

原 著

歯周疾患と全身性疾患罹患およびその危険因子との 関連性についての臨床疫学的研究

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Clinico-epidemiological study on the correlation among incidences of periodontal disease and systemic diseases in Japanese factory workers

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要約

歯周疾患と全身性疾患罹患および全身性疾患発症の危険因子との関連について検討した。調査は1994年と1998年に行い、対象者数は第1回1,577名、第2回1,530名であった。歯周疾患と統計的に有意な関連性が認められたのは高血圧症と糖尿病であった。1994年の高血圧症の発症頻度はCPI値0、1、2群(歯周疾患軽度)と比較してCPI値3群(中等度)は1.28倍(95% C.I. 0.71-2.30)、CPI値4群(重度)は2.04倍(95% C.I. 1.01-4.16)高かった。糖尿病は歯周疾患軽度に比べ中等度は14.12倍(95% C.I. 1.81-110.0)、重度は9.51倍(95% C.I. 1.00-97.68)高かった。1998年も同様の傾向が認められた。全身性疾患発症の危険因子との関連では、2回の調査とも、血清総コレステロール値が歯周疾患軽度に比べて中等度、重度は統計的に有意に高値を示した。以上の結果から、歯周疾患と高血圧症、糖尿病などの疾患の発症や進展と統計的に有意な関連性が示された。

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Abstract

A cross-sectional study was conducted twice (in 1994 and 1998) on approximately 2,000 employees of

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a large plant to investigate the effect of periodontal disease on the incidence of systemic diseases and their risk factors. A statistically significant correlation was detected with hypertension; the probability for the development of hypertension rose in proportion to the increase in severity of periodontal disease; and the probability doubled for those in the group with the most advanced state of periodontal diseases, compared with those who had no periodontal disease or suffered from very mild conditions. The serum total cholesterol level increased proportionally and with statistical significance in the group with severe periodontal disease. Although no statistical significance was noted, the serum triglyceride level increased and serum HDL cholesterol level decreased in proportion to the severity of the periodontal disease. Odds ratio of Serum CRP exceeded the base level in the group with severe periodontal disease, the difference being statistically significant. The progression of periodontal disease raises the probability of developing diabetes mellitus. The results suggested that there was significant relationship between periodontal disease and prevalence of diabetes mellitus and hypertension.

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《Key words》 periodontal disease, systemic diseases, hypertension, diabetes mellitus, serum lipid

I . Introduction

At the start of the 21st century, Japan faces the problems of a rapidly aging society and she strives to extend a healthy life as well as to prolong life expectancy by improving the quality of life of the aged. For this purpose, the Ministry of Health, Labor and Welfare has been working on a "Healthy Japan 21" project, a campaign to improve its citizens' health by actively promoting policies that emphasizes the primary prevention of disease. To implement these policies, it is necessary to identify the risk factors for disease and make an effort to control them. Thus studies on risk factors for life styles related diseases were conducted in the fields of public health and epidemiology. Traditional risk factors e.g., hypercholesterolemia, hypertension, and smoking were re-evaluated and investigations have been extended to recently discovered risk factors, such as blood fatty acid and antioxidant levels, plasma fibrinogen content, serum C-reactive protein (CRP) level, leukocyte count, and systemic inflammatory substance content^{1,2)} e.g., certain cytokine.

Among these research activities, periodontal disease has come to be noted as a new risk factor for those conditions that affect the circulatory system like cardiac diseases^{3, 4)}. This disease, a very common oral condition that affects the Japanese population, is a bacterial infection caused by *Porphyromonas gingivalis*, a periodontal pathogen that resides in dental plaques, and other related organisms. It has been said that more than 80% are affected. When these organisms proliferate at an abnormal rate in the gingival sulcus, the gingiva becomes erythematous and swell; and the gingival attachment region recedes from the tooth surface. This results in the formation of a periodontal pocket, destruction of the alveolar bone, and finally the loss of the tooth⁵⁾. Thus it may be said that periodontal disease is responsible for oral dysfunctions such as inadequate mastication because teeth are missing and marked deterioration of one's oral condition. It has been a traditional belief that the effects of periodontal disease are limited to the oral cavity; but in the field of dentistry, this

diseases have been frequently found in patients with general disease, such as cardiac disease and diabetes mellitus. Recently, research has been rapidly expanded to clarify the interaction between oral functions and the cranial nerves, the relationship between oral and metabolic diseases, and the correlation of tooth loss with digestive system diseases. Subsequently periodontal diseases act as risk and exacerbating factors for systemic diseases, such as cardiac conditions and diabetes mellitus⁶⁾.

