RESEARCH ARTICLE

Association of periodontitis with serum osteoprotegerin level in type 2 diabetic postmenopausal women

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Abstract

Objective: To evaluate the association of periodontitis with serum osteoprotegerin level according to glycaemic state in postmenopausal type 2 diabetic women.

Method: The case-control study was conducted from June 2019 to May 2020 at the National Diabetes Centre, Mustansiriyah University, Baghdad, Iraq, and comprised postmenopausal diabetic women with good glycaemic control in group A, diabetic women with poor glycaemic control in group B, and non-diabetic healthy controls in group C. Participants were inducted by using the consecutive sampling technique. Assessment of periodontitis was done by measuring probing pocket depth, gingival recession and clinical attachment level. The ratio between serum osteoprotegerin level and glycated haemoglobin was calculated for all the subjects. Data was analysed using SPSS 24.

Results: Of the 150 subjects, 57(38%) were in group A with mean age 57.39±5.89 years, 43(28.7%) were in group B with mean age 58.91±4.95 years, and 50(33.3%) were in group C with mean age 54.92±4.62 years. Probing pocket depth, clinical attachment level and serum osteoprotegerin exhibited higher values in groups A and B compared to group C, and in group B compared to group A ($p<0.001$). There was a significant positive correlation between Probing pocket depth and serum osteoprotegerin in all groups ($p<0.05$).

Conclusion: Periodontal parameters and serum osteoprotegerin level were significantly higher in diabetic women, especially in those with poor glycaemic control, than in healthy controls, and serum osteoprotegerin level showed a significant positive correlation with probing pocket depth in all the studied groups.

Key Words: Glycated Haemoglobin, Osteoprotegerin, Gingival Recession, Glycaemic, Postmenopausal, Diabetes

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Introduction

Periodontitis (PD) is a component of the global burden of chronic diseases and is characterised by progressive destruction of the tooth-supporting apparatus[1]. It is well-established that there is a constant renewal of bones, and any bone in a healthy adult indicates a balance between resorption by osteoclasts and reformation by osteoblasts. Type 2 diabetes mellitus (T2DM), the most common metabolic disease, is characterised by disturbed homeostasis of bone formation and resorption in favour of bone loss [2]. Many studies have reported a link between T2DM and PD, but the mechanism involved in such a link remains to be elucidated[3].

Osteoprotegerin (OPG) is a soluble glycoprotein that is a member of the tumour necrosis factor (TNF) receptor superfamily and has an inhibitory effect on osteoclast differentiation and, thus, on bone resorption. This effect is by way of acting as a decoy receptor for a ligand that stimulates osteoclastogenesis, and so it decreases the ligand's action. The ligand is called receptor activator of nuclear factor-κB (RANKL) and by blocking the activity of RANKL, OPG would inhibit osteoclast differentiation[4]. Consequently, OPG level and its balance with RANKL are believed to have a potential role in bone destruc¬tion in PD[5]. Some studies have demonstrated that serum OPG level was increased in T2DM patients[6] or in pre-diabetic patients,[7] while a more recent study reported no significant increase in OPG level in T2DM patients[8].

A poor glycaemic state of T2DM patients, as determined by a higher glycated haemoglobin (HbA1c%) was noticed as a strong predictor of many diabetic complications[9]. It was also observed that patients with a well-controlled glycaemic state showed a slower rate of PD than the poorly-controlled diabetics, and, even more, a better glycaemic control could be attained after treating PD[10]. Additionally, the prevalence of PD in T2DM patients was reported to be influenced by age and gender[11].

The current study was planned to evaluate the association of PD with serum OPG level according to glycaemic state in postmenopausal T2DM women.

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Subjects and Methods

The case-control study was conducted from June 2019 to May 2020 at the National Diabetes Centre, Mustansiriyah University, Baghdad, Iraq, and comprised postmenopausal women who had been diagnosed with T2DM for at least 2 years at the time of enrolment and were on oral hypoglycaemic drugs. Those with good glycaemic control were placed in group A, diabetic women with poor glycaemic control in group B, and non-diabetic healthy controls in group C. Study participants were inducted using the consecutive sampling technique. All the studied women had had no menstrual cycle for at least one year that was age-expected and was not due to an associated medical disorder. The age of the subjects regardless of the group ranged 50-65 years.

The exclusion criteria were: intake of calcium supplements or bone active agents, a serious disease affecting bone remodelling, malignancy, renal failure, autoimmune disorders, a concurrent acute illness, a major systemic disease, an intake of a lipid-lowering agent, or being a smoker.

After getting approval from the institutional ethics review committee, the sample size was calculated using Epi-Info [12].

