

**Relationship between prehypertension/hypertension and periodontal disease: A  
prospective cohort study**

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**Running title:** Hypertension and periodontal disease

**Number of references:** 40

**Number of figures and tables:** 0 figure and 4 tables

**Conflict of interest and source of funding statement:** The authors have no conflicts of interest to declare. This study was self-supported.

**Key words:** periodontal disease, university students, blood pressure, cohort studies

## **Abstract**

### **BACKGROUND**

Most cross-sectional studies have found a significant positive relationship between periodontal disease and prehypertension/hypertension. However, these studies had limitations and there are few prospective cohort studies in young adults. The purpose of this prospective cohort study was to investigate whether periodontal disease was related to prehypertension/hypertension in Japanese university students.

### **METHODS**

Students (n = 2,588), who underwent health examinations before entering university and before graduation, were included in the analysis. The association between periodontal disease such as the percentage of bleeding on probing and Community Periodontal Index scores, and change in blood pressure status was determined.

### **RESULTS**

At the re-examination, the numbers of participants with prehypertension (systolic blood pressure 120-139 mm Hg or diastolic blood pressure 80-89 mm Hg) and hypertension ( $\geq 140/90$  mm Hg) were 882 (34.1%) and 109 (4.2%), respectively. In a logistic regression model, the risk of hypertension was significantly associated with male (OR: 6.31; 95% CI: 2.63-15.13;  $p < 0.001$ ), no habitual physical activity at baseline (OR:

2.90; 95% CI: 1.56-5.38;  $p < 0.01$ ) and periodontal disease defined as presence of both PPD  $\geq 4$  mm and BOP  $\geq 30\%$  at baseline (OR: 2.74; 95% CI: 1.19-6.29;  $p = 0.02$ ) in participants with prehypertension at baseline. On the other hand, the risk of prehypertension was not associated with presence of periodontal disease (OR: 0.93; 95% CI: 0.51-1.70;  $p = 0.82$ ).

## **CONCLUSION**

In the short-term prospective cohort study, a significant association between presence of periodontal disease and hypertension was observed in Japanese university students.

## INTRODUCTION

Hypertension is a major cause of premature death and disability in the world mainly as a result of cardiovascular disease including coronary heart disease and stroke, and other vascular diseases.<sup>1</sup> Hypertension is also highly prevalent affecting about 30% of adults as reported by the World Health Organization (WHO) and the prevalence of hypertension in the Western Pacific and South-east Asian regions range from 5 to 47% in men and 7 to 38% in women.<sup>2</sup> In addition to many dietary and lifestyle factors including smoking and alcohol consumption,<sup>3-5</sup> the role of chronic inflammation has been implicated in the aetiology of hypertension.<sup>6</sup>

Periodontal disease is one of the most widespread chronic diseases and a highly-prevalent chronic inflammatory condition associated with an increase in circulating levels of inflammatory biomarkers.<sup>7</sup> Most cross-sectional studies have found significant positive relationships between periodontal disease, blood pressure and possibly hypertension.<sup>8-17</sup> However, these studies have limitations and vary in design, participants, and definition of periodontal disease. A review also points out that prospective cohort studies are needed to determine the impact of periodontitis on blood pressure regulation and incident hypertension.<sup>18</sup> Only two prospective cohort studies have been conducted so far, and their findings varied.<sup>19, 20</sup> These studies were carried

out among adult and elderly participants, and there are few studies which assessed the relationship between hypertension and periodontal disease in young adults.

It is important to evaluate the relationship between hypertension and periodontal disease in young adults, as control of the risk factors for hypertension at an early stage is essential to prevent its occurrence. Furthermore, since prehypertension predicts an increased risk for the development of hypertension and confers an increased risk for cardiovascular events,<sup>21, 22</sup> we focused on not only hypertension but also prehypertension. We hypothesized that presence of periodontal disease may predict prehypertension/hypertension in young adults. The aim of the present prospective cohort study was to explain the relationship between prehypertension/hypertension and periodontal disease in university students.

## **METHODS**

### *Study population*

Of first-year students ( $n = 4,516$ ) who underwent both general health and oral examinations (pre-university) at the Health Service Center of Okayama University in April 2010 or 2011, 3,011 students volunteered to receive a 3-year follow-up examination before graduation in April 2013 or 2014 (follow-up rate; 66.7%). The participants included in the study had no self-reported history of hypertension and no medication history. After excluding participants who were  $\geq 30$  years old ( $n = 14$ ) and incomplete questionnaires ( $n = 409$ ), data from 2,588 students (1,278 males, 1,310 females) aged  $18.2 \pm 0.7$  years (range, 18-27 years) were analysed. The study was approved by the Ethics Committee of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (No. 1039). Written consent was obtained from all participants.

