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Association Between Type 2 Diabetes and Classification of Periodontal Disease Severity in Japanese Men and Women: A Cross-Sectional Study

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Research Article

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Posted Date: November 19th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1090945/v1

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Running title: Association between Diabetes and Periodontal Condition

The proposed type of manuscript: original article

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Keywords

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Abstract

Background: To evaluate the association between type 2 diabetes and periodontal disease severity using the rate of alveolar bone loss (ABL) and high-sensitivity C-reactive protein (hs-CRP) value as indices.

Methods: In this cross-sectional study of 372 subjects (mean age ± SD, 53.2 ± 11.8 years) from a Japanese hospital, we measured ABL and number of teeth on either panoramic radiographs or intraoral dental radiographs of all teeth. A trial classification of periodontal disease was defined as follows: I (ABL < 25%, clinically mild); II (ABL ≥ 25%, <35%, moderate); III (ABL ≥ 35%, severe); and A (hs-CRP < 440 ng/ml, mild inflammation); B (hs-CRP ≥440 ng/ml, <1,020 ng/ml, moderate inflammation); and C (hs-CRP ≥ 1,020 ng/ml, severe inflammation). Periodontal disease severity was classified into nine groups by combining ABL and hs-CRP.

Results: Forty-eight subjects had type 2 diabetes; 324 did not. Univariate analysis showed that type 2 diabetes was significantly associated with age, sex, body mass index, number of teeth, ABL, hs-CRP, and periodontal disease severity. Multivariate analysis showed significant associations between type 2 diabetes and the groups with high severity of periodontal disease. In receiver operating characteristic (ROC) curve analysis predicting the presence of diabetes, area under the ROC curve was 0.762 (95%CI = 0.688 - 0.835) for ABL, and 0.709 (95%CI = 0.635 - 0.784) for hs-CRP, which was significant.

Conclusions: This study showed that diabetes could be associated with a periodontal disease severity classification using the combination of ABL and hs-CRP.

Background

The association between systemic health and oral health is bidirectional; systemic illnesses, especially metabolic disorders, affect oral health, and it appears that oral health may affect systemic health [1]. The presence of periodontal disease often strongly correlates with type 2 diabetes. Periodontal disease is a local chronic inflammatory disease, initiated by the accumulation of a pathogenic dental plaque biofilm above and below the gum margin, within which microbial dysbiosis leads to a chronic non-resolving and destructive inflammatory response [2, 3]. There is a strong evidence that people with periodontitis have an elevated risk for dysglycemia and insulin resistance [4]. Moreover, some cohort studies have demonstrated that patients with type 2 diabetes and periodontitis have significantly higher hemoglobin A1c (HbA1c) levels compared with patients without periodontitis [4].

In 2019, one in eleven adults aged from 20 to 79 years were reported to have diabetes (463 million people) world-wide [5]. In the Western Pacific area including Japan of the world, the number of people with diabetes is predicted to increase by 31% between 2019 and 2045 [5]. Furthermore, one in two adults with diabetes are undiagnosed globally (232 million) [5]. Although there are several established and accurate screening tools for DM (A1c, fasting glucose, oral glucose tolerance test), it is important to develop an additional diagnostic method to capture at-risk patients in non-traditional clinical setting for detecting type 2 diabetes in the early stages. Periodontal disease is also an asymptomatic disease, and it has the highest prevalence of all infectious diseases.

If dentists can predict the early stages of type 2 diabetes from a periodontal examination, it could be effective as a screening procedure and reduce medical costs.

Clinical periodontal disease severity has been developed by both the American Association of Periodontology and the European Federation of Periodontology[6, 7]. However, the lack of consensus and uniformity in the definition of periodontitis within epidemiological studies is a serious problem [8]. Therefore, in 2011, the Japanese Society of Periodontology created a trial classification using the rate of alveolar bone loss (ABL) as a clinical index, together with the high-sensitivity C-reactive protein (hs-CRP) value, which is an inflammatory marker [9]. However, little information is available about the association between classifications of periodontal disease severity and the condition of type 2 diabetes.

