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Original Article

Evaluation of Bone Turnover Indicators before Dental Implant Insertion in Osteoporotic Patients: A Case-Control Investigation

Giorgiana Corina Muresan[1], Mihaela Hedesiu[2], Ondine Lucaciu[1*], Sanda Boca[3], Nausica Petrescu[1]

[1] Department of Oral Health, Iuliu Hatieganu University of Medicine and Pharmacy, 400012 Cluj-Napoca, Romania.
[2] Department of Oral Radiology, Iuliu Hatieganu University of Medicine and Pharmacy, 400006 Cluj-Napoca, Romania.
[3] Interdisciplinary Research Institute in Bio-Nano-Sciences, Babes-Bolyai University, 400271 Cluj-Napoca, Romania.

***E-mail** ✉ ondineluc@yahoo.com

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ABSTRACT

Understanding bone biology is crucial to ensure the success and longevity of dental implants. This study aimed to evaluate the use of bone turnover markers (BTMs) as a diagnostic method to assess bone quality in patients undergoing dental implant surgery before treatment. This single-center, case-control, cross-sectional study conducted at a private institution in Chennai included patients with a single edentulous space lasting for at least 6 months. Saliva samples were collected alongside routine blood tests before implant surgery to measure BTM levels using enzyme-linked immunosorbent assay (ELISA). Data analysis was performed using an independent t-test in SPSS software. The study found that bone turnover markers such as BALP, Osteocalcin, CTX-1, and NTX-1 were elevated in osteoporotic patients ($P < 0.05$), suggesting a higher likelihood of dental implant failure. Evaluation of bone turnover markers in saliva provides an effective approach to determining bone quality for dental implant placement, supporting treatment planning. The variation in BTM levels offers a promising biological indicator for assessing jawbone health, complementing radiological assessments for implant placement.

Keywords: Osteoporosis patient, Bone turnover marker, Innovation, Dental implant.

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Introduction

Bone turnover markers play a crucial role in bone resorption and formation, reflecting the ongoing process of bone remodeling [1]. This process is the primary mechanism behind osteoporosis. Osteoporosis is a systemic skeletal condition characterized by weakened, brittle bones because of the loss of bone tissue, resulting in an elevated risk of fractures. The World Health Organization (WHO) defines osteoporosis as a condition where bone formation decreases by approximately 25%, while osteopenia refers to a decline in bone mineral density by 10-25%. Bone is a dynamic tissue, undergoing constant cycles of regeneration and degradation [2]. Research on muscle biopsies from individuals with osteoporosis has shown that muscle fibers, particularly type II fibers, shrink, with the extent of atrophy correlating to the level of bone mineral density loss [3].

Osteoporosis develops when the formation of new bone is impaired, or when the loss of old bone cannot be compensated for Dai *et al.* [4]. Several factors contribute to osteoporosis, including inadequate calcium intake, poor nutrition, estrogen deficiency following menopause, genetic factors, and

gastrointestinal surgeries [5, 6]. Osteoporosis can affect individuals of any race, though older women, particularly those of white or Asian descent who have gone through menopause, are at the highest risk. Early stages of osteoporosis typically present no symptoms, but as bones become more fragile, clinical signs appear. These may include back pain from fractured or collapsed vertebrae, height loss, a hunched posture, and an increased tendency to suffer fractures [7]. Weight-bearing exercise, a nutritious diet, and medical treatments can help strengthen weakened bones or slow further bone loss [8, 9].

The development of osteoporosis is influenced by various factors, and accumulating research indicates its potential connection to oral health problems such as periodontal disease, reduced jawbone density, and tooth loss [10]. Osteoporosis can impact osseointegration, a crucial factor in the success of dental implant procedures. The balance between bone formation and resorption can be assessed through bone turnover markers [11]. In recent years, numerous biomarkers have been utilized to accurately and sensitively measure bone growth and resorption [12]. Biomarkers for bone formation include alkaline phosphatase (ALP), procollagen type 1 N-terminal propeptide (P1NP), bone-specific alkaline phosphatase (BALP), osteocalcin (OC), and procollagen type 1 C-terminal propeptide (P1CP). Indicators of bone resorption include tartrate-resistant acid phosphatase 5b (TRAP 5b), hydroxyproline (HYP), hydroxylysine (HYL), deoxypyridinoline (DPD), and pyridinoline (PYD). Several proteins, such as osteoprotegerin (OPG), RANKL, dickkopf-1 (DDK-1), and sclerostin, regulate the processes of bone resorption and formation [13-15].

