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Review Article

Periodontal disease may increase the risk of coronary heart disease in Chinese population: evidence from a meta-analysis

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Abstract: Aims: Many publications have been devoted to understanding the association between periodontal disease and coronary heart disease (CHD) susceptibility but seem to obtain inconsistent results. A meta-analysis was performed in this paper to quantitatively clarify the relationship between periodontal disease and CHD in the Chinese population. Methods: We searched articles related to this topic from the following databases (date range: from the beginning to July 2020): PubMed, Embase, Web of Science, the Cochrane Library, the Chinese Biomedical Database, and the Chinese National Knowledge Infrastructure. The overall and subgroup analyses were performed using the fixed-effects model to test for homogeneity or the random-effects model to test for heterogeneity. The strength of association between periodontal disease and CHD risk was evaluated by odds ratios (ORs) and 95% confidence intervals (CIs). Results: There were 2,777 CHD cases and 2,655 controls from 18 studies included in the meta-analysis. Overall, we found a positive association between periodontal disease and CHD risk in all of the included Chinese subjects (OR=3.42, 95% CI, 2.58-4.53). Subgroup analyses based on geographic location and sources of control were also performed. The results of subgroup analyses were entirely consistent with those of the overall analysis. Furthermore, a significant association was found among the measures of periodontal disease (e.g., attachment loss, periodontal index, two or more clinical indications, and gum recession and CHD assessment method) according to WHO criteria and coronary arteriography. Conclusions: Collectively, the meta-analysis indicated that periodontal disease could cause CHD susceptibility in the Chinese population. However, our study had some limitations, and more researches involving a larger number of participants from different background are needed to verify these results.

Keywords: Periodontal disease, coronary heart disease, meta-analysis, Chinese population

Introduction

At present, cardiovascular diseases account for 30% of all deaths worldwide. Moreover, the great majority of the disease burden is borne by developing countries [1]. The number of coronary heart disease (CHD)-related deaths dropped significantly in the United States after peaking in around 1968 [2]. However, CHD has become a public health problem in the past few decades in China. The CHD mortality rate (per 100,000 people per year) in China rose from 95.3 in 1999 to 103.4 in 2008 [3]. In 2008, the crude incidence rate of ischemic heart disease was 12.7% in China's urban population [4]. Although some influence factors of CHD risk have been explored, much about CHD cannot be explained by traditional risk factors. In recent publications, several pieces of evidence addressed the causes of chronic inflammation in CHD [5]. Interestingly, the periodontal disease was found to be related to the elevation of several markers of chronic inflammation. Therefore, we assumed an etiologic association between periodontal disease and CHD risk. The research on the association between periodontal disease and CHD risk started a century ago. A large number of systematic reviews and meta-analyses have assessed the potential association between periodontal disease and the

increased risk of CHD [6-14]. But according to a scientific statement made by the American Heart Association in 2012, it was expounded that not enough evidence had been mastered to determine the causal relationship between periodontal disease and the CHD risk [15]. It still remained unclear whether this relationship was affected by ethnicity. Thus, we conducted a meta-analysis to explore the potential association between periodontal disease and CHD risk in the Chinese population.

Materials and methods

This study was conducted following the guidelines by the PRISMA Group.

Publication search and inclusion criteria

Articles related to this topic were searched in PubMed, Embase, Web of Science, the Cochrane Library, the Chinese Biomedical Database [CBM], and the Chinese National Knowledge Infrastructure [CNKI] databases from beginning to July 2020. The following keywords were used: ("coronary heart disease" OR "coronary disease" OR "heart disease" OR "ischemic heart disease" OR "myocardial infarction") AND ("periodontal disease" OR "periodontitis") AND ("China" OR "Chinese"). No language restrictions were imposed. Moreover, the reference lists of the identified studies were manually checked to include other potentially eligible papers. Articles were selected if they satisfied the following criteria: (1) case-control studies; (2) studies devoted to discussing the association between periodontal disease and CHD risk; (3) studies specifying odds ratios (ORs) and 95% confidence intervals (CIs); (4) studies involving the Chinese population; (5) the study with the more complete data was used if two or more studies had partial overlaps. However, reviews, letters, case reports, and editorial articles were excluded.

