Table 3.

Parameter Estimates From Multivariate Linear Regression Models Evaluating Each Independent Variable in Relation to Periodontal Parameters

	Dependent Variable					
	Mean PD (mm)			Mean AL (mm)		
Independent Variables	Coefficient	SE	*P* Value	Coefficient	SE	*P* Value
Age (years)	−0.0002	0.028	0.99	0.034	0.036	0.34
Number of teeth	−0.056	0.009	<0.001	−0.12	0.011	<0.001
Smoking history (pack-years)	0.007	0.001	<0.001	0.012	0.002	<0.001
Toothbrushing frequency (times/day)	−0.069	0.032	0.030			
BMI (kg/m^2)	0.014	0.010	0.17	−0.016	0.012	0.19
High-density lipoprotein cholesterol (mg/dL)	−0.001	0.002	0.69	−0.003	0.002	0.15
Serum creatinine concentration (0.1 mg/dL)	−0.064	0.026	0.012	−0.064	0.032	0.046
Intercept	4.36	1.51	0.004	5.30	1.90	0.005

Mean PD R^2 = 0.107; mean AL R^2 = 0.200.

associated with the incidence of type 2 diabetes independently of BMI as a result of the reduction in this target organ of insulin. Also, other studies have confirmed that individuals with diabetes had lower levels of serum creatinine than did individuals who did not have diabetes.[8,16] In the present study, serum creatinine concentrations were inversely associated with periodontal parameters after adjusting for other confounding variables. Therefore, low serum creatinine levels may also affect periodontal health status.

A study of elite athletes found a positive correlation between serum creatinine concentration and BMI.[17] Many studies have examined the relationship between BMI, which is an index of obesity, and periodontal disease.[18-23] One study found that BMI was associated with periodontal disease only in a younger age group,[19] and another demonstrated this relationship in adult, non-smoking females but not in adult males or smoking females.[21] In contrast, another study showed a significant inverse relationship between BMI and AL in adult males.[23] Thus, previous research has produced inconsistent findings regarding the relationship between BMI and periodontal disease, and the mechanism of the relationship between these two factors remains unclear. Although high BMI is associated with obesity, increased BMI is also found in well-muscled individuals with a large amount of lean body mass. In the present study, there is no significant correlation between BMI and periodontal parameters. Because our study population consisted of physically well-trained members of the Self-Defense Force, we assume that most of them were physically fit and did not represent the general population. Thus, the analysis of the relationship between obesity and periodontal disease using BMI might be improved by considering sex differences and using other indicators, such as body-fat mass.

Exercise training has a beneficial effect on the management of body weight and is also related to the development of lean body mass.[24] Some studies have demonstrated a significant relationship between exercise and periodontal disease.[25-28] One study examining the relationship of obesity and physical fitness to periodontal disease showed that individuals with high physical fitness had a significantly lower risk for periodontal disease.[27] In an animal model, sedentary rats eating a high-fat diet had greater body weight, more body fat, and gingival oxidative stress compared with sedentary rats eating a regular diet; exercise-trained rats eating a high-fat diet had equivalent body weight, less body fat, and the same level of gingival oxidative stress as control rats.[28] It has been shown that individuals who walk for ≥30 minutes ≥5 days/week had lower circulating interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein levels compared with individuals who engaged in less walking activity.[29] Although adipose tissue produces proinflammatory cytokines, such as TNF-α, it was suggested that IL-6, which is produced and released by contracting skeletal muscle fibers as a myokine, may be involved in mediating the anti-inflammatory effect of exercise.[30] Although the mechanisms linking serum creatinine concentration to periodontal status have not been clarified, the anti-inflammatory effect of exercise may contribute to prevention of periodontal

inflammation. Additional research is needed to clarify the mechanisms underlying the relationship between serum creatinine level and periodontal health status.

In this study, some participants had high serum creatinine levels (>1.2 mg/dL) or low GFRs (<60 mL/min/1.73 m^2), which would lead to the suspicion of impaired renal function; therefore, they were excluded from the analyses of the relationship between normal serum creatinine concentration and periodontal status. However, they had lower PD and lower AL compared with individuals with normal creatinine concentrations in the present study, and the significance of the negative regression coefficient did not change when they were included in the analyses (data not shown). Because individuals were members of the Self-Defense Force, the high serum creatinine concentrations may be attributable to their muscular build and not to renal dysfunction. One recent interventional study[31] examined the effect of periodontal treatment on indices of kidney function in patients with kidney dysfunction and showed that serum cystatin C levels improved after periodontal treatment. However, serum creatinine levels and modification of diet in renal disease, as calculated by serum creatinine, urea, and albumin concentrations, did not change after periodontal treatment.[31] Serum cystatin C may have a higher discriminatory capability for renal dysfunction than do serum creatinine and urinary creatinine, especially in individuals with high muscle mass.[32] The present study demonstrates that serum creatinine concentration is inversely associated with periodontal health status, suggesting that serum creatinine concentration may confound the analyses of the relationship between periodontal disease and renal dysfunction as assessed by serum creatinine. Thus, it may be preferable to use other indices, such as creatinine clearance and cystatin C, when assessing the relationship between renal function and periodontal disease.

