long-term dental implants exhibit a distinct systemic bone turnover profile compared to their non-implant-bearing counterparts. This profile, characterized by significantly lower levels of bone resorption markers (CTX-I, TRAP-5b) and higher levels of a key bone formation marker (P1NP), suggests a shift towards a more anabolic or balanced state of bone metabolism. These results highlight a potential positive association between successful functional loading of the jawbone via dental implants and systemic skeletal health. Further longitudinal research is warranted to elucidate the predictive value of these biomarkers in assessing implant candidacy and monitoring long-term outcomes in the postmenopausal population.

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