Data extraction

The titles and abstracts of all possibly related papers were read to assess relevancy. The full texts of the articles would be reviewed if reading the title and abstract alone were not sufficient. Data were extracted from all eligible publications by two investigators independently. The following data were extracted: name of the first author; year of publication; geographic location; sources of control; number of participants; and measures of periodontal disease. Sources of control were divided into hospital-based or population-based studies. The following measures of periodontal disease in dental examinations were extracted: periodontal index, gum bleeding, attachment loss, gum recession, teeth loosening, inflammation/gingivitis, and tooth loss.

Statistical analysis

The strength of association between periodontal disease and CHD risk was assessed by ORs with 95% CIs. Z-test was used to determine whether the pooled ORs were significant or not. The heterogeneity assumption was tested by Cochran's Q statistic, and $P<0.10$ was considered as significant. When the level of heterogeneity was not significant, a fixed-effects model was used to estimate the pooled OR. Otherwise, the random-effects model was used. Sensitivity analysis was carried out by comparing the results of the fixed-effects model against those of the random-effects model. Egger's test was selected to assess the potential publication bias. All of the above analyses were performed using Stata 12.0 (College Station, TX, USA), and $P<0.05$ indicated a statistically significant difference. In addition, hierarchical analyses by geographic location and source of controls were performed to further explore the association between periodontal disease and CHD risk. Furthermore, studies reporting ORs separately for dental and CHD assessments were pooled to examine how the strength of the association varied with the assessment methods.

Results

Research characteristics

One hundred and ninety-eight articles assessing the association between periodontal disease on CHD risk were initially selected. Finally, eighteen articles [16-33] that met the inclusion criteria were included in the analysis. All of the eligible articles were published between 2001 and 2019. A flow chart representing the study selection process is shown in **Figure 1**. There were 2,777 CHD cases and 2,655 controls involved in our analysis, who were included to assess the potential association between periodontal disease and CHD risk in the Chinese

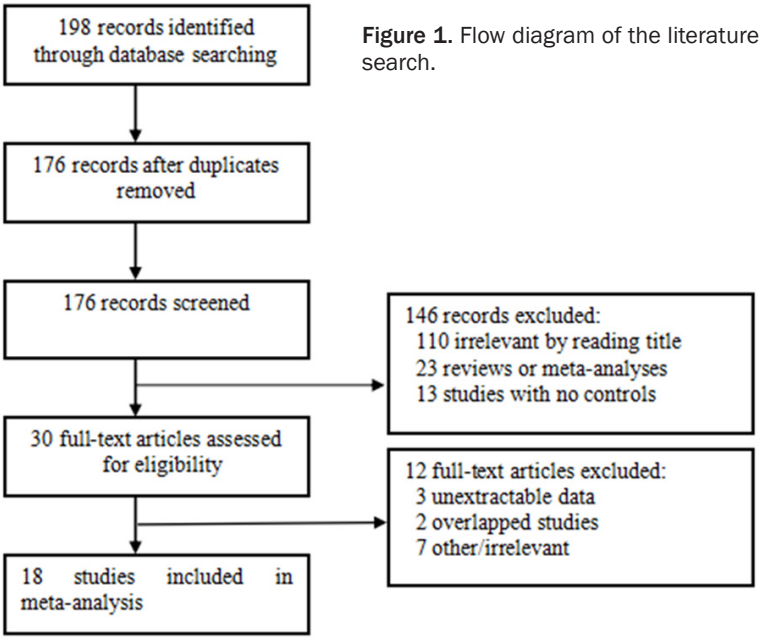

Figure 1. Flow diagram of the literature search.

population. The quality assessment of individual study was conducted with the Newcastle-Ottawa Scale [34]. The study characteristics are shown in **Table 1**.

Meta-analysis results

Overall, periodontal disease could significantly increase the risk of CHD (OR=3.42, 95% CI=2.58-4.53; **Figure 2**). Meanwhile, significant heterogeneity existed in the studies (I^2=79.5%, P<0.001). All of the results of subgroup analyses were consistent with those of the overall analysis (**Table 2**), suggesting that no single factor had a significant impact on the overall result. Furthermore, subgroup analysis was also conducted to explore the sources of heterogeneity. The subgroup analyses by geographic location and source of controls indicated a significant association between periodontal disease and CHD in the northern and southern parts of China. So did the population-based and hospital-based subgroup analyses.

