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ORIGINAL ARTICLE

Research performance of biomarkers from biofluids in periodontal disease publications

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Abstract *Background/purpose:* The biomarkers in biofluids are useful tools for evaluating the activity of periodontal disease. The purpose of this study is to evaluate the performance of publications on biomarkers and periodontal disease for four categories of biofluid.
Materials and methods: A total of 2455 documents of "original article" published in the Science Citation Index database between 1996 and 2010 were analyzed for this study. The biofluids in these original articles were subdivided into four categories of specimen: saliva, serum, plasma, and gingival sulcus fluid (GSF; including gingival crevicular fluid). The total number of articles and the number of citations per publication were defined as quantitative and qualitative indexes in this study. The *h*-index, an indicator of both quality and quantity of scientific publications, was also included in the analysis.
Results: The standard errors of the annual citations per publication for periodontal disease articles including topics on serum (2.4) or on saliva (2.9) were less than those for articles including topics on plasma (5.1) or on GSF (4.9). The lesser variation in the number citations

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reflected the consistent quality of periodontal disease articles concerning serum and saliva topics. The *h*-index was not significantly different among articles including plasma (66), serum (59), or saliva (55). The research performance of articles including GSF (*h*-index = 20) was worse than for the other three types of biofluids.
Conclusion: Results of *h*-index indicate that biomarkers in saliva, as well as in serum and plasma, are good indicators for use in studying periodontal disease.

Introduction

Periodontal disease is an inflammatory disease affecting periodontal tissues including gingiva, alveolar bone, and the periodontal ligament.[1] Studies have shown that the inflammatory response may induce systemic activation and it is thus associated with systemic diseases such as coronary heart disease, vascular diseases,[2,3] and diabetes mellitus (DM).[4] Because periodontal disease is a systemic disease, biomarkers in body fluids were used to assess the inflammatory molecules and other mediators that lead to periodontal disease and other systemic complications.

A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention" by the Biomarkers Definition Working Group of the National Institutes of Health.[5] Biomarkers in biofluids are not only helpful tools for disease diagnosis, disease prognosis, and clinical response after treatment, but can also serve as useful screening tools.[5] Linked animal models and biomarkers can be used to confirm the translation of endogenous metabolism and exposure to environmental hazards to disease mechanisms.[6] The accessibility of biofluids is a key reason for their utilization in biomarker research.

Analysis of metabolites or disease-related biomarkers in biofluids, including plasma, whole blood, serum, urine, saliva, cerebrospinal fluid, synovial fluid, semen, and tissue homogenates, has assisted in clinical diagnosis.[7] Serum and plasma represent a profile of bodily circulation, and the proteins of those specimens represent the performance of the entire body.[8] Saliva offers a noninvasive and highly accessible specimen source, and also contains potential biomarkers of oral disease.[9] Gingival sulcus fluid (GSF) includes gingival crevicular fluids collected from gingival crevices surrounding the teeth and is a serum transudate and content inflammatory exudate.[10] Using biomarkers contained in biofluids is a good way to assess inflammatory mediators that lead to periodontal disease. The purpose of this study was to evaluate the performance of publications on biomarkers and periodontal disease for four categories of biofluids listed in the Science Citation Index (SCI) database between 1996 and 2010.

Materials and methods

The search engine used in this study was the SCI database of ISI Web of Science, Philadelphia, PA, USA.[11] Document search strategies were limited as follows: the keywords of topics were "periodontitis or periodontal" and "serum or plasma or (gingival sulcus fluid) or (gingival crevicular fluid) or saliva" in the 15 years from 1996 to 2010. Based on these search strategies, a total of 2705 documents were identified.

The 2455 documents were then defined by document type as "Article" for advanced research, and further subdivided by four categories of specimens: serum, plasma, GSF (including gingival crevicular fluid), and saliva (Fig. 1). The publication numbers of original articles concerning serum, plasma, GSF, and saliva were 1137, 470, 256, and 713, respectively.