Data was collected after taking consent from all the subjects. A structured personal interview was conducted to collect information on current health status and past medical history of each participant.

The periodontal examination was carried out by a single experienced examiner, who had passed both inter- and intra-examiner calibrations. All the subjects had to have up to 15 teeth, and the third molars were included in the examined teeth. Calibrated peri¬odontal probes with William's markings were used for periodontal examination. The examination included measurement on four sites of each tooth of a participant (buccal, mesial, lingual/palatal, and distal) to determine the probing pocket depth (PPD), gingival recession and clinical attachment level (CAL) measurements[13]. The distance from the base of the gingival sulcus/periodontal pocket to gingival margin was taken as the PPD. The distance from the cemento-enamel junction to the gingival margin represented the gingival recession. These scores were then added up to indirectly obtain the CAL value.

A blood sample from all study subjects was obtained by venipuncture after overnight fasting. Part of the sample was collected in an ethylenediaminetetraacetic acid (EDTA) tube to be used for estimation of fasting blood glucose (FBG) and HbA1C on the same day of blood withdrawal. The rest of blood was allowed to clot in a plain tube, and serum was obtained by centrifugation and stored at -18ºC until the time of analysis for OPG level.

HbA1C measurement was carried out by a semi-automated bench-top system (DCA Vantage Analyser, Siemens Healthcare Diagnostics Inc. United States) in which the ratio of the concentration of HbA1C specifically and the concentration of total haemoglobin (Hb) was reported as the percent of HbA1C[14]. If the value of the ratio was ≤7 (53mmol/mol), a patient was considered in a well-controlled glycaemic state, while >7 indicated poor control[15]. FBG <100mg/dL (5.6mmol/L)[15] identified the non-diabetic controls in addition to their past medical history. Serum OPG level was measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (WKEA Med Supplies Corp., China).

Data was analysed using SPSS 24. Data was presented as frequencies and percentages as well as means ± standard deviations, as appropriate. Analysis of variance (ANOVA) test was used to determine the significance of difference among quantitative data in case of more than two independent means, and then the least significant difference (LSD) test was used to identify any significant difference between two means. For testing two sets of data, student's t-test for two independent means was used. The strength and direction of linear relationship between two quantitative parameters were measured using Pearson's correlation coefficient. P<0.05 was considered significant.

Results

Of the 150 subjects, 57(38%) were in group A with mean age 57.39±5.89 years, 43(28.7%) were in group B with mean age 58.91±4.95 years, and 50(33.3%) 57(%) were in

Table-1: Intergroup comparison of clinical characteristics, periodontal parameters and serum osteoprotegerin (OPG) levels.

Variable	Study groups			ANOVA- test	
	Group A Mean ±SD N=57	Group B Mean ±SD N=43	Control group Mean ±SD N=50	F-value	P-value
Age (year)	57.39±5.89	58.91±4.95	54.92±4.62	6.98	0.001
BMI	29.52±5.76	30.22±6.72	29.34±3.56	0.32	0.724
PPD (mm)	2.75±0. 63	3.42±0.39	1.78±0. 47	118.51	0.000
CAL (mm)	2.94±0.67	4.04±0.61	1.32±0.66	206.82	0.000
OPG (ng/L)	294.40±198.32	443.05±618.66	152.38±47.98	7.81	0.001
Duration of DM (year) for group A & group B	5.73±3.71	7.19±4.24		t-test t-value 2.24 (df:98)	P-value 0.028

BMI: Body mass index, PPD: Probing pocket depth, CAL: Clinical attachment level, SD: Standard deviation, ANOVA: Analysis of variance.

Table-2: Least significant difference (LSD) comparison.

Variable	LSD-test					
	Group A vs. Group B		Group A vs. Controls		Group B vs. Controls	
	Mean difference	P-value	Mean difference	P-value	Mean difference	P-value
Age (year)	1.52	0.152	2.47	0.016	3.99	0.000
BMI	0.70	0. 529	0.17	0.868	0.87	0.446
PPD (mm)	0.67	0.000	0.96	0.000	1.63	0.000
CAL (mm)	1.10	0.000	1.62	0.000	2.72	0.000
OPG (ng/L)	148.66	0.039	142.02	0.04	290.68	0.000

BMI: Body mass index, PPD: Probing pocket depth, CAL: Clinical attachment level, OPG: Osteoprotegerin.

