Original Article

Carboxyterminal-Telopeptide Pyridinoline Cross-Links of Type I Collagen (ICTP) as a Diagnostic Biomarker for Periodontitis and Osteoporosis in Postmenopausal Women

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Abstract

Background: The diagnosis of osteoporosis and periodontitis at a molecular level is still compromised and the clinical techniques may be prone to errors due to different factors. Available biomarkers in the oral biofluid such as carboxyterminal-telopeptide pyridinoline cross-links of type I collagen (ICTP) could provide solutions for these issues. **Objective:** Is to assess the diagnostic ability of salivary ICTP in predicting osteoporosis and periodontitis. **Materials and Methods:** This study was conducted on 160 postmenopausal women with ages ranging from 50 to 70 years old, divided into four groups: the first group: women with osteoporosis and periodontitis, the second group: women with osteoporosis and periodontally healthy, the third group: women non-osteoporosis with periodontitis, and the fourth group: women systematically and periodontally healthy. Unstimulated saliva was taken, and a periodontal examination was performed. The salivary level of ICTP was estimated by an enzyme-linked immunosorbent assay (ELISA). **Results:** The results showed that ICTP had an excellent predictor for osteoporosis in the presence and absence of periodontitis with area under the curve (AUC; 0.962, 1.000) at the proposed cutoff point at (9.920, 7.1145), respectively. As well it was a very good and excellent predictor for periodontitis in the presence and absence of osteoporosis with AUC (0.892, 0.999) at the proposed cutoff point of 10.264 and 6.657, respectively. **Conclusion:** ICTP could be considered a predictor for the diagnosis of osteoporosis in the presence and absence of periodontitis, and in diagnosing periodontitis in the presence and absence of osteoporosis.

Keywords: Biomarkers, diagnosis, ICTP, osteoporosis, periodontitis

Introduction

Osteoporosis is defined as a bone disease that results in the fragility of bone and an increased risk of fractures in the future due to a loss of bone density and changes in the bone's microarchitecture.[1] It is caused by an imbalance between bone resorption/formation rates.[2] Vitamin D deficiency and diabetes mellitus (DM) are the contributing factors for osteoporosis.[3] Diagnosed mainly by dual-energy X-ray absorptiometry (DEXA), which is used for the measurement of bone mineral density (BMD) and considered the gold standard for osteoporosis diagnosis, it was developed in the 1980s and has become the mainstay of BMD testing.[4,5] Periodontitis is a chronic inflammatory infection that destroys the supporting structures of the teeth, resulting in bone resorption and gradual connective tissue loss,[6] marked by host-mediated inflammation of the periodontal tissue, which is conjoined with plaque biofilms, leading to progressive tooth-supporting apparatus destruction and periodontal attachment loss.[7] Postmenopausal women with a reduced BMD have a greater tendency for alveolar bone loss and clinical attachment loss (CAL)[8] because inflammatory mediators are increased in the systemic and oral bones.[9] Although periodontal disease is confined locally and osteoporosis is a systemic process, bone loss

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is characteristic in both cases.[10] Some authors suggest an association between both diseases.[11] Because their main feature is influenced by common risk factors, including age, hormonal changes, cytokine presence, and so on.[12-14] Moreover, postmenopausal women with osteoporosis are susceptible to an excessive response to dental plaque.[15]

Previous studies have shown that the immune microenvironment may play an important role in the occurrence and development of osteoporosis.[16] Estrogen deficiency during the postmenopausal period, the bone structure undergoes many changes; which ultimately lead to loss of bone mass and osteoporosis, also periodontal health might be affected; particularly if oral hygiene is poor.[17] Clinical examinations including bleeding on probing (BOP), probing pocket depth (PPD), and CAL have been used for periodontitis diagnosis in addition to radiographic evidence of alveolar bone loss. These methods are reliable but depend upon a clinician's professional experience.[18] Furthermore, before an appropriate diagnosis of periodontitis, a measurable amount of alveolar bone destruction must be established to be measured clinically, a 2–3-mm threshold change was needed before exhibiting obvious destruction. This may delay the diagnosis and treatment of both diseases.[16]

Carboxyterminal-telopeptide pyridinoline cross-links of type I collagen (ICTP) is a 12–20-kD fragment produced during the digestion of type I collagen of bone by bacteria's collagenase and trypsin.[19] Collagen type I is more abundant collagen present in osseous tissue and makes around 90% of the bone's organic matrix. It showed that ICTP is highly correlated with high/low bone turnover diseases including osteoporosis in post-menopause[20] and periodontal disease.[21]

The aim of this study is to evaluate the salivary level of ICTP in periodontitis and osteoporosis in postmenopausal women. And explore the diagnostic ability of ICTP for periodontitis and osteoporosis in postmenopausal women.