The total number of publication numbers, page count, author number, citation times, and *h*-index were included as the analyzed parameters in this study. The total article number was defined as a quantitative index in this study. Because the number of publications does not reflect the quality of scientific publications, the citations per publication (CPP) was used as a qualitative index in this study. The *h*-index was first introduced by J.E. Hirsch[12] and can present both quality and quantity of scientific publications. The *h*-index reflects both the number of publications and the number of citations. It takes into consideration productivity as reflecting the importance or impact of the publications: the value of *h* is equal to the number of publications (*N*) in the list that have *N* or more citations.

Statistical methods

SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. The standard error (SE) is a

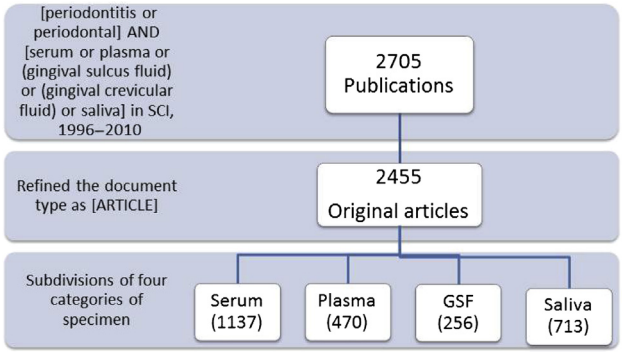

Figure 1 Search strategies and process using the Web of Science database. GSF = gingival sulcus fluid.

quantitative measure of the variability of sample means obtained from samples of size *N* drawn from the same population. The SE was used to estimate the variability of CPP in the four specimen categories. Analysis of variance (ANOVA) and Scheffe's *post hoc* test were used to compare page counts and author numbers among the four types of specimen. For all statistical tests, the level for significance was set at 0.05.

Results

According to the SCI database, a total of 2455 original articles were published on the topic of "periodontal disease and serum, plasma, saliva, or GSF" from 1996 to 2010. The average page count and author number of the 2455 original articles were 7.37 pages and 5.47 authors, respectively (Table 1). The page count of periodontal disease articles including topic on saliva (7.11 pages) was less than those of articles including topic on serum (7.45 pages) or on plasma (7.58 pages; $P = 0.005$ for ANOVA and $P < 0.05$ for Scheffe's test).

The annual periodontal disease article numbers and citations per publication (CPP) are shown in Fig. 2. The mean of the annual periodontal disease article numbers was 163.6/year. There were ~110–140 articles published between 1996 and 2004; a clear rise in publication activity was found in 2005. The greatest publication activity occurred in 2009 (283 articles), with nearly a three-fold the number of articles for 2000. The mean value of the annual periodontal disease article CPP was 19.4. The CPP remained stable (~24–26) from 1996 to 2000. Between 2001 and 2005, the CPP was largest in the year 2003 (CPP = 27), followed by 2002 (CPP = 25.0), and 2001 (CPP = 22.3).

To evaluate the research performance of the periodontal disease for the four categories of biofluid, the annual article number, and CPP were fractionalized by the publication specimen type, as shown in Fig. 3. The mean numbers of annual published periodontal disease articles including topics on serum, plasma, GSF, and saliva were 75.8, 31.3, 17.1, and 18.0 articles, respectively. The mean CPPs of periodontal disease articles including topics on serum, plasma, GSF, and saliva were 18.9, 23.8, 18.0, and 15.5, respectively. The periodontal disease articles including plasma topics had the highest CPP (annual average was 23.8) compared to articles including topic on the other three types of specimen. For periodontal disease articles including serum topics, the largest publication numbers and the highest CPP were shown in 2009 (article number = 141) and 1997 (CPP = 18.9). The standard errors of annual CPP for periodontal disease articles on serum, plasma, GSF, and saliva topics were 2.4, 5.1, 4.9, and 2.9, respectively. The smaller variation of citation times reflected the even quality of periodontal disease articles regarding serum and saliva compared to periodontal disease articles concerning plasma and GSF.

Table 1 Distribution of publication activities fractionalized by specimen types in periodontal disease articles.

	Article no.	Page count	Author no.
		Mean ± SE	Mean ± SE
Periodontal disease articles	2455	7.37 ± 0.05	5.47 ± 0.05
Article including specimen types			
Serum	1137	7.45 ± 0.07*	5.56 ± 0.07
Plasma	470	7.58 ± 0.12*	5.60 ± 0.11
GSF	256	7.32 ± 0.15	5.34 ± 0.13
Saliva	713	7.11 ± 0.10	5.39 ± 0.08
P value for ANOVA		0.005	0.21

SE = standard error.
*Significant difference ($P < 0.05$) from saliva by ANOVA and Scheffe's test.