### *Assessment of resting blood pressure*

Hypertension was defined by systolic blood pressure  $\geq 140$  mm Hg or diastolic blood pressure  $\geq 90$  mm Hg, meanwhile prehypertension was defined by systolic blood pressure 120-139 mm Hg or diastolic blood pressure 80-89 mm Hg.<sup>22</sup> Peripheral blood

pressure of the upper arm as well as heart rate was obtained by using an automatic oscillometric device (BP-203RVII, Omron, Tokyo, Japan) in accordance with the Japanese Society of Hypertension guidelines for blood pressure monitoring and the American Heart Association recommendations.<sup>23</sup> Briefly, under the supervision of public nurses, the participants sat in a chair with their legs uncrossed and their feet flat on the floor. They were instructed to avoid talking during the procedure and to position the upper arm at their heart level. Single resting blood pressure measurement was obtained. A second or third measure was taken if blood pressure values were greater than 140/90 mm Hg. The mean values of the two or three measurements on each blood pressure recording were calculated and used in the results presented here.

#### *Assessment of body mass index (BMI)*

During the general health examination, the participant's height and body weight were measured by public health nurses using Tanita body fat analyser (Model No. BF-220, Tanita Corp., Tokyo, Japan).<sup>24</sup> BMI was computed as weight in kilograms divided by the square of height in meters. Categories of BMI were determined based on the accepted cut-off values of underweight (BMI < 18.5 kg/m<sup>2</sup>), normal weight (18.5-24.9 kg/m<sup>2</sup>), overweight (25-29.9 kg/m<sup>2</sup>) and obesity ( $\geq$  30 kg/m<sup>2</sup>)<sup>25</sup> and were used to



represent body composition. However, since the number of obese participants was too low, we combined overweight and obesity for the analysis.

### *Oral examination*

Six dentists (D.E., K.K., K.I., M.Y., S.M., and T.A.) examined the oral health status of the subjects. The teeth present were counted. Periodontal condition was assessed using the Community Periodontal Index (CPI).<sup>26</sup> Ten teeth were selected for periodontal examination: two molars in each posterior sextant, and the upper right and lower left central incisors. Measurements were made using a CPI probe (YDM, Tokyo, Japan) at six sites (mesio-buccal, mid-buccal, disto-buccal, disto-lingual, mid-lingual and mesio-lingual) per tooth. The percentage of teeth exhibiting bleeding on probing (%BOP: number of BOP-positive teeth per total number of teeth) was calculated. BOP is an earlier and more sensitive indicator of inflammation than visual signs of inflammation (redness and swelling).<sup>27</sup> Thus, we also assessed %BOP as an indicator of periodontal disease in this study.<sup>26</sup> Levels of dental plaque and calculus were assessed using the simplified oral hygiene index (OHI-S).<sup>28</sup> Good intra- and inter-examiner agreement was achieved for repeated probing pocket depth (PPD) measurements in the 10 teeth used for CPI (Kappa statistic, > 0.8).

### *Questionnaire*

A questionnaire was used to assess general and oral health behaviour. In addition to gender, age and general health condition, the questionnaire included the following items: 1) frequently consuming fatty foods (yes/no); 2) frequently eating green vegetables (yes/no); 3) frequently eating sweets (yes/no); 4) frequently drinking (sugar-sweetened) soft drinks (yes/no); 5) habitual physical activity (everyday/sometimes/never); 6) habitual drinking of alcohol (everyday/sometimes/never); 7) smoking status (current/past/never); 8) daily frequency of tooth brushing (1/2/ $\geq$  3); 9) use of dental floss (yes/no); and 10) regular visits to dental clinics for check-ups once or more a year (yes/no).<sup>29-31</sup> Since the numbers of participants who drink alcohol everyday and get physical activity everyday were too low, we combined the two categories; ‘everyday’ and ‘sometimes’ for the analysis. There were no past smokers in this study.

### *Statistical analysis*

Because we considered that both prehypertension and hypertension were important for young adults to keep their health, three subgroup analyses were performed: i) a change

from normal blood pressure to prehypertension/hypertension during 3 years, ii) a change from prehypertension to hypertension during 3 years and iii) keeping hypertension during 3 years.

Periodontal disease was defined using two criteria: i) presence of PPD  $\geq$  4 mm (CPI score = 3 or 4),<sup>24</sup> or ii) presence of PPD  $\geq$  4 mm and BOP  $\geq$  30% (active periodontal pocket).<sup>32</sup> We selected these two categories in order to avoid underestimation.