Materials and Methods

Study design

A case–control observational study was done to achieve the goal of the current research, in Baghdad teaching hospital on postmenopausal women in the age range of 50–70 years old that attended to conduct DEXA scan. An informed consent form was obtained from each participant before the enrollment of the study. The study started in January 2022 and ended in June 2022.

Case definition

The periodontitis cases included were determined according to one of the following provisions mentioned below:

1- Interdental CAL is detectable at ≥ 2 non-adjacent teeth, or
2- Buccal or oral CAL ≥ 3 mm with PPD ≥ 3 mm was detectable at ≥ 2 teeth.[22]

Additionally, all periodontitis cases were generalized (more than 30% of teeth included in loss of attachment), with unstable status (PPD ≥5 mm or PPD 4 mm with BOP). While patients with healthy periodontium should be with intact periodontium (PPD ≤3 mm and BOP ≤10%).[23]

Osteoporosis was determined by specialists depending on the score of the density of bone mass which was specified by using a (DEXA) scan depending on T-score, determined by WHO classification of BMD measurements in which the T-score was > -2.5 for osteoporosis.[24] Regarding study design and results reporting, this clinical study adheres to "STROBE, or Strengthening the Reporting of Observational Studies in Epidemiology."

Inclusion criteria

All the postmenopausal women were systematically healthy (except the case definition above), had not taken medications in the last 3 months and at least had 20 teeth.

Exclusion criteria

Patients with a history of any systemic disease, or underlying systemic disease that affects periodontal and osteoporosis status. As well as patients who have undergone any previous periodontal treatment or are under active periodontal therapy. Furthermore, the patient has taken antibiotics in the last 3 months or any drug that may affect periodontal or osteoporosis status such as corticosteroids. Females who used medications such as calcium and vitamin D, or who experienced early menopause, or underwent hysterectomy or oophorectomy, or were on hormone replacement therapy, could all have an impact on the study's findings. Smokers and alcoholics were also excluded from the study.

Grouping and sample size

After excluding patients that did not fit into the criteria, a pilot study was done on 40 samples (10 samples from each group) depending on the salivary concentration of ICTP that was investigated by enzyme-linked immunosorbent assay (ELISA) and the calculation of sample size was done by using this formula[25]:

$$\text{Sample size} = r + \frac{1}{r} \times (\text{SD})^2 \times \frac{\left(Z\beta + \frac{Z\alpha}{2} \right)^2}{d^2}$$

According to the above formula, the acceptable sample size was 156 patients which were turned into 160 to eliminate sample dropout. The sample was divided into four groups, which were distributed equally among the four groups with an allocation ratio of 1:1:1:1 three study groups and one control group, divided as follows: Forty postmenopausal women with osteoporosis and periodontitis. Forty postmenopausal women with osteoporosis and periodontally healthy. Forty postmenopausal women with non-osteoporosis and

periodontitis. Forty postmenopausal women with non-osteoporosis and periodontally healthy (control group).

Clinical periodontal examination

UNC-15 probe was used for periodontal examination which include full mouth plaque index (PLI),[26] BOP,[27] PPD,[28] and CAL.[29] This was done on six surfaces of the tooth except for plaque index done on four tooth surfaces using a disclosing agent.

Saliva collection and analysis

Three ml of unstimulated saliva was collected in a sterile container in the morning hours (9–11 AM) after rinsing their mouth with water according to the method proposed by Henson and Wong.[30] The patients were instructed not to consume any food or water or engage in oral hygiene procedures before the time of saliva collection and before the time of periodontal examination and were instructed to sit in an upright position and spit into a sterile container. The salivary sample was centrifuged for 15 min at 3000 rpm to isolate the cellular debris from salivary supernatants and the salivary fluid was stored in a clean Eppendorf tube and frozen at about -80°C. At the time of analysis, the samples were defrosted, given some time to warm up to room temperature, and centrifuged again to ensure the removal of all debris associated with the sample. Commercially available ELISA kits purchased from Shanghai YL Biont, China, were used for detecting the levels of protein in salivary samples. The analysis was done according to the manufacturer's instructions for the kit. Which depends on the biotin double antibody sandwich method to assess the Human ICTP. The ICTP was applied to the wells, which were coated previously with ICTP monoclonal antibody. Anti-ICTP antibodies were added with labeled biotin to combine with streptavidin-HRP, which makes an immune complex. The free enzymes after incubation were eliminated by washing. Finally, A and B substrates were added which turn the solution into blue in a dark field, the blue color will turn into yellow with the effect of acid. There was a positive association between the color of the solution and the ICTP concentration.