Table 2 shows a regression analysis of the citation numbers and page count or author number in periodontal disease articles. For each increase of one page, the number of citations increased by 1.19 for periodontal disease articles. The number of citations significantly increased with page count for periodontal disease articles on plasma ($P < 0.01$), GSF ($P < 0.001$), and saliva ($P < 0.01$) topics, but this positive relationship was not shown for periodontal disease articles on serum topic ($P = 0.06$). After being subdivided into biofluid categories, the change in citation numbers was greatest for periodontal disease articles including on GSF topics; 1.19 citations in periodontal disease articles increased to 2.21 citations in periodontal disease articles on GSF topics. Fig. 2 showed that the number of periodontal disease articles increased but the CPP decreased from 2006. Because citation numbers are likely to be affected by the time elapsed between article publication and the date of data collection, the length of time since article publication was used as a control variable in the multiple-regression model (Model II). In Model II of citation numbers and page counts regression, after adjusting for length of time since article publication, the β value of Model II was slightly increased over Model I. For each increase of one author, the citation numbers increased from 0.03 (Model I) to 1.78 (Model II) in periodontal disease articles including saliva topic, when the length of time since article publication was taken into account. The page count may increase with author number. After adjusting for length of time since article publication and author number (Model III), the relationship between citation number and page count was the same as for Model II. The relationship between citation number and page count was not influenced by the author numbers. For each increase of one author, the citations increased from 1.78 (Model II) to 0.42 (Model IV) in periodontal disease articles including topics on saliva. The association between citation number and author numbers was influenced by the page count in periodontal disease articles including saliva topic. The results show that time span is a key factor for the association between citation numbers and author numbers in periodontal disease articles discussing saliva.

Fig. 4 shows the quality and quantity of periodontal disease articles including serum, plasma, GSF, and saliva topics. The CPP was significantly higher for periodontal disease articles on plasma topic (CPP = 19.19) compared to those for periodontal disease articles on GSF topic (CPP = 12.67) or on saliva topic (CPP = 13.17). The *h*-index showed its highest values for periodontal disease articles

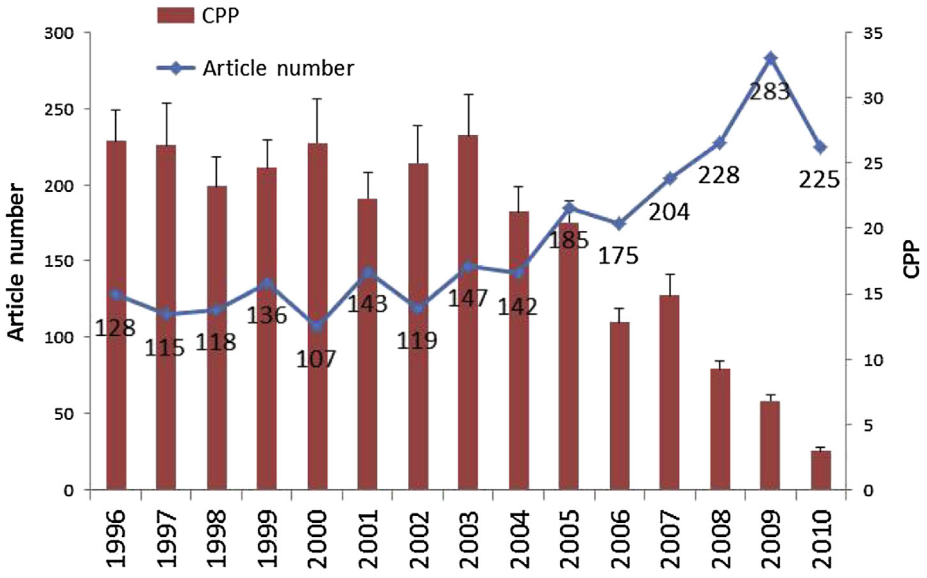

Figure 2 Periodontal disease annual article numbers and citations per publication (CPP).

including serum topic, and was lowest for periodontal disease articles including GSF topics. The research performance of periodontal disease articles including GSF (*h*-index = 20) was lower than the periodontal disease articles including other 3 types of specimen.