There are some limitations of this study. Because the study was cross-sectional, we could not determine the causality or mechanism of the relationship between serum creatinine concentration and periodontal disease. Because we conducted partial periodontal examinations, we may have underestimated the proportion of individuals with periodontal disease;[33] this underestimation may have affected our findings regarding the relationship between serum creatinine concentration and periodontal disease. We could not obtain information regarding the use of interdental brushes and regular dental checkups, although these are important elements that affect periodontal health status. We should consider these variables in the future. Because the study participants in a previous cohort study examining the relationship between lower serum creatinine levels and incidence of type 2 diabetes were Japanese males,[7] we selected male members of the Japan Self-Defense Force as the study participants. In fact, although most of the members were males, they were physically well-trained members of the Self-Defense Force. Therefore, characteristics of them would not represent those of the general population of the same age. So, our data may differ from those in individuals selected from the general population. Indeed, sex differences may also affect this relationship. In fact, one case-control study of adult females provided preliminary evidence that serum creatinine levels were higher in periodontitis patients than in control individuals.[34] Additional studies in the general population should seek to clarify the relationship between serum creatinine concentration and periodontal disease.

CONCLUSIONS

The present study suggests a significant inverse association between normal serum creatinine concentrations and periodontal disease. Although periodic health examinations are widely conducted for the maintenance of adult health, oral health examinations that include the assessment of periodontal status are much less commonly performed. Attention should be paid to the periodontal health status of adult males who do not undergo periodic oral health examinations or maintenance therapy and have low serum creatinine concentrations.

ACKNOWLEDGMENTS

This work was supported by Grants-in-Aid for Scientific Research 22390401, 22406034, and 23390483 from the Ministry of Education, Science, Sports, and Culture of Japan and by the department budget of the Kyushu University, Fukuoka, Japan. The authors report no conflicts of interest related to this study.

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Submitted September 12, 2011; accepted for publication February 8, 2012.

Periodontal Status and Metabolic Syndrome in Middle-Aged Japanese

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Background: Metabolic syndrome (MetS) increases the risk of various lifestyle-related diseases. Although some studies have reported a significant relationship between periodontal status and MetS, little information exists about the nature of the relationship between periodontal health status and MetS.

Methods: Comprehensive health examinations of 6,421 Japanese individuals (aged 34 to 77 years) were performed. Five components (obesity, high blood pressure, low high-density lipoprotein cholesterol, hypertriglyceridemia, and high plasma glucose) of MetS were evaluated, and individuals with ≥3 positive components were defined as having MetS. The periodontal parameters were periodontal probing depth (PD) and clinical attachment level (CAL), and each parameter was divided into three categories (none/mild: ≤3 mm; moderate: 4 to 5 mm; and severe: ≥6 mm).

Results: When PD and CAL were analyzed separately in multivariate models, both parameters were significantly associated with MetS. In a multivariate logistic regression analysis using a combination of PD and CAL as an independent variable, individuals with severe PD and severe CAL or with moderate PD and moderate CAL had significantly higher odds ratios for MetS, but severe CAL without severe PD was not significantly associated with MetS.

Conclusion: The results of this study suggest that periodontal status, particularly in individuals suspected to have untreated periodontal infection indicated by ≥4 mm PD, is significantly associated with MetS. *J Periodontol 2012;83:1363-1371.*

KEY WORDS

Epidemiology; metabolic syndrome X; periodontal disease.