Statistical analysis

To calculate the results, Statistical Package for Social Science (SPSS) software, version no. 25, was used to analyze the findings while graph pad prism was used to draw figures. First, the Shapiro–Wilk test and Levene test were done to assess the normality of distribution and the homogeneity of the variances, respectively, descriptive statistics which include means and standard deviations were illustrated. Then to compare the measured variables between groups one-way ANOVA test was performed, and the Games–Howell test was performed to test any statistically significant difference between each group. Finally, the receiver operating characteristic (roc) curve was done to differentiate periodontal health from periodontitis in subjects with and without osteoporosis, and osteoporosis from normal subjects in subjects with and without periodontitis, as well as to assess the diagnostic ability of this biomarker in these diseases. The significance level was established at 5%.

Ethical approval

It was also conducted following ethical guidelines, including the World Medical Association Declaration of Helsinki, granted by the relevant committee of ethics in the College of Dentistry, University of Baghdad (ref. number: 449, January 19, 2022).

Result

A total of 160 postmenopausal women with an age range of 50–70 years were included in the present study and they were distributed equally among the four groups. Concerning the demographic data, the mean age and BMI among groups were nonsignificant among groups. Whereas the clinical periodontal parameters revealed a significant difference among groups, since the osteoporotic with periodontitis group had significantly higher, PLI, BOP, CAL, and salivary ICTP among groups. As shown in Table 1 and Figure 1(A–D), the multiple comparisons of PLI %, BOP %, and PPD showed a significant difference between periodontitis groups and periodontally healthy groups regardless of the presence or absence of osteoporosis with a non-significant difference between periodontitis group. Furthermore, Figure 1(D)

Table 1: Descriptive statistics of study groups

Parameter	Groups				
	Osteoporosis + periodontitis	Osteoporosis + healthy periodontium	Non-osteoporosis + periodontitis	Control	*P* value
Age	60.2093 ± 6.367	56.95 ± 4.899	58.9756 ± 5.096	53.41 ± 4.35	0.25
BMI	28.8860 ± 2.101	29.6560 ± 2.77	28.5803 ± 2.252	29.39 ± 1.729	0.221
PLI	92.18 ± 15.66	14.74 ± 2.53	82.85 ± 8.4	15.02 ± 2.1	0.000
BOP	59.55 ± 2.82	5.32 ± 1.05	46.18 ± 2.60	3.45 ± 0.18	0.000
PPD	4.00 ± 0.577	1.725 ± 0.67	4.14 ± 0.69	1.71 ± 0.6	0.000
CAL	5.62 ± 1.96	—	5.34 ± 1.11	—	0.64
ICTP	12.43 ± 1.86	9.73 ± 1.26	8.73 ± 0.71	4.65 ± 0.23	0.000

PLI: plaque index, BOP: bleeding on probing, PPD: probing pocket depth, CAL: clinical attachment loss, ICTP: pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen

ANOVA test was done for all comparisons except CAL done by unpaired *t* test

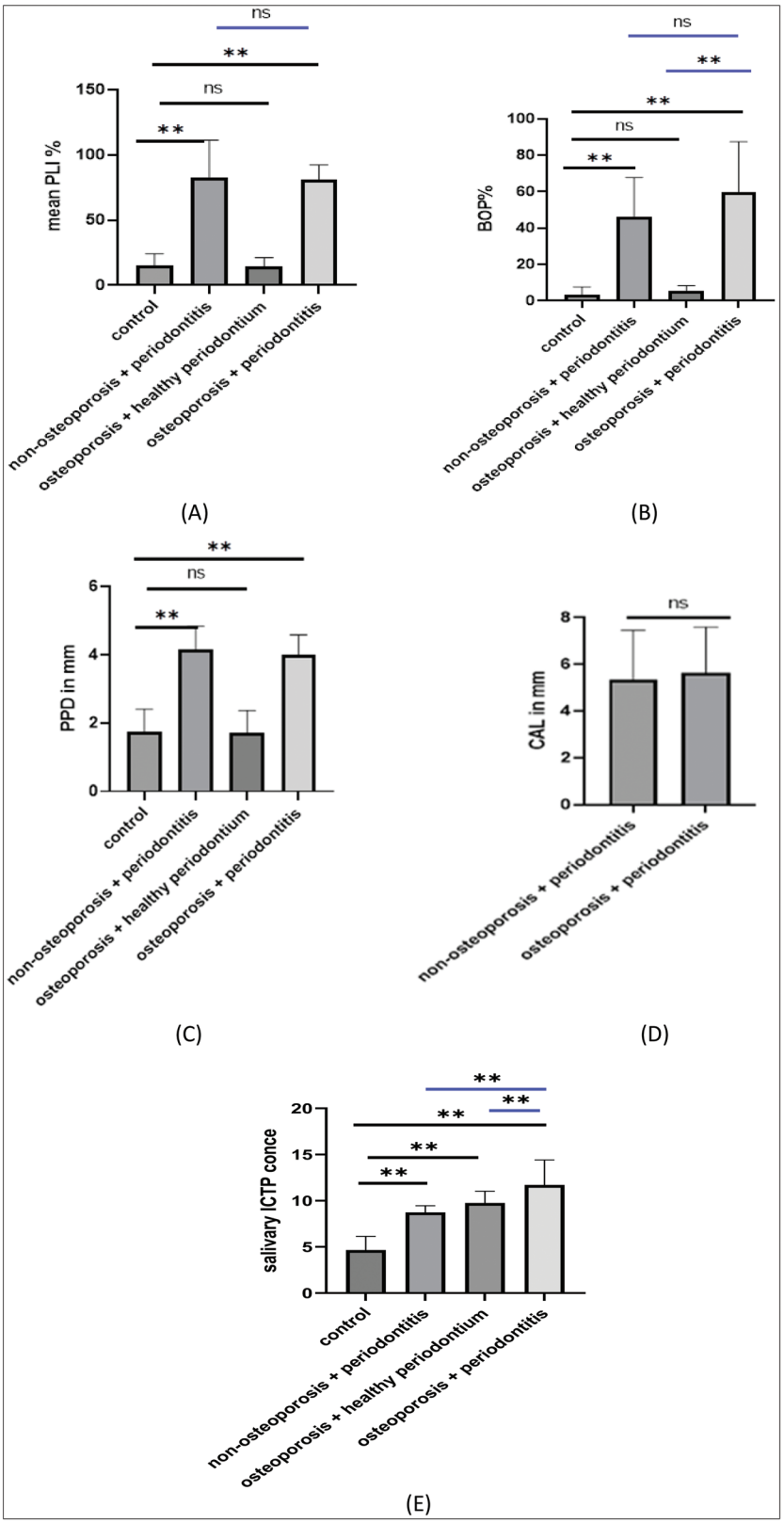

Figure 1: Multiple Games–Howell test comparison of periodontal parameters and salivary ICTP concentration in ng/mL among study and control groups. (A), (B), and (C) illustrate the multiple comparisons of plaque index percentage (PLI %), bleeding on probing percentage (BOP %), and probing pocket depth (PPD). (D) Represent a comparison of clinical attachment loss (CAL). (E) revealed a salivary concentration of Pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (ICTP) in ng/mL. The black line indicates comparisons with a control group while the blue line indicates comparisons between study groups. ** *P* value < 0.001, ns: nonsignificant at *P* value ≥ 0.05

represents a comparison of CAL with the non-significant difference between the periodontitis groups. Finally, regarding the comparison of salivary concentration ICTP in Figure 1(E) it was statistically significant between the control group and all other groups, additionally a significant difference between osteoporosis with periodontal health and osteoporosis with periodontitis

Based on the result from the ROC curve, which is used to differentiate health from disease for both periodontitis and osteoporosis, it was found that ICTP was an excellent biomarker for diagnosis of osteoporosis regardless of the presence or absence of periodontitis at the proposed cutoff point (9.920, 7.1145) ng/mL in the presence and absence of periodontitis, respectively, as shown in Table 2 and Figure 2(A and B). Whereas for diagnosis of periodontitis, it was found that ICTP was a very good biomarker for diagnosis of periodontitis in the presence of osteoporosis at the proposed cutoff point (10.264). Besides, it was an excellent biomarker for the diagnosis of periodontitis in systematically healthy at the proposed cutoff point (6.657), as revealed in Table 2 and Figure 3(A and B).