Some articles explained the indicators used in dental examinations and CHD assessment: attachment loss, periodontal index, two or more clinical indications, gum recession, alveolar bone loss, WHO criteria, and coronary arteriography. A significant association was found between the measures of periodontal disease with attachment loss, periodontal index, two or more clinical indications, and gum recession as well as CHD assessment method with WHO criteria and coronary arteriography (**Table 2**). However, there was an insignificant association between dental assessment method with alveolar bone loss.

Sensitivity analysis and publication bias

Sensitivity analysis was carried out to assess the stability of the results. All of the pooled ORs were significant in both the overall analysis and subgroup analyses. Hence, the sensitivity analysis suggested that the findings from the present research were relatively stable (**Table 2**). The publication bias was detected using a funnel plot and Egger's test (**Figures 3** and **4**). However, the Egger's test (t=2.70, P=0.016) was significant.

Discussion

The associations between periodontal disease and the risk of CHD and cardiovascular diseases have been studied for many years. These diseases seem to share several common features, such as high incidence in the elderly, smokers, and hypertensive patients [35]. Since periodontal disease and CHD are common diseases, quantifying the association between them is vital for promoting public health [9]. Our study assessed the association between periodontal disease (the severity of which was judged by attachment loss, periodontal index, gum recession, and alveolar bone loss) and CHD risk and found that periodontal disease might be a risk factor for CHD in the Chinese population. These analyses also provided the current assessment of the relationship between periodontal disease and CHD risk. The present study was intended to clarify the influence for Chinese only and therefore to reduce the influence of different geographic location background or lifestyle.

Our meta-analysis included 18 studies involving 2,777 CHD cases and 2,655 controls. Pooled results from these studies suggested that periodontal disease patients had an over-

Table 1. Characteristics of studies included in the meta-analysis

References	Geographic areas	Sources of control	CHD Case number	Control number	CHD Cases		Controls		Quality score	Dental assessment method	CHD assessment method
					Periodontal disease	No periodontal disease	Periodontal disease	No periodontal disease			
Chen 2001	Guangdong	PC	40	40	33	7	10	30	6	attachment loss	WHO criteria
Lin 2001	Beijing	HC	88	128	47	41	49	79	7	periodontal index	WHO criteria
Liu 2003	Tianjin	PC	216	216	92	124	26	190	8	periodontal index	coronary arteriongraphy
Huang 2003	Shaanxi	HC	146	136	76	70	44	92	7	two or more clinical indications	coronary arteriongraphy
Tang 2004	Guangxi	HC	250	250	156	94	115	135	7	periodontal index	-
Liu 2006	Shandong	HC	45	40	36	9	19	21	7	periodontal index	WHO criteria
Zhang 2006	Xinjiang	HC	277	238	152	125	71	167	7	attachment loss	coronary arteriongraphy
Zhang 2006a	Shandong	HC	76	74	40	36	25	49	6	attachment loss	coronary arteriongraphy
Li 2006	Shaanxi	HC	357	305	307	50	220	85	8	periodontal index	coronary arteriongraphy
Meng 2008	Heilongjiang	PC	150	150	87	63	49	101	8	gum recession	WHO criteria
Wu 2008	Hunan	HC	77	75	65	12	26	49	6	gum recession	coronary arteriongraphy
Dong 2009	Guangdong	PC	161	162	122	39	97	65	8	alveolar bone loss	coronary arteriongraphy
Chen 2011	Guangdong	HC	46	34	37	9	10	24	7	alveolar bone loss	coronary arteriongraphy
Zhang 2012	Hebei	HC	162	162	110	52	89	73	7	gum recession	coronary arteriongraphy
Liu 2016	Guangdong	PC	276	235	152	124	70	165	8	two or more clinical indications	WHO criteria
Zhang 2016	Hebei	PC	200	200	109	91	9	191	8	two or more clinical indications	-
Lu 2017	Jiangsu	HC	150	150	126	24	96	54	7	two or more clinical indications	coronary arteriongraphy
Li 2019	Shaanxi	PC	60	60	13	47	7	53	6	two or more clinical indications	-

HC, hospital controls; PC, healthy population controls.