Epidemiological studies in this area that can boast high accuracy are scarce in Japan. Many of the studies that have been conducted present problems in survey methods; sample size, control of confounding factors, follow-up periods, error determination, and the possibility of selection bias. In the present survey, a cross-sectional study was conducted twice in 1994 and 1998 on approximately 2,000 employees of a large plant to investigate the effect of periodontal disease on the incidence of systemic diseases and their risk factors.

II. Methods

1. Outline of the study

Periodic health and dental examinations were conducted in April of 1994 and 1998 on approximately 2,000 employees of a large petroleum chemistry plant that was located in Osaka Prefecture to observe the relationship between systemic and dental diseases, and to measure the correlation between dental disease and risk factors for systemic disease.

In addition to the standard periodic health examination that was conducted mostly by nurses and physicians, one dentist, 3 dental hygienists, and one medical technologist participated in the dental examination and a survey on the life style of the subjects. To establish uniform diagnostic criteria to be applied to the

dental examination, a two-day seminar on the test items was held at the Osaka Prefecture College of Health Science, located at Habikino City, Osaka Prefecture.

Prior to the examinations, the test subjects were informed of the test items and details of the study. On the day of the examination, the subjects, who had fasted from the previous night, reported to the designated examination site in the plant, underwent standard procedures like blood sample collection, and responded to questions about his life style similar smoking and drinking of alcoholic beverages. For the survey on life style, a questionnaire was filled out by each participant. Then the dental examination was given with a special emphasis on the diagnosis of periodontal diseases. The data from these examinations and the questionnaires were compiled and used for statistical analysis to detect any relationship among dental diseases, systemic diseases, and their risk factors.

2. Eligibility for participation

The employees worked in a petroleum chemical plant where the major products were resins; vinyl chloride and polypropylene and chemical products like ammonia and urea. The employees included those who worked at the plant sites on 3-shifts; but most operated computer-controlled machinery so they were not likely to be exposed to toxic substances.

There were 1,860 and 1,747 participants for the first and second examinations, respectively. The requirements for participation to this project were:

- 1) Males between 20- and 59-years-old,
- 2) Available for both the routine health and dental examinations,
- 3) No abnormalities, such as fatigue or a common cold reported by subjects on the day of the health examination.

The periodic health and dental examinations were conducted within a 10-day period from April 5th to the 16th, 1994 and from April 7th to the 18th, 1998; excluding Saturdays and Sundays. About 200 subjects were examined each day.

The final number of test subjects was 1,577 and 1,530 for the first and second studies, respectively. To defend human rights, the research methods, details of the questions, and risks were explained to the participants and their informed consent was obtained. On the same occasion, they were informed that the study was being conducted for the welfare of the employees and the results were to be used for their health care; participation in the project was totally voluntary; their privacy would be protected; and those in charge of the project were ready to answer any questions that they might have. After these explanations were given, the prospective test subjects were strongly encouraged to participate.

For the protection of the participant's privacy, disclosure of the research data was restricted; and for the statistical analyses a code was assigned to each subject so that he could not be identified when the results were published.

3. Test Items

1) Blood pressure and blood chemical analyses

The following were determined: systolic and diastolic blood pressure, serum total cholesterol, serum triglyceride, serum HDL cholesterol level, and serum CRP. After the subject had rested for a while, he was instructed to sit down so that a nurse could measure the systolic and diastolic blood pressures at the right forearm by using an automatic sphygmometer (HEM-706 Fuzzy; Omron Corporation). The serum total cholesterol level was determined by an enzyme method; serum triglyceride level by

free glycerol elimination method; serum HDL cholesterol level by a heparin-manganese precipitation method; and serum CRP content by latex immunoassay. The accuracy of the analyses was controlled by double blind tests. For each item, the variation of the coefficient for the blinded duplicate was set at less than 5%. An automatic analyzer, Olympus AU-5200, was used for the determination.

The blood chemical analyses were conducted in the laboratory of the university where the author was affiliated. The protocols were the same in 1994 and 1998.