The purpose of this study was to evaluate the association between type 2 diabetes and the severity of periodontal disease using ABL and the hs-CRP value as indices. Furthermore, we investigated whether ABL and hs-CRP could associate with type 2 diabetes with the aim of using it as a new screening tool.

Methods

Design and subjects

The design was a cross-sectional study. Participants were 322 subjects who had a medical checkup in the medical examination center of Matsumoto Dental University Hospital and 50 patients who visited the department of periodontology at Matsumoto Dental University Hospital from 2012 to 2015 (a total of 372 patients: 252 men and

120 women). The mean age (standard deviation) of the subjects was 53.2 (11.8) years. Of these, 48 were diagnosed with type 2 diabetes by their home doctors and were receiving medication and insulin injection therapy. Age, sex, body height, body weight, and current smoking history were obtained from the medical records of each subject. Before the start of this study, written informed consent was obtained from all subjects for their participation in the study, according to the Declaration of Helsinki.

The following were exclusion criteria for this study. (1) Those who are pregnant or may become pregnant. (2) Those who have uncontrolled severe cardiac disease, renal dysfunction, or hepatic dysfunction. (3) Those who are taking antibody drugs or anti-inflammatory drugs for autoimmune diseases. (4) Those who have taken any antibacterial drugs at the time of investigation. All subjects were informed of the results of this study in accordance with the ethics guidelines of the Ministry of Health, Labour and Welfare and the Ministry of Education, Culture, Sports, Science and Technology. The Institutional Review Board for Clinical Research at Matsumoto Dental University reviewed and approved this study protocol (no. 0151, approval date: 31st January, 2012.).

Assessment of ABL using oral radiographs and hs-CRP

Either panoramic radiographs or intraoral dental radiographs of all teeth were taken during a medical examination or reassessment examination. Panoramic radiographs were taken with a digital AZ3000® device (Asahi Roentgen Ind. Co. Ltd, Kyoto, Japan) and intraoral dental radiographs were taken with a full-mouth set using DIGORA® Optime (Soredex Orion Corp., Tuusula, Finland).

One periodontist with 5 years of experience examined the radiographs and recorded the number of teeth

and the ABL. Implants, supernumerary teeth, and third molars were excluded from the number of teeth. Residual roots without a cap for an overdenture were also excluded. Teeth with caries or periapical lesions were not excluded.

ABL was assessed on a panoramic radiograph or intraoral radiographs [10] by measuring the distance between the cement-enamel junction (CEJ) and the alveolar crest (AC) and between the CEJ and the root apex at two sites (mesial and distal) on each tooth. The apex was defined as the most apically located point of the root. In teeth restored with fillings or crowns, the most apical limit of the restoration was considered equivalent to the CEJ. Finally, ABL was calculated as a CEJ-AC/CEJ-apex [11].

Hs-CRP values were measured from the serum with a Latex agglutination/nephelometry method in the SRL Hachioji Lab (Tokyo, Japan). Blood was collected by a clinical technician in the clinical laboratory in Matsumoto Dental University Hospital. The collected blood was centrifuged (28 °C, 5 min, 3,600 rpm) and stored in serum.

Classification of periodontal disease by severity

The classification used in this study is a new trial classification of periodontal disease. The classification is based on the following categories: ABL of less than 25% is clinically mild (I), 25% or more and less than 35% is moderate (II), 35% or more is severe (III). On the other hand, a hs-CRP value of less than 440 ng/ml is mild inflammation (A), 440 ng/ml or more and less than 1020 ng/ml is moderate (B), and 1020 ng/ml or more is severe (C). Combining ABL with hs-CRP yields nine classifications of periodontal disease severity [9]

(Figure 1).