In order to realize the information of research trend in four biofluid categories, we analyzed the CPP of the top 10 biomarker appearances in keywords in Table 3. The total numbers of keywords in categories of serum, plasma, saliva, and GSF were 14796, 6418, 8984, and 3313,

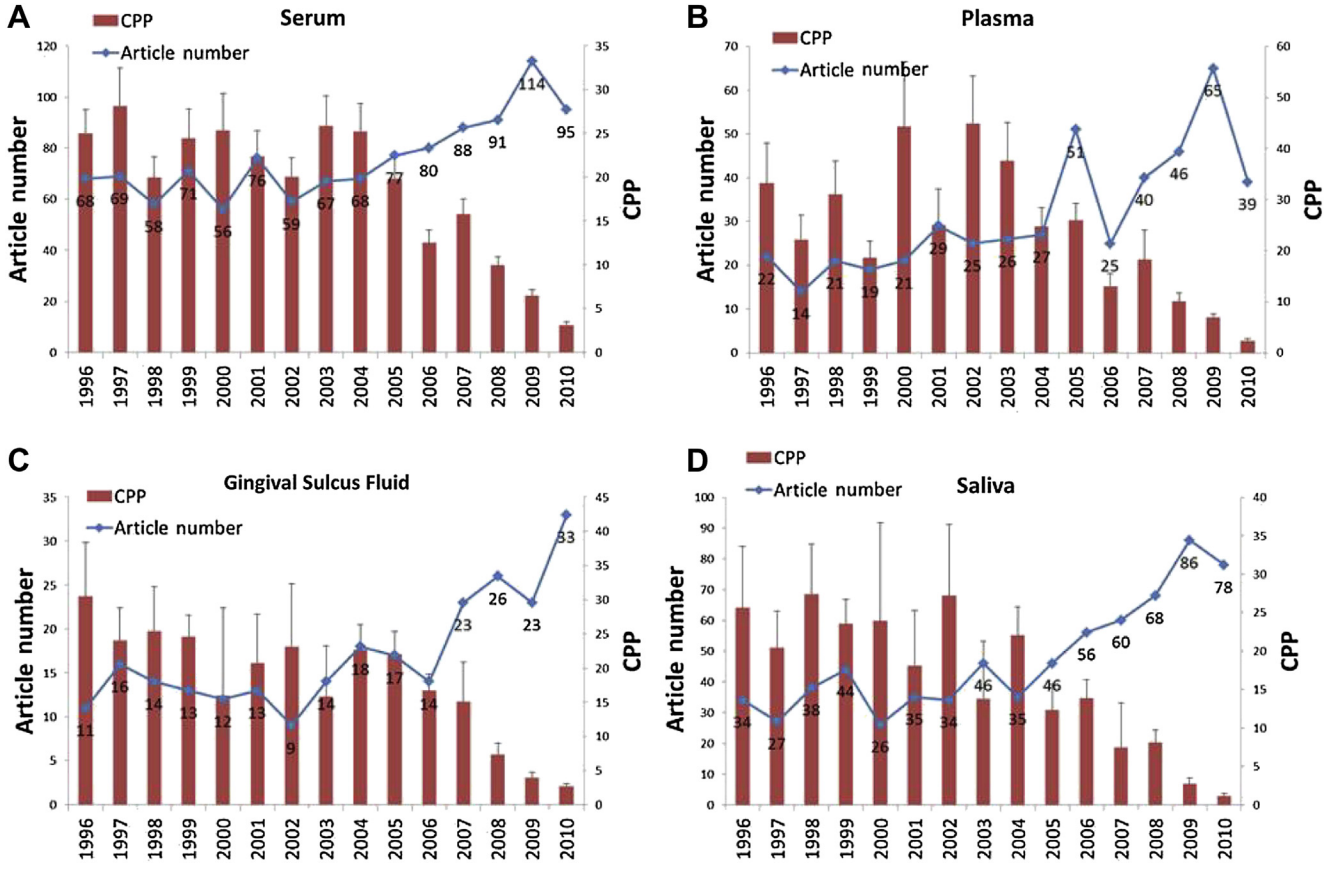

Figure 3 Periodontal disease annual article numbers and citations per publication (CPP) in fractionalized specimen categories. (A) Periodontal disease article including serum. (B) Periodontal disease article including plasma. (C) Periodontal disease article including gingival sulcus fluid. (D) Periodontal disease article including saliva.