Discussion

Developing a new method at a molecular level to diagnose periodontitis and osteoporosis is an urgent issue. Consequently, the current study was conducted on postmenopausal women to investigate the diagnostic ability of ICTP to differentiate periodontitis and osteoporosis from healthy status. Saliva is a highly valuable tool for the early detection and monitoring of oral and systemic diseases.[31] Interestingly, patients with osteoporosis and periodontitis had significantly higher salivary levels of ICTP compared to patients with osteoporosis or periodontitis. The elevated level of ICTP indicated a degradation product of type I collagen found in bone, which was present in higher quantity in osteoporosis and periodontitis patients, while periodontally healthy patients have the lowest concentration. Besides, the present study found that ICTP is an excellent biomarker in diagnosing osteoporosis in the presence and absence of periodontitis. Whereas for periodontitis, ICTP seemed to be a very good biomarker for diagnosing periodontitis in the presence of osteoporosis and an excellent biomarker in the absence of osteoporosis.

This could be attributed to the fact that appeared in recent years, that the same cytokines affect bone and immune cells, which have similar progenitor cells in common. Osteoporosis and periodontal disease are functionally related, and immune cell infiltration is crucial for the onset and progression of both conditions.

Table 2: Diagnostic ability of salivary ICTP for osteoporosis and periodontitis

Biomarker and disease	Sensitivity	Specificity	AUC	95%	Cutoff point (ng/mL)
ICTP in osteoporosis and periodontitis	0.953	0.976	0.962	0.913–1.000	9.920
ICTP in osteoporosis with healthy periodontium	1.000	1.000	1.000	1.000–1.000	7.1145
ICTP in periodontitis with osteoporosis	0.930	0.825	0.892	0.972–0.812	10.264
ICTP in periodontitis and systematically healthy	0.976	0.974	0.999	0.997–1.000	6.657

AUC: area under the curve, ICTP: pyridinoline cross-linked carboxyterminal telopeptide of type I collagen

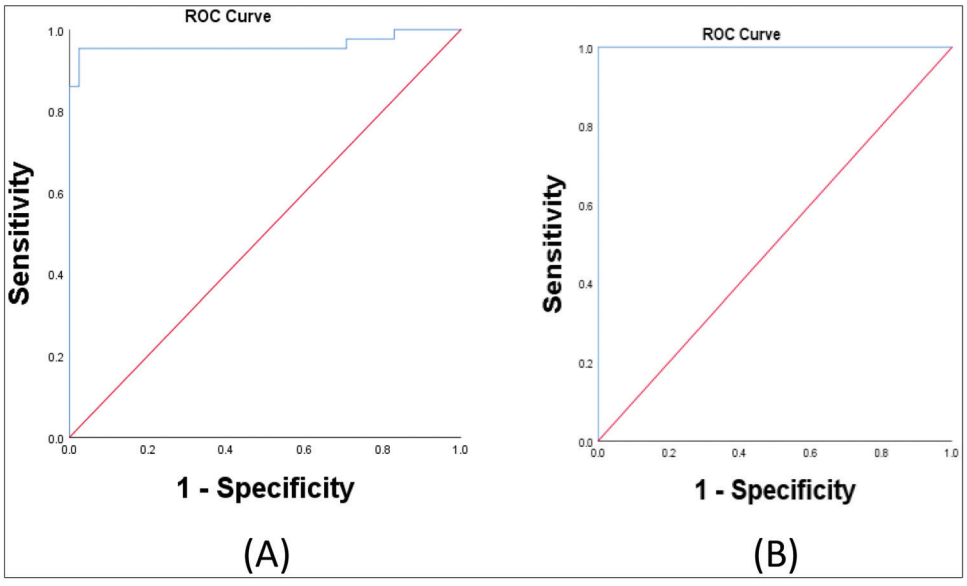

Figure 2: ROC curve of salivary ICTP for osteoporosis vs. control in patients with (A) periodontitis and (B) healthy periodontium. ROC = receiver operating characteristic