2) Dental examination

The dental examinations were conducted by an experienced dentist and 3 dental hygienists. The subject sat on a simple chair designed for dental examinations, with his head positioned securely. A light was arranged to permit accurate examination. About 5 minutes were allocated for each examination.

The progression of periodontal diseases was expressed by using the Community Periodontal Index (CPI), which was based on a method proposed by Ainamo, et al⁷⁾. Specifically, the oral cavity was divided into 6 sections and the periphery of one or two teeth, representing each section, was examined with a Periodontal Probe (Yamaura, Inc.) designated by WHO. The clinical findings of these representative teeth in each section were expressed in numerals: the severest findings was assigned to that section. The CPI values were: 0, unremarkable; 1, gingival hemorrhage during or after probing; 2, dental calculi over or under the gingival margin; 3, a periodontal pocket depth of 6 mm or more. When a representative tooth was missing, a substitute tooth was selected for evaluation. If all the teeth were missing, the subject was excluded from the evaluation. In this study, the maximum CPI among the 6

sections was used as the numeral representing the degree of progression of periodontal disease in that subject.

3) Diseases that the subjects suffered from

The diagnoses given at the periodic health examinations at the plant or by physicians at other medical facilities were used to designate the disease that the subject suffered from at the time of the survey. These were: hypertension (ICD a-0901), diabetes mellitus (ICD a-0402), liver disease (ICD a-1106), heart disease (ICD a-0902, a-0903), gout (ICD a-1300), skin disease (ICD a-1200), gastritis (ICD a-1105), gastric and duodenal ulcers (ICD a-1104), and hyperlipidemia (ICD a-0400).

4. Statistical analysis

The relationship between systemic diseases and the extent of periodontal diseases was determined as follows: the progression of periodontal disease was assigned to one of 3 categories (a CPI of 0, 1, and 2; CPI of 3; and CPI of 4), which was used as an independent variable. For the dependent variable, the presence or absence of any of the above-listed 10 types of diseases was used. After adjusting for age, a logistic regression analysis was performed⁸⁾.

For the correlation between the risk factors for systemic and periodontal diseases, the aforementioned category expressing the progression of periodontal disease was used as the independent variable, the serum lipid content and blood pressure as dependent variables. After adjusting for age, analysis of covariance was performed. To determine this correlation, those who were suffering from any of the diseases were excluded: only the data from healthy subjects were used for the analysis. Extreme numerical test results that might affect the statistical examinations were excluded from the analyses as outliers, which were

defined as follows: serum total cholesterol, 241 mg/dl or higher; serum HDL cholesterol, 81 mg/dl or more; serum triglyceride, 151 mg/dl or more; systolic blood pressure, 141 mmHg or higher; and diastolic pressure, 91 mmHg or higher. For the serum CRP, the standard range was set at 0.00 to 0.30 mg/dl, according to the findings of Otani, et al⁹⁾.

For the software for statistical analyses, Macintosh Statview Ver.5.0 were used. The significance level was set at $p < 0.05$.

III. Results

1. The relationship between systemic and periodontal diseases

The results from the logistic regression analysis after adjustment for age of the relationship between the 10 types of systemic diseases and periodontal diseases for 1994 and 1998 are given in Table 1. In both surveys, a statistically significant correlation was found between periodontal disease and hypertension or diabetes mellitus. Compared to the group with a CPI of 0, 1, and 2, the incidence of hypertension for 1994 for the group with a CPI of 3 was 1.28 times (odds ratio, 1.28; 95% confidence level, 0.71 to 2.30). The incidence for the group with a CPI of 4 was 2.04 times (odds ratio, 2.04, 95% confidence level, 1.01 to 4.16). The findings for 1998 were generally the same. The incidence of diabetes mellitus in the group with a CPI of 3, when compared to the group with a CPI of 0, 1, and 2, was 14.12 times (odds ratio, 14.12; 95% confidence level, 1.81 to 110.0); and for the group with a CPI of 4, it was 9.51 times (odds ratio, 9.51; 95% confidence level, 1.00 to 97.68). Again, the 1989 data for diabetes mellitus were generally identical.