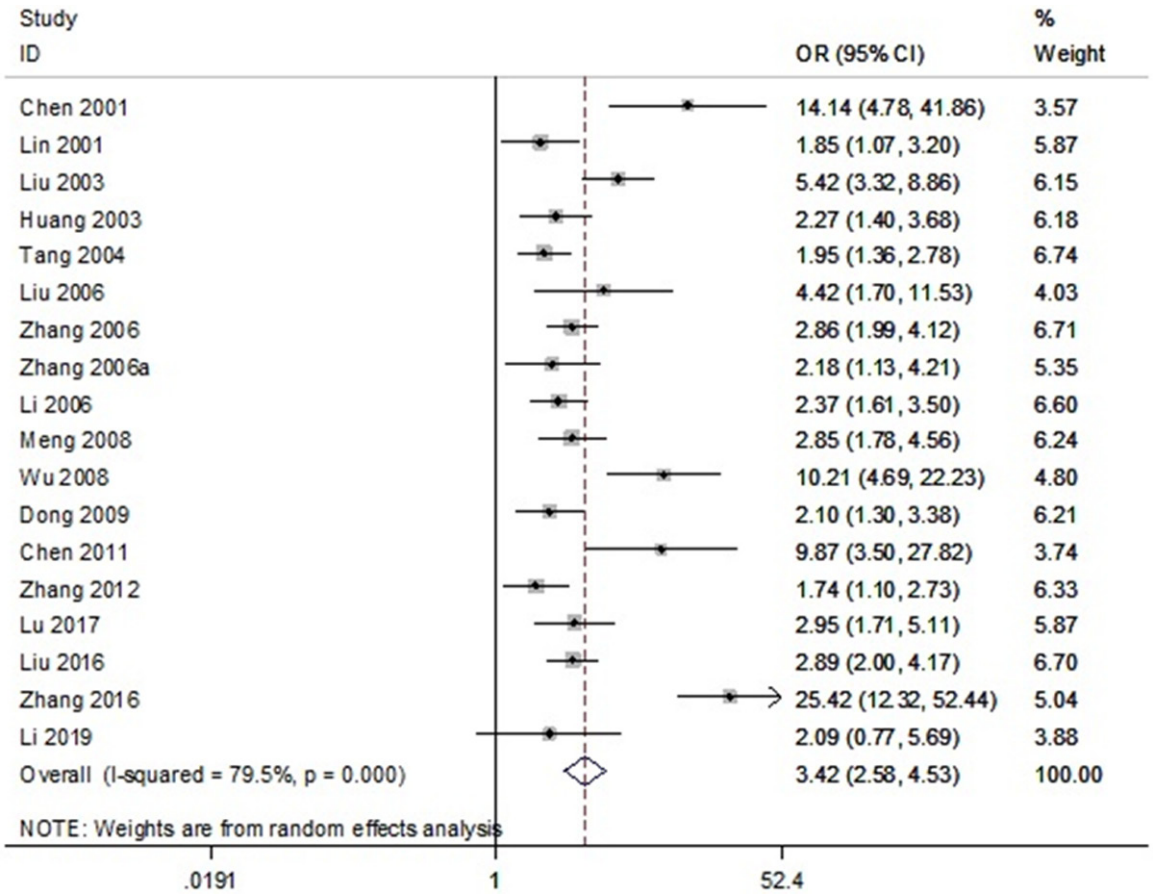

Figure 2. The forest plot on the association between periodontal disease and CHD risk in total analysis.

Table 2. The association between periodontal disease and CHD risk among Chinese

Analysis model	n	ORr (95% CI)	ORf (95% CI)	P_h
Total analysis	18	3.42 (2.58-4.53)	3.03 (2.69-3.41)	0.000
Geographic areas				
South China	8	3.60 (2.42-5.36)	2.83 (2.38-3.35)	0.000
North China	10	3.25 (2.13-4.97)	3.23 (2.74-3.80)	0.000
Control sources				
Healthy population controls	7	4.69 (2.58-8.53)	4.10 (3.37-4.98)	0.000
Hospital controls	11	2.75 (2.10-3.58)	2.52 (2.17-2.93)	0.002
Dental assessment method				
attachment loss	3	3.86 (1.74-8.56)	3.10 (2.29-4.19)	0.012
periodontal index	5	2.75 (1.82-4.17)	2.60 (2.11-3.19)	0.007
two or more clinical indications	5	3.97 (1.87-8.41)	3.82 (3.05-4.79)	0.000
gum recession	3	3.49 (1.47-8.27)	2.82 (2.10-3.78)	0.001
alveolar bone loss	2	4.24 (0.93-19.21)	2.78 (1.81-4.25)	0.008
CHD assessment method				
WHO criteria	5	3.31 (2.10-5.24)	2.96 (2.33-3.76)	0.021
coronary arteriongraphy	10	3.08 (2.27-4.19)	2.85 (2.44-3.33)	0.000