Saliva has been suggested as a diagnostic medium for various systemic diseases. In a study, bone turnover markers were measured from the saliva of both healthy and osteoporotic individuals. These biomarkers offer an early assessment of the bone turnover rate, an evaluation that can be reliably obtained through DXA. Thanks to the extensive expertise and research capabilities of our team, we have been able to produce high-quality publications on this topic [16-31]. The success of dental implants is primarily determined by osseointegration, and this study's main objective is to utilize bone turnover markers as a diagnostic tool to evaluate bone quality in patients scheduled for dental implant surgery before the procedure.

Materials and Methods

Patient selection

A case-control study was carried out in the prosthodontics department of a university hospital. G Power software was utilized to calculate the required sample size, which included 80 patients, divided into two groups: 40 with diagnosed osteoporosis and 40 without any signs of osteoporosis. All participants had a single edentulous space lasting 1 to 2 years, had not undergone any osteoporosis treatment, and didn't display objective or subjective symptoms such as back pain caused by a collapsed or fractured vertebra, loss of height over time, or a hunched posture (**Figure 1**). Patients with multiple missing teeth, long-term edentulous areas, extensive edentulism, or periodontal issues were excluded from the study. All selected participants were fully informed about the research and provided voluntary, written consent.

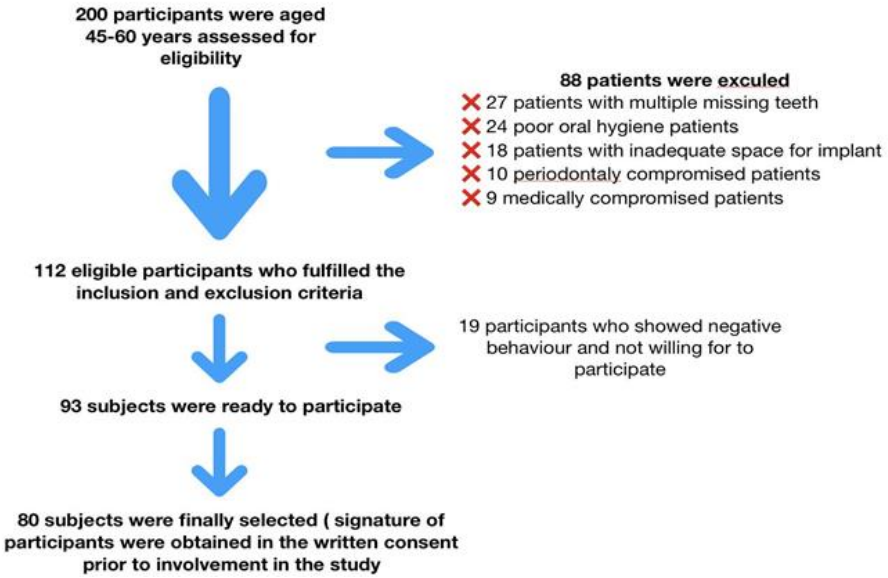

Figure 1. Criteria for patient inclusion.

Study design

Case-control study

Measurement of bone turnover markers

Bone turnover marker (BTM) levels in saliva samples were measured using enzyme-linked immunosorbent assay (ELISA), conducted alongside routine blood tests before implant surgery. A morning sample was collected from participants who had fasted and refrained from physical activity for 24 hours as instructed. Saliva samples were stored at -70 °C until analysis. Osteocalcin (OC) and osteopontin, both specific bone formation markers, were evaluated.