No statistically significant correlation was found between periodontal disease and the other 8 clinical entities; liver disease, cardiac

Table 1 Results of multivariate logistic regression analysis for incidence of systemic diseases and progression of periodontal disease

Variables	1994 year			1998 year		
	Logistics coefficient	Standard error	Odds ratios	Logistics coefficient	Standard error	Odds ratios
Hypertension						
CPI 0,1,2			1.00			1.00
CPI 3	0.248	0.298	1.28(0.71-2.30)	0.240	0.355	1.27(0.63-2.55)
CPI 4	0.714*	0.363	2.04(1.00-4.16)	0.785*	0.402	2.19(1.01-4.83)
Diabetes Mellitus						
CPI 0,1,2			1.00			1.00
CPI 3	2.648*	1.047	14.12(1.81-110.00)	1.439	1.117	4.22(0.47-37.69)
CPI 4	2.253*	1.188	9.51(1.00-97.68)	2.239*	1.159	9.39(1.00-91.09)
Liver Disease						
CPI 0,1,2			1.00			1.00
CPI 3	-0.728	0.515	0.48(0.18-1.33)	0.652	0.658	1.92(0.53-6.97)
CPI 4	-0.616	0.801	0.54(0.11-2.59)	-0.175	1.160	0.84(0.09-8.15)
Heart Disease						
CPI 0,1,2			1.00			1.00
CPI 3	1.810	1.086	6.11(0.73-51.39)	-1.039	0.889	0.35(0.06-2.02)
CPI 4	1.616	1.267	5.03(0.42-60.35)	0.337	0.808	1.40(0.29-6.82)
Gout						
CPI 0,1,2			1.00			1.00
CPI 3	-1.439	0.811	0.24(0.05-1.16)	0.010	0.664	1.01(0.28-3.71)
CPI 4	-0.993	1.104	0.37(0.04-3.23)	-0.515	1.137	0.60(0.06-5.54)
Skin Disease						
CPI 0,1,2			1.00			1.00
CPI 3	-0.041	0.616	0.96(0.29-3.21)	-1.798	1.093	0.17(0.02-1.41)
CPI 4	-0.248	1.128	0.78(0.09-7.12)	-0.628	1.127	0.53(0.06-4.86)
Gastritis						
CPI 0,1,2			1.00			1.00
CPI 3	-1.163	1.184	0.31(0.03-3.18)			
CPI 4	-0.035	1.237	0.97(0.09-10.92)			
Gastric Ulcer						
CPI 0,1,2			1.00			1.00
CPI 3	0.728	0.767	2.07(0.46-9.31)	0.112	0.795	1.12(0.24-5.32)
CPI 4				-0.272	1.196	0.76(0.07-7.95)
Duodenal Ulcer						
CPI 0,1,2			1.00			1.00
CPI 3	-0.735	0.695	0.48(0.12-1.88)	0.154	0.744	1.17(0.27-5.01)
CPI 4				-0.069	1.175	0.93(0.09-9.35)
Hyperlipidemia						
CPI 0,1,2			1.00			1.00
CPI 3	0.553	1.259	1.74(0.15-20.51)			
CPI 4	0.928	1.497	2.53(0.14-47.59)	-0.112	0.948	0.89(0.14-5.74)

CPI score : Community Periodontal Index Odds ratios adjusted for age. * : p<0.05

disease, gout, skin disease, gastritis, gastric and duodenal ulcers, and hyperlipidemia.

For 1998 only, the relationship between a loss of teeth due to periodontal diseases and systemic diseases was examined but no statistically

significant relationship was found with any of the systemic conditions. Data are not shown.

2. Relationship between periodontal disease and serum lipid level and blood pressure

After adjusting for age, an analysis of

covariance was performed on the relationship between the extent of periodontal disease and serum lipid levels or blood pressure obtained at the 1994 and 1998 surveys (Table2). In both years, a statistically significant correlation was found with serum total cholesterol level. Compared to the group with a CPI value of 0, 1, or 2, the total cholesterol level was significantly high for the group with a CPI of 3 or 4. For 1998 only, a covariance analysis was performed after adjustment for age on the correlation among tooth loss due to periodontal diseases, serum lipid level, and blood pressure. The serum total cholesterol and serum triglyceride levels and systolic blood pressure were found to be significantly high for the group with missing teeth due to periodontal disease, in comparison with the others (Table 3).