Statistical analysis

Initially, univariate analyses with the t-test and the chi-squared test were used to evaluate the differences in age, sex (binary), body mass index (BMI), current smoking history, number of teeth, ABL (three groups), and hs-CRP value (three groups) and between subjects with and without type 2 diabetes. Next, multivariate logistic regression analysis was undertaken with forward selection adjusting for age, sex (binary), BMI, current smoking history (binary), number of teeth, and the nine classifications of periodontal disease severity. Receiver operating characteristic (ROC) curve analysis was employed to identify asymptomatic type 2 diabetes in relation to ABL and hs-CRP value. According to the method suggested by Swets [12], the area under the ROC curve (AUROC) was determined as follows: less accurate ($0.5 < \text{AUROC} < 0.7$), moderately accurate ($0.7 < \text{AUROC} < 0.9$), highly accurate ($0.9 < \text{AUROC} < 1$), and perfect tests ($\text{AUROC} = 1$). All comparisons were two-sided and performed at a $p = 0.05$ level of significance. Statistical analysis was performed using SPSS® ver. 26.0 for Windows (IBM Japan, Tokyo, Japan).

Results

The characteristics of all participants are shown in Table 1. Forty-eight of the subjects had type 2 diabetes and 324 did not. The mean ages (SD) of the type 2 diabetes group and the non-diabetic group were 62.6 (9.8) years and 51.8 (11.4) years, respectively. There were significant differences in age ($p < 0.001$), sex ($p = 0.032$),

BMI ($p = 0.001$), number of teeth ($p < 0.001$), ABL ($p < 0.001$), hs-CRP ($p < 0.001$), and periodontal disease severity classification ($p < 0.001$) between the type 2 diabetic group and the non-diabetic group.

Figure 1 shows the distribution of subjects in the nine groups: 119 in group IA, 87 in group IIA, 25 in group IIIA, 33 in group IB, 29 in group IIB, 11 in group IIIB, 26 in group IC, 32 in group IIC, and 10 in group IIIC. The distribution of type 2 diabetes was the highest in group IIIC with 60.0%, followed by group IIIB with 54.5%, and group IIIA with 28.0% (Table 1).

Multivariate logistic regression analysis with forward selection adjusted for covariates revealed that the presence of type 2 diabetes was significantly associated with age (Odds ratio [OR] = 1.082, 95% confidence interval [CI] = 1.042 - 1.1124, $p < 0.001$) and BMI (OR = 1.175, 95% CI = 1.061 - 1.301, $p = 0.002$). Additionally, the presence of type 2 diabetes was significantly associated with periodontal disease severity group IIIA (OR = 5.108, 95%CI = 1.346 - 19.381, $p = 0.017$), group IIIB (OR = 9.626, 95%CI = 1.950 - 47.528, $p = 0.005$), and group IIIC (OR = 12.386, 95%CI = 2.464 - 62.276, $p = 0.002$) when compared with group IA (Table 2).

In the ROC analysis predicting the presence of type 2 diabetes, the AUROC was 0.762 (95%CI = 0.688 - 0.835, $p < 0.001$) for ABL, and 0.709 (95%CI = 0.635 - 0.784, $p < 0.001$) for hs-CRP (Figure 2).

Discussion

This is the first study to show the association between type 2 diabetes and a classification of periodontal disease severity using the combination of ABL and hs-CRP in Japanese people. Furthermore, it was found that ABL, which can be identified by oral radiographs taken at the time of dental treatment, and hs-CRP may be candidates for identifying individuals with asymptomatic type 2 diabetes.

158 Several cohort studies have reported that periodontal disease affects the onset of diabetes and glycemic
159 control [13-20]. The US National Health and Nutrition Examination Survey showed that the prevalence of diabetes
160 in patients with periodontal disease was approximately twice as high as in patients without periodontal disease
161 [18, 19]. In a cohort study in Hisayama town, it was reported that the prevalence of periodontal disease was
162 significantly higher in Japanese patients who developed impaired glucose tolerance over 10 years than in those
163 who did not [15]. Moreover, periodontal disease and type 2 diabetes have an interactive relationship, although
164 there is little detailed data on the relationship between the two diseases in Japan. One reason for this gap in the
165 literature is that there has been no unified standard for evaluating periodontal disease.
166 A consensus report, jointly prepared by the editorial board of the American Academy of Periodontology
167 and the American Society of Cardiology and published simultaneously in the American Journal of Cardiology and
168 the Journal of Periodontology, also provides clinical parameters for further research. It stressed the need for more
169 advanced diagnosis of periodontitis by severity, such as the use of biomarkers and proof of ABL by using
170 radiographs [21]. Therefore, in 2011, the Periodontal Medicine Committee of the Japanese Society of
171 Periodontology established criteria for diagnosing the severity of periodontal disease, which are used as the
172 standard when conducting research. ABL is classified into three stages based on the data of previous studies [22,
173 23]: clinically mild, clinically moderate, and clinically severe. Errors are unlikely to occur in the measurement of
174 ABL; however, it does not reflect the situation when a periodontal pocket has healed. The hs-CRP value, which
175 is a biomarker for inflammation, was defined according to the Hisayama study [24] and consists of three stages:
176 mild inflammation, moderate inflammation, and severe inflammation. Hs-CRP is not a marker specific to