ORr: Odd ratio for random-effects model; ORf: Odd ratio for fixed-effects model; P_h: *P* value for heterogeneity test.

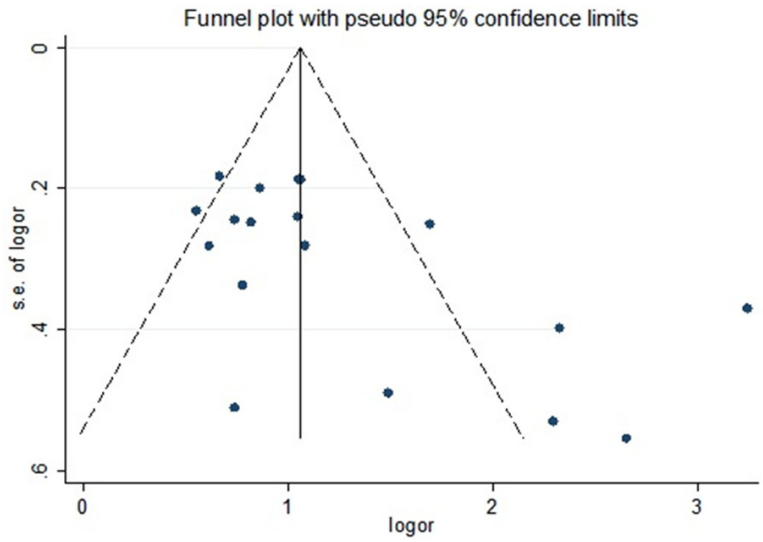

Figure 3. Publication bias assessment using Begg's funnel plot.

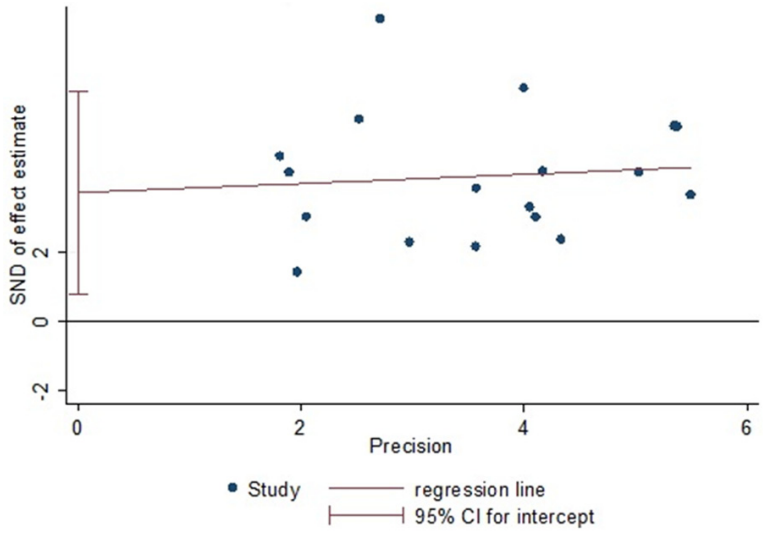

Figure 4. Egger's linear regression.

all 3.42-fold increased risk of CHD compared to those without periodontal disease or the general Chinese population. Hierarchical analysis was also conducted to further explore the influence of geographic location and sources of control. A significant association was found between periodontal disease and CHD risk in the northern and southern parts of China. Similar findings were obtained from hospital-based and population-based subgroup analyses. In addition, a significant association was found among the measures of periodontal disease with attachment loss, periodontal index, two or more clinical indications, and gum recession as well as CHD assessment method with WHO criteria and coronary arteriography.