Table 2 Regression analysis on the citation numbers and page count or author number in periodontal disease articles.

	Model I[a]		Model II[b]		Model III[c]		Model IV[d]	
Page counts	β	SE	β	SE	β	SE		
Periodontal disease articles	1.19***	0.18	1.29***	0.17	1.26***	0.16		
Articles including specimen types								
Articles including serum	0.54^{+}	0.28	0.68*	0.27	0.57*	0.26		
Articles including plasma	1.68**	0.53	1.87**	0.51	1.82**	0.51		
Articles including GSF	2.21***	0.49	2.46***	0.44	2.45***	0.52		
Articles including saliva	1.27***	0.28	1.32**	0.25	1.31***	0.25		
Author numbers	β	SE	β	SE			β	SE
Periodontal disease articles	0.36^{+}	0.21	1.03*	0.20			0.97**	0.20
Articles including specimen types								
Articles including serum	0.62*	0.28	1.51***	0.27			1.46***	0.27
Articles including plasma	0.11	0.59	0.84	0.57			0.68	0.57
Articles including GSF	0.22	0.59	0.62	0.55			0.55	0.52
Articles including saliva	0.03	0.31	1.78***	0.16			0.42	0.31

$+0.1 > P > 0.05$
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.
[a] Univariate analysis.
[b] Adjusted for length of year from article publication to 2011.
[c] Adjusted for author number and length of year from article publication to 2011.
[d] Adjusted for page count and length of year from article publication to 2011.

respectively. The most appearances of biomarkers in keywords in the categories of serum, plasma, saliva, and GCF were by C reactive protein (CRP), CRP and interleukin 6 (IL-6), immunoglobulin A (IgA), and interleukin 1 β (IL-1β), respectively. The inflammatory factors, such as interleukin family and matrix metalloproteinase family also appeared in the top ten biomarkers of keywords. When using the CPP as the research performance index, the largest CPP of biomarkers in categories of serum, plasma, saliva, and GSF were IL-6 (CPP = 22.26), CRP (CPP = 54.44), matrix metalloproteinase 9 (MMP-9; CPP = 38.14), and MMP-9 (CPP = 54.40), respectively. On the point of research performance, the article topic including CPR or IL-6 had the best research performance in whole body circulation fluids such as serum and plasma. The article topics including MMP-9 or MMP-8 had the best research performance in oral fluids such as saliva and GCF.

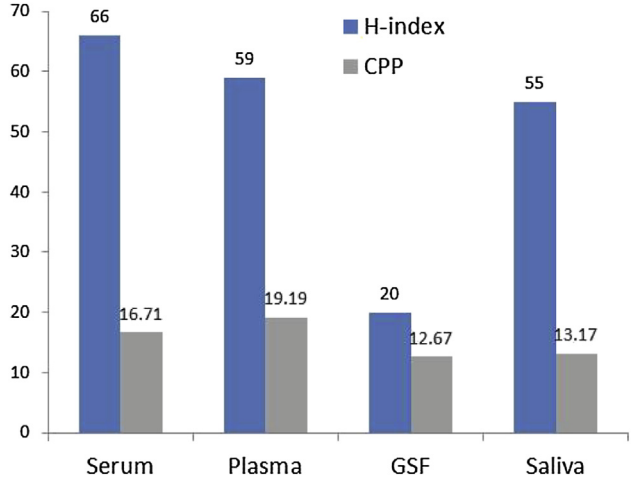

Figure 4 Periodontal disease article citations per publication (CPP) and *h*-index in the fractionalized specimen categories.