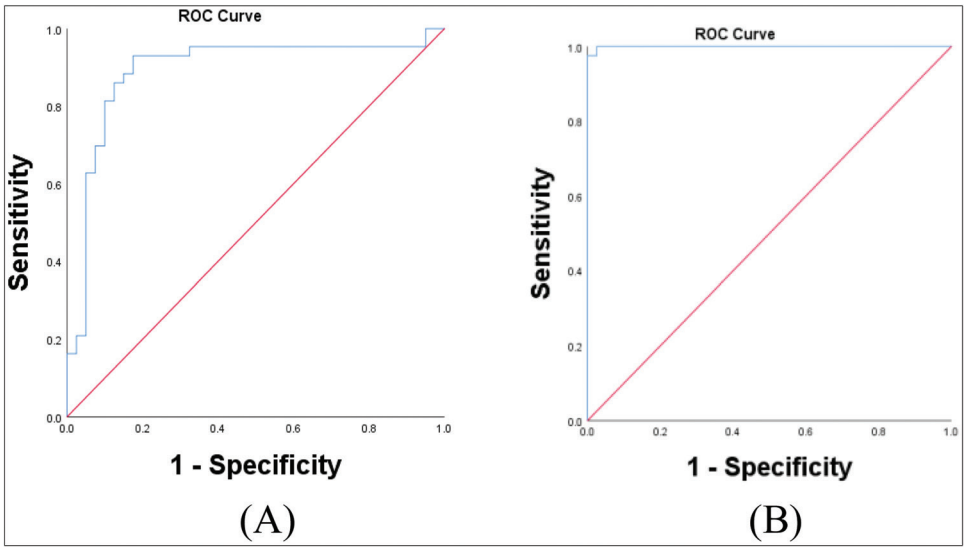

Figure 3: ROC curve of salivary ICTP for periodontitis vs. control in patients with (A) osteoporosis and (B) systemically healthy. ROC = receiver operating characteristic

Osteoblasts' and osteoclasts' homeostasis is regulated by factors including the balance of Th1/Th2/Treg cells, inflammatory T cells (Th17), and macrophages, which in turn impacts osteoporosis and periodontal disease.[16,32] Furthermore, menopause affects a woman's oral health, this alteration includes gingival inflammation and calculus accumulation.[33]

Concerning clinical periodontal parameters, PLI, BOP, and PPD were significantly higher in periodontitis compared with the healthy periodontium group irrespective of the presence or absence of osteoporosis. Because dental biofilm or plaque is the primary cause of periodontal disease. The subgingival microbiome's main periodontal pathogens have been found to have some degree of virulence, and they have been linked to the pathophysiology and etiology of the condition substantially.[34] Whereas for BOP, and probing pocket depth could be credited to the local tissue response change due to systemic inflammatory mediators such as cytokines (e.g., tumor necrosis factor and interleukins [IL-1β and IL-6] known to be higher in patients with periodontitis and patients with systemic bone loss).[35,36] This coincides with a study done by Juluri *et al.*[17] in 2015 who showed no clinical significance regarding PLI, or BOP and PPD in postmenopausal women with periodontitis irrespective of the presence or absence of osteoporosis. And studies done by Mahmood[37] and Abdulmajeed[38] showed a significant difference in PLI, BOP, and PPD between periodontitis and the healthy group.

A point that should be considered, the result of ICTP in the current research seems to be more promising since it can make a diagnosis for a disease even with the presence of another disease, also it is cost-effective, which is considered a strong point for the present study. On the contrary, some authors reported that when using biomarkers in the diagnosis, their vulnerability to certain local and systemic diseases may affect their concentration in the oral fluids; hence, their accuracy could be compromised.[39,40] Additionally, the high number of study participants according to the previously determined sample size makes the result more relevant. Moreover, the use of the ROC test for salivary ICTP not only for determining sensitivity and specificity but also for comparing the level of biomarkers in health and disease, which was not previously considered regarding this biomarker in both diseases. However, the study was done on postmenopausal women only as osteoporosis is mostly associated with it, and this might be considered a limitation that should be exceeded in future studies concerning the validity of this biomarker in the diagnosis of the disease of periodontium. Ultimately, the findings of the current study concerning the diagnosis of both diseases were unique as no available literature regarding salivary ICTP in both diseases to compare with it; however, translation of the results into clinical applications requires validation by further trials.

Conclusion

The present investigation revealed that ICTP was statistically significant between the control group and all other groups, additionally a significant difference between osteoporosis with periodontal health and osteoporosis with periodontitis. Furthermore, it had an excellent diagnostic ability in diagnosing osteoporosis in the presence and absence of periodontitis, as well as in diagnosing periodontitis in the presence or absence of osteoporosis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Authors' contributions

All authors contributed equally to the data collection, examination, manuscript writing, reading, and approving the final version of the manuscript.

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