3. Relationship between serum CRP and periodontal diseases

A logistic regression analysis was performed for 1998 (after adjusting for age) on the relationship between serum CRP content and the progression of periodontal disease (Fig.1). The frequency at which the serum CRP level exceeded the normal range for the group with a CPI of 3 was 1.15 times (odds ratio, 1.15; 95% confidence level, 0.74 to 1.80); and for the group with a serum CPI of 4, 1.82 times (odds ratio, 1.82; 95% confidence level, 1.03 to 3.39), both in comparison with the frequency for the group with a CPI of 0, 1, and 2.

IV. Discussion

The relationship between dental and systemic diseases has been understood as the latter affecting the former in most instances. It was

Table 2 Analysis of covariance for incidence of periodontal disease and serum fat, blood pressure

Variables	1994 year			1998 year		
	n	Mean±S.D.	F values	n	Mean±S.D.	F values
Total cholesterol (mg/dl)						
CPI 0,1,2	605	180.5±27.5	4.526*	703	188.8±28.0	3.521*
CPI 3	421	185.1±25.6		511	192.7±25.1	
CPI 4	84	187.6±26.2		126	193.7±25.8	
Triglyceride (mg/dl)						
CPI 0,1,2	473	85.6±29.4	0.531	559	92.9±30.23	1.922
CPI 3	301	88.8±31.3		367	96.1±28.11	
CPI 4	64	94.9±32.1		98	100.0±30.9	
HDL-cholesterol (mg/dl)						
CPI 0,1,2				768	54.6±12.1	0.077
CPI 3				553	52.8±12.1	
CPI 4				155	51.3±12.1	
Systolic blood pressure (mm/ Hg)						
CPI 0,1,2	725	124.3±10.4	0.419	605	124.8± 9.9	1.911
CPI 3	467	125.0±10.1		419	125.5± 9.3	
CPI 4	100	127.3± 9.6		96	126.0± 9.4	
Diastolic blood pressure (mm/Hg)						
CPI 0,1,2	759	76.1± 9.3	0.076	706	75.8± 8.9	1.108
CPI 3	511	77.1±10.4		466	77.3± 8.1	
CPI 4	110	78.9± 8.0		120	78.2± 8.1	

CPI score : Community Periodontal Index n : Number of subjects S.D.: Standard Deviation
 * : p<0.05 Adjusted for age.

Table 3 Analysis of covariance for missing teeth and serum fat, blood pressure

Variables	n	Mean±S.D.	F values
Total cholesterol (mg/dl)			
N group	739	189.3±26.8	6.072*
P group	592	192.9±26.5	
Triglyceride (mg/dl)			
N group	584	92.3±30.4	5.178*
P group	436	97.8±28.5	
HDL-cholesterol (mg/dl)			
N group	810	54.7±11.9	0.279
P group	656	52.6±12.4	
Systolic blood pressure (mm/Hg)			
N group	630	125.0± 9.8	0.692
P group	481	125.5± 9.5	
Diastolic blood pressure (mm/Hg)			
N group	731	76.1± 8.9	4.319*
P group	549	77.3± 8.1	

Adjusted for age. n : Number of subjects S.D.: Standard Deviation
 N group: Number of missing teeth = 0
 P group: Number of missing teeth ≥ 1
 * : $p < 0.05$

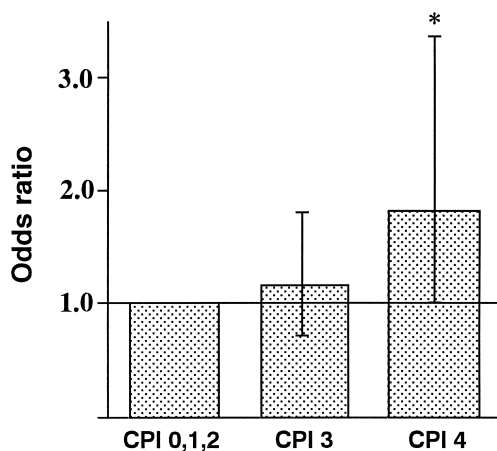


Fig. 1 Relationship between CRP and progression of periodontal disease

*: $p < 0.05$

CPI score: Community periodonta Index

a common belief that systemic diseases exert a formidable effect on the course of dental diseases, as attested to become worse of periodontal disease when complicated by diabetes mellitus or immunologic deficiency syndrome; and gingival hyperplasia caused by anti-

convulsants¹⁰.