Discussion

In general, research activities have been expanding every year. The number of journals and their annual volumes of articles have been increasing. In this study, the publication numbers increased with years, and the results showed that interest in the research topic of "periodontal disease" and "biofluids" increased throughout the world. According to our results, publications increased ~30% in 2005 (185 articles) compared to 2001–2004 (average was 137 articles of 2001–2004). Although the number of articles has gradually increased in recent years, CPP, a qualitative index of publication, was highest in 2003. This phenomenon may be because publications that studied the association between periodontal disease and biofluids had been fully investigated in 1996–2003.

Citation numbers can be affected by many factors, such as the participation of coauthors who may contribute self-citations, and the topic of the publication; especially publications on new techniques and methodologies. In this study, citation numbers increased with page counts. This may be because more page numbers provided a greater amount of significant information, or more important novel results were discussed in the article, and more authors may have contributed to the publications. The association between page counts and citation numbers or biofluid categories may not reflect scientific significance because the page count is limited by the publication criteria of individual journals. In periodontal disease articles including saliva topic, the association between citation numbers and

Table 3 The CPP of the top 10 biomarkers appearance in keywords.

CPP Ranking	Serum (N = 1137)			Plasma (N = 470)			Saliva (N = 713)			GSF (N = 256)		
	Keywords	N (%)	CPP	Keywords	N (%)	CPP	Keywords	N (%)	CPP	Keywords	N (%)	CPP
1	IL-6	97 (8.53)	22.26	CRP	27 (5.74)	54.44	MMP-9	14 (1.96)	38.14	MMP-9	5 (1.95)	54.40
2	CRP	117 (10.29)	22.21	IL-6	27 (5.74)	43.48	MMP-8	24 (3.37)	31.13	MMP-8	13 (5.08)	32.46
3	MMP-8	10 (0.88)	21.50	PDGF	12 (2.55)	34.50	8-OHdG	6 (0.84)	20.33	Type I collagen	4 (1.56)	25.00
4	Type I collagen	37 (3.25)	20.46	TGF-β	12 (2.55)	31.50	CRP	8 (1.12)	18.63	TNF-α	13 (5.08)	24.00
5	IL-1β	70 (6.16)	19.24	MMP-8	8 (1.70)	30.88	IL-10	7 (0.98)	17.71	IL-6	20 (7.81)	20.00
6	IL-10	26 (2.29)	19.08	Type I collagen	8 (1.70)	23.00	Cystatins	20 (2.81)	16.85	IL-8	7 (2.73)	19.71
7	IgG2	41 (3.61)	17.46	ALP	12 (2.55)	22.08	IL-1β	17 (2.38)	12.24	Cystatins	11 (4.3)	19.27
8	ALP	69 (6.07)	15.54	IL-10	10 (2.13)	20.80	IL-8	6 (0.84)	10.83	IL-1β	30 (11.72)	17.83
9	TAS	31 (2.73)	13.71	VEGF	11 (2.34)	16.27	IgA	31 (4.35)	10.55	CRP	7 (2.73)	11.29
10	NF-κB	30 (2.64)	11.37	IL-1β	15 (3.19)	11.67	IL-6	20 (2.81)	9.25	ALP	9 (3.52)	10.33

8-OHdG = 8-oxo-7,8-dihydro-2′-deoxyguanosine; ALP = alkaline phosphatase; CPP = citations per publication; CRP = C-reactive protein; IgA = immunoglobulin A; IgG2 = immunoglobulin G2; IL = interleukin; MMP = matrix metalloproteinase; NF-κB = nuclear factor kappa B; PDGF = platelet-derived growth factor; TAS = total antioxidant status; TGF-β = transforming growth factor β; TNF-α = tumor necrosis factor α; VEGF = vascular endothelial growth factor.

author numbers was significant when the length of time since article publication was taken into account. This may be because more author numbers provided a greater amount of specimens, novel ideas, new techniques, and methodologies to improve the reliability and quality power of studies.

The term "bibliometrics" was first introduced by Pritchard[13] and defined as "the application of mathematics and statistical methods to books and other media of communication". Bibliometrics is also used as a method to analyst the quantitative of scientific and technological literatures. There are many bibliometric indicators used to measure the quality of scientific literature, including article counts, impact factors, journal rankings, the number of citations, and the *h*-index.[14] Self-citation is a factor that may affect those indicators, because authors cite their earlier studies to enhance the perceived reliability or value of their publications. The rate of author self-citation in the area of general medicine (328 journal articles) was 6.5%.[15] This study showed that the author number significantly increases with self-citation rate (r = 0.11, P = 0.04).[16] Counting author self-citation times is a limitation in this study because the article number in this study (n = 2455) is more than five times greater than other studies that refer to the topic of author self-citation. Further studies should focus on the association between self-citation and research performance indicators in oral medicine when the personal unique research identification is well established.