Table-3: Correlation of OPG levels with periodontal parameters in diabetic patients and controls,

Variable	Study group	Value	Periodontal parameters	
			PPD	CAL
OPG (ng/L)	Group A	Correlation coefficient	0.321	0.241
	N=57	P-value sig. (2-tailed)	0.015	0.071
	Group B	Correlation coefficient	0.398	0.278
	N=43	P-value sig. (2-tailed)	0.008	0.071
	Control group	Correlation coefficient	0.280	0.021
	N=50	P-value sig.(2-tailed)	0.049	0.882

PPD: Probing pocket depth, CAL: Clinical attachment level, OPG: Osteoprotegerin.

group C with mean age 54.92±4.62 years. Clinical characteristics, periodontal parameters and serum OPG levels of all the study groups were noted and compared (Tables 1-2).

PPD, CLA and serum OPG exhibited higher values in groups A and B compared to group C, and in group B compared to group A ($p<0.001$). There was a significant positive correlation between PPD and serum OPG in all groups (Table 3).

Discussion

The current study investigated serum level of OPG as a bone-remodelling factor in relation to parameters of PD in T2DM postmenopausal women. The selection of postmenopausal women was because of the reported influence of gender on serum level of OPG, and because such women are more prone to bone disease[16].

The study's noticeable finding was the significant positive correlation between serum levels of OPG and PPD values in all study groups; the higher the OPG level, the more severe was PD. This is in agreement with many studies that reported a correlation between serum OPG level and periodontal parameters[17-19]. However, this finding primarily contradicted an expected physiological role of OPG, which is supposed to be an inhibitor of osteoclast differentiation, and thus to have an inhibitory effect on bone resorption. Such a role of OPG is because of its action as a decoy receptor and its binding with the ligand RANKL and preventing it from binding and activating specific receptor RANK on proosteoclasts, and so there would be no increase in osteoclastogenesis[20]. One of the probable explanations of this paradoxical phenomenon might be an existence of a disorder in the binding of OPG with RANKL with a development of a compensatory increase in OPG level in patients with diabetes or PD, or both. Hence, OPG level increases, but with no effect on RANKL/RANK association, and so osteoclastogenesis remains dominant and periodontal destruction becomes more aggressive in diabetic patients[2].

On studying the influence of T2DM itself, it was found that PD parameters, including PPD and CAL values, were higher in patient groups than in healthy controls. This finding agreed with earlier studies[21]. It was earlier assumed that a variation in host response mechanisms might be responsible for more periodontal destruction, and the results of studies about the significance of variation in subgingival microbiota in patients with diabetes as a pathogenetic cause of PD are still controversial[22].

On investigating the influence of glycaemic control, the current study found a more severe PD in poorly-controlled T2DM patients than in well-controlled patients, which is in line with literature[23]. This may be related to a more intensive formation of advanced glycation end-products (AGEs) in poorly-controlled diabetics, and AGEs are regarded as initiators or amplifiers of inflammation when they bind to the cellular receptors of AGEs (RAGEs). Such binding of AGEs to RAGEs would activate the nuclear factor NF-kB-regulated pathway and result in the release of cytokines, and the induction of an inflammatory response. AGE-RAGE binding can also result in an increased intracellular oxidative stress and depletion of detoxifying mechanisms and the conversion of temporary pro-inflammatory reactions into sustained cellular dysfunction and diminishment of immune responses [24].

Conclusion

Higher serum OPG levels were found to be associated with the presence and more severe PD in T2DM postmenopausal women, particularly those with poor glycaemic control. This suggested that OPG level may be a contributory factor in the pathogenesis of PD in T2DM patients, especially in those with poor glycaemic control. It also highlighted the importance of a tight glycaemic control as a part of PD management in such patients.