Epidemiological studies are now being conducted on the relationship between oral and systemic diseases: since 1990, a number of studies have been introduced in which the conventional belief was completely reversed, by citing the effect that dental diseases have on systemic diseases. Led mainly by Western research groups, these studies provided the proof that periodontal diseases are not necessarily limited to the oral cavity and under the influence of systemic diseases; but they are often responsible for the development of systemic conditions, such as cardiovascular diseases, diabetes mellitus, and even the premature delivery of infants of low birth weight^{11,12}.

These studies are still in an early stage and reliable epidemiological data are scarce. Except for the study on periodontal diseases and diabetes mellitus, there have hardly been any studies on the relationship between periodontal and systemic diseases in Japan. To offer much

needed data in this area, the present two cross-sectional epidemiological surveys were conducted on approximately 2,000 employees of a large plant to study the relationship among periodontal diseases, systemic diseases, and their risk factors.

In Europe and the United States, studies have been conducted on the relationship between periodontal and cardiovascular diseases. Among them, there are 4 highly reliable controlled studies, which reported that those individuals affected by periodontal disease, in contrast to those without the disease, have a 20 to 180% greater risk of developing a cardiovascular disease¹³⁾. In addition, there are 5 cohort studies that spanned 6 to 18 years, in which it was concluded that, as in the controlled studies cited above, those individuals who had a periodontal disease at the start of the study, in comparison with those without, had a 20 to 180% greater risk of developing a cardiovascular disease. A positive correlation was noted between the progression of periodontal disease and the risk of developing a cardiovascular disease: the risk continues to increase as the oral condition advances. In another study, the severity of periodontal diseases was graded at 5 levels according to the extent of loss of alveolar bone at the start of the study. These patients were followed-up for 18 years, during which the incidence of cardiovascular disease was observed. It was reported that the extent of alveolar bone loss was positively related to the occurrence of cardiovascular disorders during this period¹⁴⁾.

In the Atherosclerosis Risk in Communities (ARIC) study¹⁵⁾ in which 45- to 64-year-old subjects participated in a program conducted in 4 areas in the United States, it was shown that after adjusting for obesity, blood pressure, serum total cholesterol level, the existence of diabetes mellitus, and smoking, the group

suffering from periodontal disease with an attachment loss of at least 3 mm that amounted to 60% or more in the oral cavity, in comparison with normal conditions, showed a risk of developing cardiovascular disease that was greater by 50%. In the same study, a positive correlation was found between the progression of periodontal disease and Carotid intimal-medial wall thickness (IMT), showing that the severity of periodontal disease is proportional to hypertrophy of the arterial walls¹⁶⁾. This finding indicates that periodontal disease is advanced and the probability of developing a cardiovascular disease is advanced. To explain the relationship between a periodontal disease infected by oral bacteria and systemic diseases, the following mechanism is suggested: inflammatory substances released into the blood in response to an oral inflammatory reaction may eventually affect the cardiovascular system. If so, the inflammatory substances released by the periodontal disease act not only on the periodontal tissue: they also affect cardiac tissue. For example, stimulation by an endotoxin that is released by the causative agent of periodontal disease causes monocyte activation, resulting in excessive generation of substances such as PGE₂, IL-1, and TNF- α ¹⁷⁾. By promoting oxidative stress, these substances cause inflammatory tissue destruction, such as alveolar bone resorption in the periodontal tissue. The same substances are transported to the cardiovascular system, where they cause potent oxidative stress, which results in lipid peroxidation, transformation of macrophages into foam cells, cholesterol deposition, proliferation of vascular smooth muscles, and thrombogenesis. Subsequently, an arteriosclerotic process affects the blood vessels, with eventual development of a cardiovascular disease.

The two cross-sectional studies conducted in

1994 and 1998 described in this report did not prove that there is a statistically significant correlation between the incidence of cardiac disease and the severity of periodontal disease. This lack of correlation may be explained as follows: the cardiac diseases of the subjects were not limited to those of ischemic origin but they were inclusive of all types; and there were not enough individuals with cardiac conditions to prove a clear-cut correlation with periodontal diseases. A statistically significant correlation was detected with hypertension, one of the most serious risk factors for heart disease; the probability for the development of hypertension rose in proportion to the increase in severity of periodontal disease; and the probability doubled for those in the group with the most advanced state of periodontal diseases, compared with those who had no periodontal disease or suffered from very mild conditions. This significant relationship with hypertension, a risk factor for cardiac disease, suggests that if follow-up observations are conducted, those with a periodontal disease will be most likely to develop a cardiovascular disease.