There have been several published meta-analyses suggesting that periodontal disease may contribute to the risk of CHD [6-14]. There is still a lack of standardized protocols for determining periodontal disease and CHD. Some of the researches used self-report, which might underestimate the level of disease, while other studies involving the cases of gingivitis and periodontitis might overestimate the disease prevalence. Thus, this problem is better addressed through a meta-analysis in order to reach a consensus. On the other hand, we only included the Chinese population using consistent evaluation criteria for periodontal disease and CHD, and conducting subgroup analyses by geographic location and source of controls. Two more databases (CBM and CNKI) in Chinese language were searched and more Chinese participants included in our study than the previous meta-analyses. Furthermore, the pooled OR for the association between periodontal disease and CHD risk in our study was higher than those in the published meta-analyses with populations except Chinese. Sensitivity analysis confirmed the reliability and stability of our findings. Thus, our meta-analysis strongly supported the association between periodontal disease and CHD risk in the Chinese population.

Several limitations were present in our work. Firstly, a publication bias was identified, as most included studies reported positive results and they were more likely to be published. Secondly, we were unable to further analysis that may be affected by aging, cigarette smok-

ing, alcohol consumption, and dietary structure due to the limited data in each included study. Thirdly, CHD is a complex disease with many etiological factors, including environmental and genetic factors. However, some of the included studies in our meta-analysis did not consider the effects of environmental factors on CHD.

Conclusion

In conclusion, the meta-analysis indicated that periodontal disease might cause CHD susceptibility in the Chinese population. Although some limitations existed in our study, more researches recruiting a larger number of participants from different backgrounds are needed to verify our findings. We recommend preventing CHD by maintaining periodontal health, given the high mortality rate of cardiovascular diseases and the relatively minor morbidity of periodontal therapy.

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Disclosure of conflict of interest

None.

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References

[1] Gaziano TA. Cardiovascular disease in the developing world and its cost-effective management. Circulation 2005; 112: 3547-3553.

[2] Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Shay CM, Spartano NL, Stokes A, Tirschwell DL, VanWagner LB, Tsao CW; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2020 update: a report from the American heart association. Circulation 2020; 141: e139-e596.

[3] Jiang G, Wang D, Li W, Pan Y, Zheng W, Zhang H and Sun YV. Coronary heart disease mortality in China: age, gender, and urban-rural gaps during epidemiological transition. Rev Panam Salud Publica 2012; 31: 317-324.

[4] Li X, Zhang Y, Wang M, Lv X, Su D, Li Z, Ding D, Xia M, Qiu J, Hu G and Ling W. The prevalence and awareness of cardiometabolic risk factors in Southern Chinese population with coronary artery disease. ScientificWorldJournal 2013; 2013: 416192.

[5] Ridker PM, Hennekens CH, Buring JE and Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Eng J Med 2000; 342: 836-843.

[6] Madianos PN, Bobetsis GA and Kinane DF. Is periodontitis associated with an increased risk of coronary heart disease and preterm and/or low birth weight births? J Clin Periodontol 2002; 29: 22-36; discussion 37-8.

[7] Janket SJ, Baird AE, Chuang SK and Jones JA. Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003; 95: 559-569.

[8] Scannapieco FA, Bush RB and Paju S. Associations between periodontal disease and risk for atherosclerosis, cardiovascular disease, and stroke. A systematic review. Ann Periodontol 2003; 8: 38-53.

[9] Khader YS, Albashaireh ZS and Alomari MA. Periodontal diseases and the risk of coronary heart and cerebrovascular diseases: a meta-analysis. J Periodontol 2004; 75: 1046-1053.

[10] Bahekar AA, Singh S, Saha S, Molnar J and Arora R. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis. Am Heart J 2007; 154: 830-837.

[11] Mustapha IZ, Debrey S, Oladubu M and Ugarte R. Markers of systemic bacterial exposure in periodontal disease and cardiovascular disease risk: a systematic review and meta-analysis. J Periodontol 2007; 78: 2289-2302.