Paired *t*, unpaired *t*, and chi-square tests were used to determine whether there were any significant differences between baseline and re-examination, or two groups according to blood pressure category. Using a logistic regression model, both odds ratio (OR) and 95% confidence interval (CI) were calculated. Change to prehypertension/hypertension during the 3-year follow-up was used as a dependent variable. Age, gender, smoking status, BMI, frequently consuming fatty foods, number of teeth present, OHI-S, presence of periodontal disease at baseline were added as independent variables in the multivariate analysis. We also performed multiple imputation with five different values for handling missing data. A statistical program (PASW version 18.0, IBM, Tokyo, Japan) was used for statistical analyses.

## RESULTS

The blood pressure and body mass values of the 2,588 participants at baseline and follow up are shown in Table 1. There were significant differences in both systolic and diastolic blood pressure values between baseline and follow-up ( $p < 0.001$ ). The number of participants with prehypertension/hypertension significantly decreased after the 3 year-follow up ( $p < 0.001$ ).

Table 2 shows the characteristics at baseline based on blood pressure. Among participants with normal blood pressure at baseline ( $n = 1,287$ ), there were significant differences in the gender ( $p < 0.001$ ), BMI category ( $p < 0.01$ ), number of teeth present ( $p = 0.01$ ), OHI-S ( $p = 0.02$ ) and BOP category ( $p = 0.04$ ) between the normal blood pressure and prehypertension/hypertension groups at the follow-up. In participants with prehypertension at baseline, there were significant differences in the gender ( $p < 0.001$ ), number of subjects frequently consuming fatty foods ( $p = 0.04$ ) and habitual physical activity ( $p < 0.01$ ) between the normal blood pressure/prehypertension and hypertension groups at the 3 year-follow up. In participants with hypertension at baseline, there was only a significant difference in the heart rate ( $p = 0.01$ ) between normal blood pressure/prehypertension and hypertension groups at the 3 year-follow up.

In the logistic regression analyses, the risk of having prehypertension/hypertension

after 3 years was significantly associated with “male” (OR: 4.03; 95% CI: 2.95-5.49;  $p < 0.001$ ) and “overweight” (OR: 2.72; 95% CI: 1.06-7.00;  $p = 0.04$ ) at baseline in the participants with normal blood pressure at baseline (Table 3). However, there was no significant relationship between periodontal disease and prehypertension/hypertension after 3 years (Table 3 and 4). In participants with prehypertension at baseline, the risk of having hypertension was significantly associated with “male” (OR: 6.31; 95% CI: 2.63-15.13;  $p < 0.001$ ) and “no habitual physical activity” (OR: 2.90; 95% CI: 1.56-5.38;  $p < 0.01$ ) at baseline (Table 4). Furthermore, the risk of hypertension was significantly associated with periodontal disease defined as presence of PPD  $\geq 4$  mm and BOP  $\geq 30\%$  (active periodontal pocket) at baseline (OR: 2.74; 95% CI: 1.19-6.29;  $p = 0.02$ ) (Table 4). In participants with hypertension at baseline, the risk of keeping hypertension was significantly associated with “overweight” (OR: 2.41; 95% CI: 1.06-5.47;  $p = 0.04$ ) at baseline when periodontal disease was defined as presence of PPD  $\geq 4$  mm (Table 3).

## DISCUSSION

Most cross-sectional studies have found significant positive relationships between periodontal disease, blood pressure and possibly hypertension.<sup>9-18</sup> In the present study, the numbers of participants with presence of PPD  $\geq$  4 mm and BOP  $\geq$  30% in the normal blood pressure, prehypertension and hypertension groups at baseline were 92 (7.1%), 107 (9.3%), 22 (14.6%), respectively, with significant difference between the groups (chi-square tests,  $p < 0.01$ ) (cross-sectional analysis). In this prospective study among Japanese university students, the risk of having hypertension after 3 years was significantly associated with periodontal disease defined as presence of PPD  $\geq$  4 mm and BOP  $\geq$  30% (active periodontal pocket) at baseline after adjusting for confounding factors. Our results were supported by a previous prospective cohort study among 1,023 Japanese employees (mean age: 37.3 years, range: 20-56 years).<sup>19</sup> The results suggest that presence of periodontal disease may be a risk factor for developing hypertension in people with prehypertension.

In another prospective cohort of 31,543 male professionals (dentists, pharmacists, optometrists, podiatrists, osteopaths and veterinarians) aged 40-75 years in USA,<sup>20</sup> there was not a significant relationship between self-reported periodontal disease at baseline and incident hypertension during 20 years of follow-up.<sup>20</sup> In contrast with the previous

report, our results showed a significant relationship between presence of periodontal disease and hypertension. The discrepancy between our study and the previous study could possibly be explained by the difference in age at baseline (18-27 vs. 40-75 years), follow-up period (3 vs. 20 years) and definition of periodontal disease (presence of PPD  $\geq 4$  mm and BOP  $\geq 30\%$  vs. self-reported periodontal disease).