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References

1. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol 2018;89(Suppl 1):s173-82. doi: 10.1002/JPER.17-0721
2. Wu YY, Xiao E, Graves DT. Diabetes mellitus related bone metabolism and periodontal disease. Int J Oral Sci 2015;7:63-72. doi: 10.1038/ijos.2015.2
3. Stöhr J, Barbaresko J, Neuenschwander M, Schlesinger S. Bidirectional association between periodontal disease and diabetes mellitus: a systematic review and meta-analysis of cohort studies. Sci Rep 2021;11:13686. doi: 10.1038/s41598-021-93062-6
4. Martin TJ, Sims NA. RANKL/OPG; Critical role in bone physiology. Rev Endocr Metab Disord 2015;16:131-9. doi: 10.1007/s11154-014-9308-6.
5. Czupkallo L, Rahnama M, Kielbowicz D, Lobacz M, Kozicka-Czupkallo M. Bone metabolism and RANKL/RANK/OPG trail in periodontal disease. Curr Issues Pharm Med Sci 2016;29:171-5. DOI: 10.1515/cipms-2016-0036
6. Gunes M, Temizkan S, Apaydin T, Ilgin C, Haklar G, Gogas Yavuz D. Serum osteoprotegerin levels, endothelial function and carotid intima-media thickness in type 2 diabetic patients. J Diabetes Complications 2021;35:108073. doi: 10.1016/j.jdiacomp.2021.108073
7. Bilgir O, Yavuz M, Bilgir F, Akan OY, Bayindir AG, Calan M, et al. Relationship between insulin resistance, hs-CRP, and body fat and serum osteoprotegerin/RANKL in prediabetic patients. Minerva Endocrinol 2018;43:19-26. doi: 10.23736/S0391-1977.17.02544-5.
8. Sassi F, Buondonno I, Luppi C, Spertino E, Stratta E, Di Stefano M, et al. Type 2 diabetes affects bone cells precursors and bone turnover. BMC Endocr Disord 2018;18:55. doi: 10.1186/s12902-018-0283-x
9. Fasil A, Biadgo B, Abebe M. Glycemic control and diabetes complications among diabetes mellitus patients attending at University of Gondar Hospital, Northwest Ethiopia. Diabetes Metab Syndr Obes 2018;12:75-83. doi: 10.2147/DMSO.S185614
10. Engebretson S. Periodontal disease and glycemic control in diabetics. Evid Based Dent 2014;15:93-4. doi: 10.1038/sj.ebd.6401040
11. Han K, Park JB. Clinical implications of age and sex in the prevalence of periodontitis in Korean adults with diabetes. Exp Ther Med 2018;15:3865-73. doi: 10.3892/etm.2018.5880
12. Sullivan KM, Dean A, Soe MM. OpenEpi: a web-based epidemiologic and statistical calculator for public health. Public Health Rep 2009;124:471-4. doi: 10.1177/003335490912400320
13. Holtfreter B, Albandar JM, Dietrich T, Dye BA, Eaton KA, Eke PI, et al. Standards for reporting chronic periodontitis prevalence and severity in epidemiologic studies: Proposed standards from the Joint EU/USA Periodontal Epidemiology Working Group. J Clin Periodontol 2015;42:407-12. doi: 10.1111/jcpe.12392
14. Eaton SE, Fielden P, Haisman P. Glycated haemoglobin (HbA1c) measurements in subjects with haemoglobin variants, using the DCA 2000. Ann Clin Biochem 1997;34:205-7. doi: 10.1177/000456329703400215
15. Marathe PH, Gao HX, Close KL. American Diabetes Association Standards of Medical Care in Diabetes 2017. J Diabetes 2017;9:320-4. doi: 10.1111/1753-0407.12524
16. Shieh A, Ruppert KM, Greendale GA, Lian Y, Cauley JA, Burnett-Bowie SA, et al. Associations of Age at Menopause With Postmenopausal Bone Mineral Density and Fracture Risk in Women. J Clin Endocrinol Metab 2022;107:e561-9. doi: 10.1210/clinem/dgab690
17. Aldahlawi S. Evaluation of serum RANKL and OPG concentrations in patients with periodontitis in Saudi Arabia. Int J Pharm Res Allied Sci 2019;8:45-51.
18. Gama A, Navet B, Vargas JW, Castaneda B, Lézot F. Bone resorption: an actor of dental and periodontal development? Front Physiol 2015;6:319. doi: 10.3389/fphys.2015.00319
19. Sojod B, Chateau D, Mueller CG, Babajko S, Berdal A, Lézot F, et al. RANK/RANKL/OPG Signalization Implication in Periodontitis: New Evidence from a RANK Transgenic Mouse Model. Front Physiol 2017;8:338. doi: 10.3389/fphys.2017.00338
20. Yasuda H. Discovery of the RANKL/RANK/OPG system. J Bone Miner Metab 2021;39:2-11. doi: 10.1007/s00774-020-01175-1.
21. de Miguel-Infante A, Martinez-Huedo MA, Mora-Zamorano E, Hernández-Barrera V, Jiménez-Trujillo I, de Burgos-Lunar C, et al. Periodontal disease in adults with diabetes, prevalence and risk factors. Results of an observational study. Int J Clin Pract 2018:e13294. doi: 10.1111/ijcp.13294. [ahead of print].
22. Matsha TE, Prince Y, Davids S, Chikte U, Erasmus RT, Kengne AP, et al. Oral Microbiome Signatures in Diabetes Mellitus and Periodontal Disease. J Dent Res 2020;99:658-65. doi: 10.1177/0022034520913818
23. Preshaw PM, Bissett SM. Periodontitis and diabetes. Br Dent J 2019;227:577-84. doi: 10.1038/s41415-019-0794-5
24. Singh VP, Bali A, Singh N, Jaggi AS. Advanced glycation end products and diabetic complications. Korean J Physiol Pharmacol 2014;18:1-. doi: 10.4196/kjpp.2014.18.1.1