[12] Humphrey LL, Fu R, Buckley DI, Freeman M and Helfand M. Periodontal disease and coronary heart disease incidence: a systematic review and meta-analysis. J Gen Intern Med 2008; 23: 2079-2086.
[13] Blaizot A, Vergnes JN, Nuwwareh S, Amar J and Sixou M. Periodontal diseases and cardiovascular events: meta-analysis of observational studies. Int Dent J 2009; 59: 197-209.
[14] Leng WD, Zeng XT, Kwong JS and Hua XP. Periodontal disease and risk of coronary heart disease: an updated meta-analysis of prospective cohort studies. Int J Cardiol 2015; 201: 469-472.
[15] Lockhart PB, Bolger AF, Papapanou PN, Osinbowale O, Trevisan M, Levison ME, Taubert KA, Newburger JW, Gornik HL, Gewitz MH, Wilson WR, Smith SC Jr and Baddour LM; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association? A scientific statement from the American Heart Association. Circulation 2012; 125: 2520-2544.
[16] Chen WL, Yan Y and Wang QY. Relationship between the changes of serum C- reactive protein in patients with coronary heart disease and periodontal disease. Chinese General Practice 2001; 4: 859-860.
[17] Lin YG and Li WL. Assessing the relationship between periodotal infection and coronary heart disease in elderly people. J Clin Stomatol 2001; 17: 15-16.
[18] Liu CL. Clinical observation of chronic periodontitis and coronary heart disease. J Modern Stomatol 2003; 17: 374-375.
[19] Huang HM, Wang QT and Yan SP. A clinical questionnaire about the relationship between the periodontal disease and coronary heart disease. Chin J Conserv Dent 2003; 13: 218-221.
[20] Tang LY and Huang W. Study on the relationship between periodontal disease and coronary heart disease. Acta Medicinae Sinica 2004; 17: 959-960.
[21] Liu P, Zhang Y, Wang SJ, Zhang FH and Zheng PH. Correlation between periodontal disease and coronary atherosclerotic heart disease. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2006; 28: 169-172.
[22] Zhang YM, Zhong LJ, He BX, Nie J, Wang X and Li WC. Study on the correlation between coronary heart disease and chronic periodontitis. Zhonghua Liu Xing Bing Xue Za Zhi 2006; 27: 256-259.
[23] Zhang DJ, Liu H and Zhao XZ. Research of the relationship between the periodontal and coronary heart disease. Chin J Conserv Dent 2006; 16: 38-40.
[24] Li GZ, Xu L, Quan ZL, Kou Z, Cai L, Su L, Li X and Zhong X. Study on the correlation between periodontal disease and coronary heart disease in the elderly: a report of 662 cases. J South Med Univ 2006; 26: 1652-654.
[25] Meng PS, Wei ZM, Bai XF and Li ZQ. Research of the relationship between the periodontal disease and coronary heart disease. Chin J Med Guide 2008; 10: 486-487.
[26] Wu ZZ and Yao XL. Study on the relationship between periodontal disease and coronary atherosclerotic heart disease. Modern Med J 2008; 36: 185-187.
[27] Dong LW, Xing CY, Wang XH and Huang W. Research of the relationship between the periodontal disease and coronary heart disease. J Dental Prev Treat 2009; 17: 357-361.
[28] Chen JX. Investigation and analysis of the correlation between coronary heart disease and periodontitis. Chinese Community Doctors 2011; 13: 163.
[29] Zhang LP, Li XQ, Zhou GX and Fan HM. Periodontal disease was an independent risk factor of coronary heart disease by multi-factors Logistic regression analysis. Clinical Medicine of China 2012; 28: 284-286.
[30] Lu YZ, Fan B, Cao XY and Wang LS. Clinical study on the relationship between periodontal disease and coronary heart disease. Journal of Nantong University (Medical Sciences) 2017; 37: 565-567.
[31] Liu YY. Correlation analysis on coronary heart disease and chronic periodontitis. J Modern Stomatol 2016; 30: 169-172.
[32] Zhang L. Clinical treatment of chronic periodontitis and coronary heart disease. General Journal of Stomatology 2016; 3: 24, 26.
[33] Li T and Ruan K. Clinical study on the relationship between periodontitis and coronary heart disease. Electronic Journal of General Stomatology 2019; 6: 24, 27.
[34] Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M and Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
[35] Beck JD, Slade G and Offenbacher S. Oral disease, cardiovascular disease and systemic inflammation. Periodontol 2000 2000; 23: 110-120.