Periodontal disease has been suggested as a risk factor for stroke, coronary heart disease, peripheral arterial disease and hypertension.<sup>18, 33, 34</sup> A recent review suggests that the causal relation has been considered to be both direct and indirect, and there is a pathophysiological link of periodontitis to hypertension.<sup>18</sup> Our results support the causal relationship between periodontal disease and hypertension. The presence of periodontal disease defined as presence of PPD  $\geq 4$  mm and BOP  $\geq 30\%$  was associated with hypertension in this study. BOP is an earlier and sensitive indicator of inflammation,<sup>27</sup> and deepened PPD with BOP (+) increase a risk of progression of periodontal disease.<sup>35</sup> It should be noted that progression of periodontal disease during these 3 years may be associated with blood pressure, since periodontal status can change during the 3 year-university life.<sup>31</sup>

In this study, the risk of having prehypertension/hypertension after 3 years was significantly associated with overweight at baseline in the participants with normal

blood pressure ( $< 120/80$  mm Hg). A previous study reports that BMI is an independent and important predictor of blood pressure among young individuals (25-55 years),<sup>36</sup> which supported our results. On the other hand, in participants with prehypertension at baseline, the risk of having hypertension was significantly associated with no habitual physical activity at baseline. The American Heart Relationship promotes primordial prevention for keeping blood pressure  $< 120/80$  mm Hg to achieve cardiovascular health.<sup>37</sup> Taken together, maintenance of normal weight and habitual physical activity are important factors for young adults in keeping normal blood pressure, and preventing hypertension and future diseases.

Of 151 participants with hypertension at baseline, 48 participants (31.8%) still had hypertension in this study. The risk of keeping hypertension was significantly associated with overweight at baseline when periodontal disease was defined as presence of PPD  $\geq 4$  mm. Weight loss is a valuable treatment goal in hypertensive patients.<sup>38</sup> Thus, we should encourage participants with hypertension to improve overweight during undergraduate days.

We focused on both prehypertension and hypertension, and then three subgroup analyses were performed: i) a change from normal blood pressure to prehypertension/hypertension during 3 years, ii) a change from prehypertension to



hypertension during 3 years and iii) having hypertension during 3 years. Because only 5 participants developed hypertension and 222 developed prehypertension from normal blood pressure, we combined these two cases (the change to prehypertension and that to hypertension). On the other hand, when we used another definition; a change from normal blood pressure/prehypertension to hypertension, the risk of hypertension was significantly associated with periodontal disease defined as presence of PPD  $\geq 4$  mm and BOP  $\geq 30\%$  at baseline (OR: 2.63; 95% CI: 1.18-5.88;  $p = 0.02$ ), which also supported our hypothesis.

The present study had other limitations. First, blood pressure was measured only one time if the value was lower than 140/90 mm Hg, because of a limited amount of time to measure it in our routine health screening. According to the American Heart Association recommendation, a minimum of 2 readings should be taken at intervals of at least 1 minute, and the average of those readings should be used to represent the blood pressure.<sup>23</sup> Second, all participants were recruited from students at Okayama University. This may limit the ability to extrapolate these findings to the general population. Third, we should consider a selection bias, which may lead to over- or underestimation of the true relationship since the follow-up rate (66.7%) was low in this study. We performed multiple imputation with five different values, because, in recent

years, multiple imputation has emerged as a methodology for handling missing data. The trend of results was similar with original findings. In the logistic regression analyses, the risk of having hypertension after 3 years was significantly associated with periodontal disease defined as presence of PPD  $\geq$  4 mm and BOP  $\geq$  30% (active periodontal pocket) at baseline in the participants with prehypertension at baseline (OR: 2.52; 95% CI: 1.11-5.71;  $p = 0.03$ ), which supported our conclusion. However, there were statistically significant differences in both systolic and diastolic blood pressure at baseline between participants who were followed up in this study and subjects who were not ( $120.0 \pm 13.1$  vs.  $122.1 \pm 13.6$  mm Hg and  $72.3 \pm 8.4$  vs.  $73.3 \pm 8.8$  mm Hg, respectively) ( $p < 0.001$ ). The participants who were followed up may have been healthier than the whole population; therefore, the results of this single study should be interpreted with some caution. Fourth, the number of incident cases and the total sample size of the study population were rather small particularly in the short follow-up. In fact, the short follow-up is potentially the major issue of why an association was not found. Finally, we cannot deny the possibility that other potential confounding factors, such as dietary salt intake<sup>39</sup> and delayed heart rate recovery<sup>40</sup> may have affected the observed relationships, because our study was combined with routine health screening and the data obtained were limited.

In conclusion, within the limitations of this short-term prospective cohort study, a significant association between presence of periodontal disease and hypertension was observed in Japanese university students.

**Acknowledgements**

The authors have no conflicts of interest to declare. This study was self-supported.

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