177 periodontal disease; however, it is a highly sensitive marker suited to measuring periodontal disease, which is
178 regarded as a mild chronic inflammation. Previous studies have reported that hs-CRP levels are often high in
179 patients with severe periodontitis and decrease with treatment [23, 25]. This study is also an important
180 epidemiological study to evaluate whether these classifications are valid.

181 The main result of this study was that the rate of ABL had a higher AUROC value than hs-CRP,
182 suggesting that individuals who have type 2 diabetes may be identified from the results of ROC analysis.
183 Furthermore, in logistic regression analysis, the IIIA, IIIB, and IIIC groups with an alveolar bone resorption rate
184 of 35% or more were associated with type 2 diabetes, regardless of the hs-CRP value. These findings indicate that
185 the rate of ABL caused by periodontal disease, which is an oral factor, may be closely associated with type 2
186 diabetes. Therefore, it is possible that the rate of ABL that is easily calculated from X-rays can predict type 2
187 diabetes with high probability. In the present study, a dentist measured the rate of ABL, however, we calculated
188 the intra-class correlation coefficient (ICC) assuming that two dentists measured it. The intra- rater reliability was
189 0.94±0.07 and the inter- rater reliability was 0.89, which ensured reliability.

190 Probing of periodontal pockets has been considered essential to determine the extent of periodontal tissue
191 destruction. However, in infected and inflamed periodontal tissue, the probing test itself often causes bleeding.
192 There is a risk that oral bacteria will penetrate the bleeding site and induce bacteremia and infective endocarditis.
193 Another concern is that patients may be infected with coronavirus disease 2019 (COVID-19). Dental treatment at
194 close range presents a high risk of infection. Until the risk of COVID-19 is resolved, it may be necessary to
195 diagnose type 2 diabetes with a test that can be performed outside the oral cavity. Our findings help diagnose

196 periodontal disease and identify at-risk patients for type 2 diabetes.

197 There are some limitations in this study. First, all subjects visited Matsumoto Dental University Hospital,
198 and thus lived in a specific region of Japan; they were not representative of the entire population. Second, we did
199 not show an association between type 2 diabetes and elevated glycated hemoglobin level, elevated low-density
200 lipoprotein cholesterol level, albuminuria, smoking, or elevated blood pressure. Third, the variability in the
201 number of classifications of periodontal disease severity into nine groups should be improved for better analysis.
202 As the confidence interval in multivariate logistic regression analysis was large in this result, we should plan to
203 increase the number of subjects in severe periodontal disease. The strength of this study is that ABL measured
204 from X-ray images taken during dental treatment associated with type 2 diabetes with a high probability, and
205 therefore patients can be urged to consult the internal medicine department to receive interventions for lifestyle
206 improvement. We previously reported that alveolar bone resorption was effective as a screening factor for carotid
207 artery calcification [26]. We plan to continue investigating further possible associations of ABL with systemic
208 diseases.

209 This study showed the association between type 2 diabetes and a classification of periodontal
210 disease severity using the combination of ABL and hs-CRP in Japanese patients. Furthermore, it was found that
211 ABL, which can be identified by oral radiographs taken at the time of dental treatment, and hs-CRP may be
212 candidates for identifying individuals with underdiagnosed type 2 diabetes.

213

214 Acknowledgments

The authors thank the study participants and the staff of Matsumoto Dental University Hospital.

Author's contributions

Study design: N.Y., A.T.; Data collection: Y.I., N.Y.; Formal analysis and writing: A.T., N.Y., Y.I., N.D.; Data-interpretation: A.T., N.Y., N.D.; Critical review: N.U. All authors have read and agreed to the publication of the final version of the manuscript.