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Metabolic syndrome (MetS) is a combination of several metabolic risk factors, such as abdominal obesity, high blood pressure, lipid abnormality, and hyperglycemia, and increases the risk of various lifestyle-related diseases, such as cardiovascular conditions.[1,2]

In 2007, one cross-sectional study showed that individuals exhibiting more components of MetS had a higher odds ratio (OR) for a greater periodontal probing depth (PD) and clinical attachment level (CAL).[3] Also, other cross-sectional studies demonstrated that individuals with MetS had a higher risk for poor periodontal status[4-9] and that individuals with poor periodontal status had a higher risk for MetS.[10-13] Also, in some case-control studies, individuals with MetS had poor periodontal status compared with individuals without MetS.[14,15] Only one cohort study reported that individuals with ≥4 mm PD at baseline had a significantly increased risk of MetS 4 years later.[16]

In studies examining the relationship between periodontal status and MetS, many used PD to evaluate periodontal status using the Community Periodontal Index and other criteria based on a partial or full mouth periodontal examination, panoramic radiographs, or a self-reported questionnaire.[3-16] Some studies evaluated PD and CAL separately,[3,14] and others used the criteria of the Centers for Disease Control and Prevention and the American Academy of Periodontology[17] using PD and CAL.[6,10]

doi: 10.1902/jop.2012.110605

Although PD and CAL are intimately related periodontal parameters, the relative importance of the two periodontal parameters to MetS is unclear. Thus, examining this relationship may assist in elucidating the relationship between periodontal disease and MetS. In the present study, the relationships of PD and CAL to MetS, using cross-sectional data from periodic comprehensive health examinations, at a company in Japan, were separately and simultaneously examined.

MATERIALS AND METHODS

Study Population

From April 2003 to March 2004, 14,998 employees (11,633 males and 3,365 females; 19 to 93 years of age) underwent periodic comprehensive health examinations at a company in Japan. Of these, 6,829 employees received a workplace oral health examination. The present study included 6,421 individuals (4,944 males and 1,477 females, aged 34 to 77 years old) with ≥20 teeth and sufficient data for analysis.

Written informed consent was obtained from all individuals, and the ethics committee of the Kyushu University Faculty of Dental Science, Fukuoka, Japan, approved the study design, data collection methods, and procedure for obtaining informed consent.

Measurements

Each individual received an oral health examination that evaluated tooth and periodontal conditions while in a supine position, under sufficient artificial light, in a normal dental chair. Periodontal condition, based on the method of the Third National Health and Nutrition Examination Survey[18] was examined. Dentists (Hiromasa Tsuda, Nao Suzuki, Haruka Fukamachi, Miki Kawada, Masahiro Negishi; affiliation at the time, Kyushu University Faculty of Dental Science, Fukuoka, Japan: Eriko Kurihara, Mami Shinyashiki, Kenjiro Gohara, Akiyoshi Sakai, Koji Mise; affiliation at the time, Kyushu Dental College, Kitakyushu, Japan) trained to perform oral health status inspections conducted each periodontal examination using a periodontal probe‡ and evaluated PD and CAL on mesio-buccal and mid-buccal sites of all retained teeth, with the exception of the third molars. In this report, only mesio-buccal sites are used to evaluate periodontal health status attributable to mid-buccal CAL potentially being caused by toothbrushing, not periodontitis. The interexaminer reliability of the periodontal examination on mesio-buccal sites was verified before conducting the oral health examinations. When allowing for measurement rounding by considering ±1 mm as agreement, the κ values for PD and CAL ranged from 0.76 to 1.00 mm, which indicated substantial agreement.

Each individual completed a self-administered questionnaire in advance that included their lifestyle habits and systemic disease treatment status. Two smoking parameters were examined: smoking status (never, former, or current) and amount smoked. For current smokers, the amount smoked was quantified as pack-years by multiplying the number of cigarettes each individual smoked per day by the number of years during which the individual had smoked. Smoking habit, as a categorical variable was used in statistical analyses: 1) never smoker; 2) former smoker; 3) current light smoker (<20 pack-years); and 4) current heavy smoker (≥20 pack-years). Individuals answered items concerning their frequency of alcohol intake and the types and amounts of alcoholic beverages consumed. The alcohol intake of each alcoholic beverage was converted into the weight of 100% ethanol in grams. The estimated alcohol contents were 21.5 g for a glass of Japanese sake (180 mL), 22.6 g for a bottle of beer (633 mL), 35.7 g for a glass of distilled spirits (180 mL), and 31.8 g for a glass of whiskey (100 mL). The daily amount of drinking was estimated by multiplying the weekly frequency of consuming each alcoholic beverage by the weight of ethanol in each alcoholic beverage and dividing the sum by seven (grams per day). The daily alcohol consumption was divided into four categories based on the standard drink (14 g of pure alcohol) in the United States: 1) non-drinker (0 g/day); 2) light drinker (0.1 to 14.0 g/day); 3) moderate drinker (14.1 to 28.0 g/day); and 4) heavy drinker (>28.0 g/day). The frequency of toothbrushing was divided into three categories: 1) ≤1 time daily; 2) 2 times daily; and 3) ≥3 times daily.