The most cited article was published by Kiecolt-Glaser et al[17] in the *Proceedings of the National Academy of Sciences of the United States of America*. The article was cited 325 times between 2003 and 2011. The study showed that chronic stress markers such as IL-6 may increase the susceptibility to age-related diseases. Other studies have indicated that periodontal disease is a multifactorial inflammatory disease. The periodontal breakdown-associated inflammatory process contributes to an increase in inflammatory mediators including tumor necrosis factor-α, MMP-8, CRP, IL-1, and IL-6. During the initiation and course of inflammatory responses in periodontitis, peri-implantitis, and cardiovascular diseases, proinflammatory mediators (especially MMP-8) are upregulated not only in affected tissues but also in the secreted, disease-affected, oral fluids (gingival crevicular fluid, peri-implant sulcular fluid, mouth rinse, and saliva), as well as in serum and plasma.[18,19]

Biomarkers in body fluid can be a diagnostic and screening tool for several systemic diseases, such as cardiovascular disease, cerebral infarction, rheumatoid arthritis, and diabetes.[20] Studies have recently shown that biomarkers in human body fluid play an important role in the association between periodontal disease and other related systemic diseases.[3,21,22] The discovery of biomarkers in body fluids will not only improve the process of translational medicine, but also help clarify disease mechanisms.[6] The methods for collection, storage, and even biobanking of biofluids will be developed in the UK.[23] The publication performance in countries that establish a national biobank should be an interesting issue and will need to be investigated in the future.

Biomarkers such as cytokines in serum, plasma, GCF, and saliva have been identified as inflammatory indicators of periodontal disease and other systemic diseases.[4,24] These

specimens are widely collected and used for studying the association between biomarkers and periodontal and/or systemic diseases. According to article numbers, the collective frequency of serum, plasma, and saliva publications was higher than that for GSF, and the quality and quantity of publications on GSF were lower than for the other 3 types of specimens. The inflammatory response of periodontitis is complex and produces some kind of marker by Gram-negative anaerobic bacteria, such as *Porphyromonas gingivalis*. In those condition the biomarker form GCF is better than others biofluids.[24] Blood or saliva collection is less technique-sensitive than GSF collection. Some constituents of saliva that originate from GSF can be analyzed.[25–27] Recently more and more studies have shown that the inflammatory mediators in saliva could be a biomarker for oral diseases including oral cancer and periodontal disease.[28–31] We believe that the major factor that influences research performance in the area of biomarker and periodontal disease is the accessibility and application of specimens. Results of *h*-index indicate that biomarkers in saliva, as well as in serum and plasma, are good indicators for use in studying periodontal disease.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