Funding

This study was supported by the Japan Society for the Promotion of Science, Grants-in-Aid for Scientific Research (18K09758).

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Consent for publication

Not applicable.

Competing interest

The authors declare that they have no competing interests.

Ethics approval and consent to participate

All subjects were informed of the results of this study in accordance with the ethics guidelines of the Ministry of Health, Labour and Welfare and the Ministry of Education, Culture, Sports, Science and Technology. The Institutional Review Board for Clinical Research at Matsumoto Dental University reviewed and approved this study protocol (no. 0151, approval date: 31st January, 2012.).

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Figure legends

Figure 1. Number of subjects according to classification of periodontal disease severity
( ): number of patients with type 2 diabetes

Figure 2. ROC curve of effective factors for screening for type 2 diabetes. The green line represents alveolar bone loss; the blue line represents high-sensitivity C-reactive protein value.

Figures

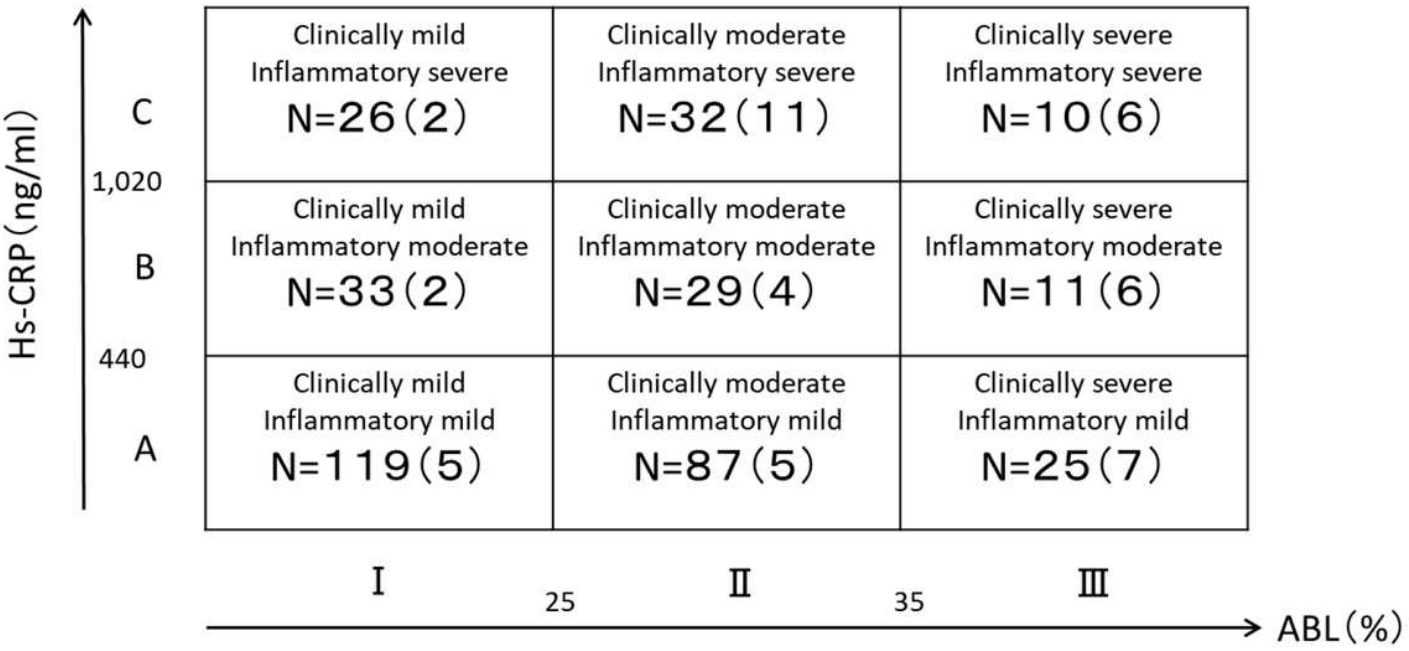

Figure 1

Number of subjects according to classification of periodontal disease severity ( ): number of patients with type 2 diabetes