Next, the correlation between periodontal diseases and potent risk factors for circulatory diseases such as serum lipid levels and blood pressure data in those who were free of heart diseases to supplement the observations on the relationship between heart and periodontal diseases.

Beck, et al¹⁴⁾ conducted an animal experiment on the dissemination of *P. gingivalis*, an oral pathogen responsible for periodontal disease, to the remainder of the body. They examined the serum CRP, amylase, and lipid contents of mice that had been infected with *P. gingivalis* and reported that in comparison with those not infected, the *P. gingivalis*-infected mice showed statistically significant increases in their

serum total cholesterol and triglyceride levels. They also conducted a histopathological study to compare the total atherosclerotic surface areas of the vasculature of the *P. gingivalis*-infected and uninfected mice and found that the atherosclerotic areas were not only much greater in the former, they continued to increase in these infected mice.

In this study, the serum total cholesterol level increased proportionally in the group with severe periodontal disease and with statistical significance. The serum triglyceride level increased and serum HDL cholesterol level decreased in proportion to the severity of the periodontal disease, although no statistical significance was noted. Serum CRP has recently been found to be a risk factor for circulatory diseases: its odds ratio exceeded the base level in the group with severe periodontal disease, the difference being statistically significant. It was interpreted that this finding on the Japanese subjects and the results from the animal experiment by Beck, et al. were similar.

The inflammatory process associated with periodontal disease starts with the following: LPS, an endotoxin that is released from the pathogenic bacteria adherent on the tooth surface, binds with specific proteins that constitute the periodontal tissue; and the complex next binds monocytes to activate the latter. The activated monocytes produce excessive quantities of PGE₂ and cytokines, such as IL-1 and TNF- α , which cause inflammation of the periodontal tissue. LPS and cytokines in the blood stream are transported into the liver that responds to these substances by releasing CRP, which explains the rise in blood CRP level. This scenario explicates why there is a high probability that the serum CRP will exceed the basal level in patients with a periodontal disease¹⁸⁾.

With regard to the relationship between periodontal disease and diabetes mellitus, the risk for diabetic patients to develop severe periodontal diseases has already been reported. In 1970, Cohen, et al¹⁹⁾ studied 21 relatively young diabetic women, compared with the normal control, diabetic patients were more likely to have gingival lesions and often exhibited attachment losses. In a recent epidemiological study on Pima Indians, who are known to develop non-insulin-dependent diabetes mellitus, it was reported that their diabetic condition is responsible for tripling the incidence of periodontal disease. For the cause of this increase among diabetic patients, Oliver, et al²⁰⁾ cited vascular changes, eosinophilic dysfunctions, and a deranged collagen synthesizing mechanism. They added that satisfactory control of blood sugar would minimize tooth loss, while prolongation of the diabetic course proportionally increases the risk for the development of periodontal disease.

Diabetes mellitus exacerbates periodontal disease and more recent reports show that this is a bi-directional process: periodontal disease may also exacerbate diabetes mellitus. Beck, et al⁴⁾ reported that treatment of periodontal disease reduced the HbA1c level of diabetic patients. The ARIC study recognized that the probability for developing diabetes mellitus is high among those who are already suffering from a periodontal disease.

Our study that was conducted on Japanese employees in an industrial plant, it was also found that the progression of periodontal disease raises the probability of developing diabetes mellitus, which coincided with the observations of others. Because this was a case-control study, it was not possible to elucidate the mutual interrelations; but similar observations were made in both the 1994 and 1998

surveys.

The results of this study, an epidemiological study on Japanese employees at an industrial plant, suggested that there was significant relationship between periodontal disease and prevalence of diabetes mellitus and hypertension.

This is a case-control and cross-sectional study: the time of onset of periodontal and other diseases such as hypertension could not be established and the "temporal aspect of correlation", one of the conditions to prove a cause-effect relationship, could not be proven. To make up for this shortcoming, large scale cross-sectional studies were conducted twice. We recognize the need for further studies by employing techniques such as cohort studies.

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