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References

1. Williams RC. Periodontal disease. *New Engl J Med* 1990;322:373–82.
2. Lockhart PB, Bolger AF, Papapanou PN, et al. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: a scientific statement from the American Heart Association. *Circulation* 2012;125:2520–44.
3. Southerland JH, Moss K, Taylor GW, et al. Periodontitis and diabetes associations with measures of atherosclerosis and CHD. *Atherosclerosis* 2012;222:196–201.
4. Chang PC, Lim LP. Interrelationships of periodontitis and diabetes: A review of the current literature. *J Dent Sci* 2012;7:272–82.
5. Atkinson AJ, Colburn WA, DeGruttola VG, et al. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther* 2001;69:89–95.
6. Fleishaker JC. *The importance of biomarkers in translational medicine. Predictive approaches in Drug discovery and development*. Oxford: John Wiley & Sons, Inc., 2012:1–22.
7. Zhang A, Sun H, Wang P, Han Y, Wang X. Recent and potential developments of biofluid analyses in metabolomics. *J Proteomics* 2012;75:1079–88.
8. Yan W, Apweiler R, Balgley BM, et al. Systematic comparison of the human saliva and plasma proteomes. *Proteomics Clin Appl* 2009;3:116–34.
9. Malamud D. Saliva as a diagnostic fluid. *Dent Clin North Am* 2011;55:159–78.
10. Lamster IB, Ahlo JK. Analysis of gingival crevicular fluid as applied to the diagnosis of oral and systemic diseases. *Ann N Y Acad Sci* 2007;1098:216–29.
11. Thomson Reuters. *Web of Science* 2010. Available at: http://webofknowledge.com/WOS; [accessed 13.08.13].
12. Hirsch JE. An index to quantify an individual's scientific research output. *Proc Natl Acad Sci U S A* 2005;102:16569–72.
13. Pritchard A. Statistical bibliography or bibliometrics. *J Document* 1969;25:348–9.
14. Johnson MH, Cohen J, Grudzinskas G. The uses and abuses of bibliometrics. *Reprod Biomed Online* 2012;24:485–6.
15. Kulkarni AV, Aziz B, Shams I, Busse JW. Author self-citation in the general medicine literature. *PLOS ONE* 2011;6:e20885.
16. Foley JA, Della SS. The impact of self-citation. *Cortex* 2010;46:802–10.
17. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, et al. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proc Natl Acad Sci U S A* 2003;100:9090–5.
18. Bermudez EA, Rifai N, Buring JE, Manson JE, Ridker PM. Relation between markers of systemic vascular inflammation and smoking in women. *Am J Cardiol* 2002;89:1117–9.
19. Wright HJ, Matthews JB, Chapple IL, Ling-Mountford N, Cooper PR. Periodontitis associates with a type 1 IFN signature in peripheral blood neutrophils. *J Immunol* 2008;181:5775–84.
20. Lagervall M, Jansson L, Bergström J. Systemic disorders in patients with periodontal disease. *J Clin Periodontol* 2003;30:293–9.
21. Bastos AS, Graves DT, Loureiro AP, et al. Lipid peroxidation is associated with the severity of periodontal disease and local inflammatory markers in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2012;97:E1353–62.
22. Rastogi P, Singhal R, Sethi A, Agarwal A, Singh VK, Sethi R. Assessment of the effect of periodontal treatment in patients with coronary artery disease: A pilot survey. *J Cardiovasc Dis Res* 2012;3:124–7.
23. Pramanik R, Thompson H, Kistler JO, et al. Effects of the UK Biobank collection protocol on potential biomarkers in saliva. *Int J Epidemiol* 2012;41:1786–97.
24. Graves DT, Jiang Y, Genco C. Periodontal disease: bacterial virulence factors, host response and impact on systemic health. *Curr Opin Infect Dis* 2000;13:227–32.
25. Lightenberg AJM, De Soet JJ, Veerman EC, Amerongen AV. Oral diseases. *Ann N Y Acad Sci* 2007;1098:200–3.
26. Taba Jr M, Kinney J, Kim AS, Giannobile WV. Diagnostic biomarkers for oral and periodontal diseases. *Dent Clin North Am* 2005;49:551–71 vi.
27. Brailo V, Vucicevic-Boras V, Lukac J, et al. Salivary and serum interleukin 1 beta, interleukin 6 and tumor necrosis factor alpha in patients with leukoplakia and oral cancer. *Med Oral Patol Oral Cir Bucal* 2012;17:E10–5.
28. Canakci CF, Cicek Y, Yildirim A, Sezer U, Canakci V. Increased levels of 8-hydroxydeoxyguanosine and malondialdehyde and its relationship with antioxidant enzymes in saliva of periodontitis patients. *Eur J Dent* 2009;3:100–6.
29. Garcia I, Tabak LA. A view of the future: dentistry and oral health in America. *J Am Dent Assoc* 2009;140:44S–8S.
30. Sexton WM, Lin Y, Kryscio RJ, Dawson 3rd DR, Ebersole JL, Miller CS. Salivary biomarkers of periodontal disease in response to treatment. *J Clin Periodontol* 2011;38:434–41.
31. Wu JY, Yi C, Chung HR, et al. Potential biomarkers in saliva for oral squamous cell carcinoma. *Oral Oncol* 2010;46:226–31.