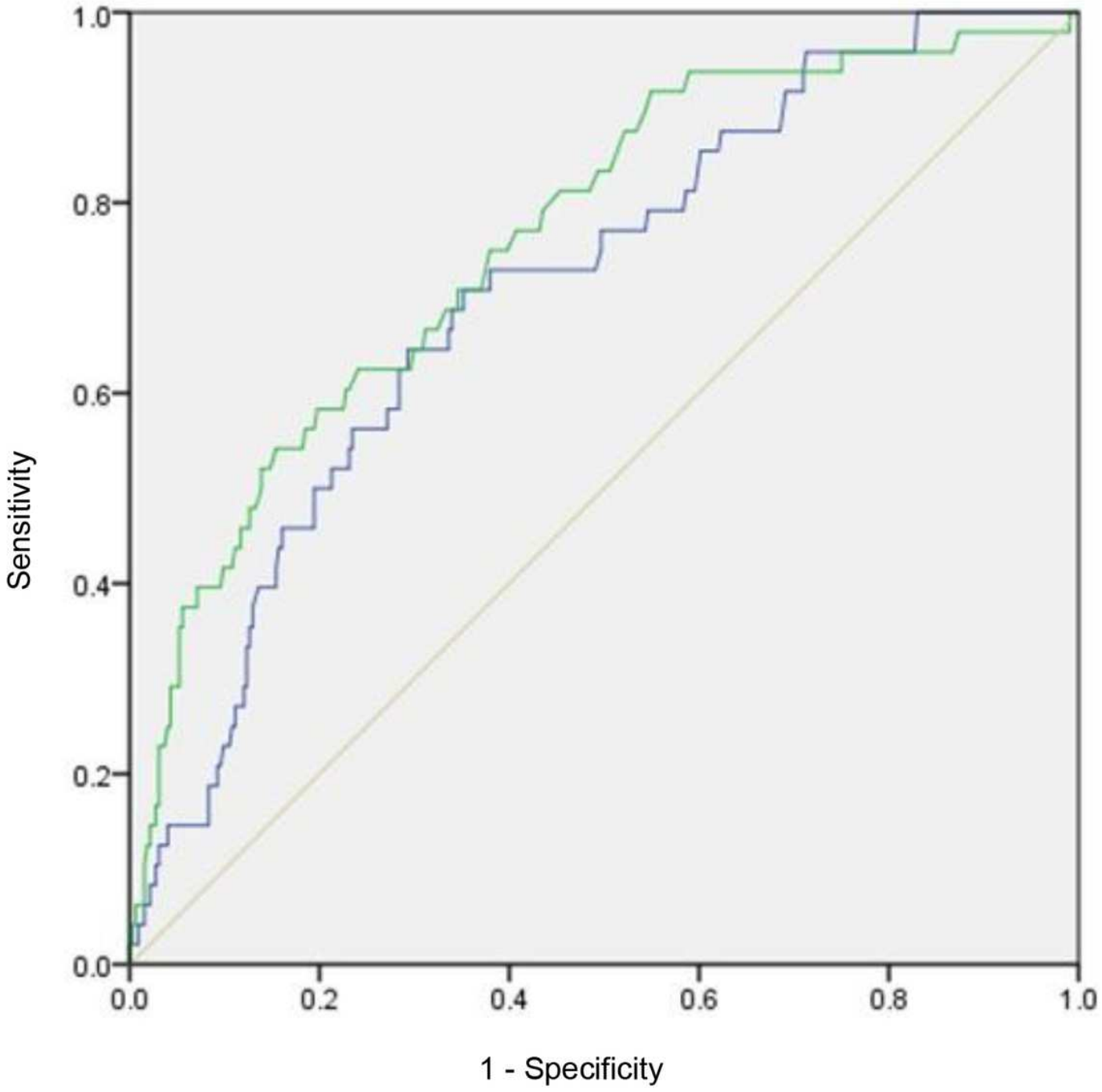

Figure 2

ROC curve of effective factors for screening for type 2 diabetes. The green line represents alveolar bone loss; the blue line represents high-sensitivity C-reactive protein value.

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