The human alkaline phosphatase (ALP) ELISA kit, purchased from Abbkine (catalog number KTE63711), was used following the manufacturer's protocol. The assay utilized a competitive inhibition enzyme immunoassay technique. The microtiter plate was pre-coated with antibodies, and both samples and standards were processed simultaneously. After adding the secondary antibody conjugated with horseradish peroxidase, incubation followed. A specific substrate for the enzyme was added, and color development was monitored. The intensity of the color was measured using an ELISA plate reader at four hundred fifty nm. The same procedure was applied to other biomarkers such as NTX, osteopontin, and osteocalcin.

The reference ranges for alkaline phosphatase (BALP) and crosslinked type I collagen N-telopeptide (NTX) were established based on healthy individuals' mean values (mean ± 1.96 SD) [17]. The typical BTM ranges were: for BALP, 3.7–20.9 ng/ml for men and 3.9–14.5 ng/ml for women; and for NTX, 9.5–17.7 ng/ml for men and 7.5–16.5 ng/ml for women. Any BTM result falling outside the normal range was categorized as abnormal.

Statistical analysis

Statistical analysis was performed using SPSS software (Statistical Package for the Social Sciences, version 20.0 for Windows, SPSS Inc., Chicago, USA). The bone turnover marker levels in healthy versus osteoporotic patients were compared. Initially, data were entered into Microsoft Excel 2016 (Office 10) and then exported for statistical analysis using SPSS version 20.0. The data were organized and analyzed using the Independent T-test, with a significance level set at $P < 0.05$.

Results and Discussion

In healthy individuals, all markers were within the normal range, while individuals with osteoporosis exhibited elevated marker levels. The difference in marker values between the healthy and osteoporotic groups was found to be statistically significant ($P < 0.05$) (**Table 1**).

Table 1. Comparison of bone turnover markers for normal and osteoporosis patients.

Markers	Group	Mean ± SD	Standard error	95% Ci (Upper)	95% (Lower)	T-value	P-value
BALP	Healthy (n = 40)	22.92 ± 3.75	0.594	-11.77	-15.214	-15.598	0.00*
	Osteoporotic (n = 40)	36.42 ± 3.97	0.628	-11.77	-15.214	-15.598	0.00*
Osteocalcin	Healthy (n = 40)	7.43 ± 3.61	3.618	-13.42	-15.957	-23.131	0.00*
	Osteoporotic (n = 40)	22.12 ± 1.74	1.744	-13.42	-15.964	-23.131	0.00*
Osteopontin	Healthy (n = 40)	12.58 ± 2.92	0.463	-7.4	-9.47	-16.2	0.00*
	Osteoporotic (n = 40)	21.02 ± 1.50	1.507	-7.39	-9.48	-16.2	0.00*
NTX-1	Healthy (n = 40)	12.9 ± 2.69	2.692	-8.07	-10.21	-17.043	0.00*
	Osteoporotic (n = 40)	22.04 ± 2.06	2.066	-8.07	-10.21	-17.043	0.00*

*Significant at $P < 0.05$; P-value was derived from an independent t-test.

The average bone alkaline phosphatase (BALP) level increased from 22.92 ± 3.75 to 36.42 ± 3.97 when comparing normal individuals with those diagnosed with osteoporosis. In individuals with normal liver function, approximately 50% of ALP levels in the blood originate from bone. The typical BALP readings for males and premenopausal women were 24.97 ± 7.0 U/L and 19.75 ± 5.6 U/L, respectively, with a detection limit of 0.7 U/L for BALP. Similar to this study, BALP is commonly used as an indicator of osteoblastic activity, particularly in the treatment of osteoporosis in both premenopausal and postmenopausal women [32]. Higher BALP activity has been observed in osteoporotic women aged over 59, reinforcing the findings of the current study [33].

Osteocalcin (OC) levels increased from 7.43 ± 3.61 to 22.12 ± 1.74 in osteoporotic individuals. Osteocalcin, a 49-amino acid protein also known as bone gamma-carboxyglutamic acid-containing protein, plays a crucial role in regulating bone mineralization, metabolism, and calcium ion balance, as produced by osteoblasts [34]. Research has shown that increases in

bone mineral density (BMD) following osteoporosis treatment with bone-forming drugs are closely linked to serum OC levels. Serum OC is recognized as a specific biomarker of osteoblast activity for evaluating bone resorption in osteoporosis. Numerous studies have emphasized the importance of osteocalcin as a biomarker for assessing the effectiveness of treatments in promoting bone growth [35].

In this study, osteopontin (OP) levels were found to be 12.58 ± 2.92 in healthy individuals and 21.02 ± 1.50 in osteoporotic patients. OP, a phosphorylated glycoprotein, is secreted by various cells, including bone cells, activated T-lymphocytes, specialized epithelial cells, and macrophages [36]. A recent study suggested that women with excessive OP expression are more susceptible to postmenopausal osteoporosis compared to those with normal OP levels [37]. Plasma OP concentrations can be utilized as a biomarker to assess the effectiveness of intermittent parathyroid hormone therapy in treating menopausal osteoporosis.

The normal NTX-1 value was 12.92 ± 2.69, while in osteoporotic patients, it was found to be 22.04 ± 2.06. NTX-1 is a byproduct of type 1 collagen breakdown, which constitutes over 90% of the organic matrix in bone, formed from procollagen type 1.

Bone turnover markers are noticeably higher in patients with osteoporosis compared to the general healthy population. Achieving primary implant stability is essential for successful peri-implant healing. A stable implant, which experiences minimal micromotion between the bone and implant (such as during angiogenesis and osteogenesis), is crucial for promoting tissue growth around the implant and ensuring positive outcomes. Several local factors, in addition to systemic ones, influence the failure or success of implant placement, including the number and distribution of dental implants, periodontal health, occlusion, and biting forces.

Despite a growing body of research, only a limited number of studies have focused on how changes in mandibular bone metabolism are impacted by systemic bone metabolic diseases, especially concerning endosseous implant placement and overdenture insertion. Research investigating the link between skeletal osteoporosis, oral osteoporosis, and dental implant loss due to low bone quality and quantity has found no direct connection between systemic BMD status, mandibular BMD, bone quality, and implant failure. Researchers proposed that radiographic bone quality assessments, which are more useful than peripheral bone density measurements, offer the best approach for evaluating bone quality before implant insertion [38].

This study introduces a simpler method of evaluating bone metabolism through salivary biomarkers, which have proven to be as effective as radiographic techniques. Further research by Von Wowern and Gotfresden [39] explored the marginal bone loss around dental implants in osteoporotic edentulous jaws. Their findings indicate that while patients with more advanced osteoporosis experience greater marginal bone loss, endosseous implants remain a viable treatment option for these individuals. Since bone turnover markers reflect bone remodeling, which has been assessed using ELISA from salivary indicators, it is hypothesized that the increased bone turnover corresponds with a decrease in bone mineral density (BMD).

Bone quality is a multifaceted characteristic that varies significantly among individuals, making it difficult to categorize universally. This study primarily focused on bone turnover markers (BTMs), which are key clinical indicators of bone health. However, an elevation in BTM levels has not been consistently proven to be a reliable predictor of fractures in prospective studies [40]. A more comprehensive approach to diagnosing jaw bone quality might involve combining radiographic techniques with biological assessments, such as analyzing bone turnover markers.

Patients with elevated BTM levels demonstrated significantly lower cancellous bone density compared to those with normal BTM levels, suggesting that the cancellous bone quality was poorer at baseline in the abnormal group. To accurately evaluate bone strength, it is crucial to assess both BTMs and cancellous bone density, particularly for female patients undergoing implant procedures.

Traditionally, radiographic methods have been used to assess jaw bone quality; however, they do not provide a fully accurate evaluation of bone structure. Utilizing salivary bone turnover markers for bone quality assessment can address this gap. This approach not only helps in predicting the early stages of osteoporosis, particularly in women but also supports better patient management and prevention strategies for the disease.

Conclusion

Bone turnover markers offer significant potential as clinical biomarkers for assessing bone health before implant procedures. Additional animal and clinical studies are required to further explore their utility. The variation in bone turnover marker levels presents a promising biological method for evaluating jawbone conditions, complementing radiological assessments in determining suitability for implant placement.

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