The following five components were used to define MetS based on the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)[19] criteria, excluding the assessment of waist circumference: 1) obesity (body mass index [BMI] ≥25 kg/m^2); 2) high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg); 3) low serum high-density lipoprotein (HDL) cholesterol (<40 mg/dL for males and <50 mg/dL for females); 4) hypertriglyceridemia (triglycerides ≥150 mg/dL); and 5) high plasma glucose (fasting plasma glucose ≥100 mg/dL). Individuals being treated for hypertension were counted as positive for high blood pressure, and those being treated for diabetes were counted as positive for high plasma glucose. Individuals with ≥3 positive components were defined as having MetS.

Statistical Analyses

Individuals were divided into two groups: 1) those with MetS (n=958; 14.9%) and 2) those without MetS

‡ PCP-11, Hu-Friedy, Chicago, IL.

Table 1.

Characteristics of Individuals According to Presence or Absence of MetS

Variable	Absence of MetS (n = 5,463)	Presence of MetS (n = 958)	*P* Value
	Median (Quartile, Third Quartile)		
Age (years)	43 (38, 54)	46 (39, 55)	<0.001*
Number of teeth	28 (27, 29)	28 (27, 29)	0.107*
Alcohol consumption (g/day)	6.1 (1.5, 18.4)	12.5 (2.6, 35.8)	<0.001*
BMI (kg/m^2)	22.3 (20.5, 24.0)	26.3 (25.0, 28.1)	<0.001*
Systolic blood pressure (mmHg)	116 (107, 127)	134 (127, 141)	<0.001*
Diastolic blood pressure (mmHg)	72 (66, 80)	84 (78, 90)	<0.001*
Fasting plasma glucose (mg/dL)	94 (89, 99)	104 (99, 113)	<0.001*
HDL cholesterol (mg/dL)	59.3 (49.9, 71.1)	45.8 (38.8, 53.8)	<0.001*
Triglyceride (mg/dL)	88 (62, 123)	180 (141, 246)	<0.001*
CRP (mg/dL)	0.04 (0.02, 0.07)	0.08 (0.04, 0.15)	<0.001*
Sex [n (%)]			
Female	1,405 (25.7)	72 (7.5)	<0.001†
Male	4,058 (74.3)	886 (92.5)	
Toothbrushing (times/day) [n (%)]			
≤1	1,477 (27.0)	406 (42.4)	<0.001†
2	2,865 (52.4)	445 (46.5)	
≥3	1,121 (20.5)	107 (11.2)	
Smoking habit [n (%)]			
Never	3,791 (69.4)	580 (60.5)	<0.001†
Former	344 (6.3)	91 (9.5)	
Current light (<20 pack-years)	856 (15.7)	154 (16.1)	
Current heavy (≥20 pack-years)	472 (8.6)	133 (13.9)	
Periodontal PD (mm)			
None/mild (≤3)	4,136 (75.7)	645 (67.3)	<0.001†
Moderate (4 to 5)	994 (18.2)	223 (23.3)	
Severe (≥6)	333 (6.1)	90 (9.4)	
CAL (mm)			<0.001†
None/mild (≤3)	3,194 (58.5)	491 (51.3)	
Moderate (4 to 5)	1,566 (28.7)	298 (31.1)	
Severe (≥6)	703 (12.9)	169 (17.6)	

* Mann-Whitney *U* test.
† Mantel-Haenszel χ^2 test.

(n = 5,463; 85.1%). PD and CAL were each divided into three categories using the interproximal values of the periodontal examination: 1) none/mild PD (≤3 mm; n = 4,781); 2) moderate PD (4 to 5 mm; n = 1,217); and 3) severe PD (≥6 mm; n = 423); 4) none/mild CAL (≤3 mm; n = 3,685); 5) moderate CAL (4 to 5 mm; n = 1,864); and 6) severe CAL (≥6 mm; n = 872). Differences in continuous variables between the two groups were evaluated using the Mann-Whitney *U* test. Differences in proportions were evaluated using the Mantel-Haenszel χ^2 test. Univariate and multivariate logistic regression analyses were performed to determine the effects of PD and CAL categories and other variables on MetS by calculating the ORs and 95% confidence intervals (CIs). Because the correlation between PD and CAL categories was very strong, these categories were separately analyzed first in multivariate models. A categorical variable was then generated that combined PD and CAL categories, and this variable was entered into the multivariate model. Variables found to be significantly related to MetS in univariate

Table 2.

Characteristics of Individuals According to Periodontal Status

	PD			CAL		
	None/Mild (n = 4,781)	Moderate/Severe (n = 1,640)		None/Mild (n = 3,685)	Moderate/Severe (n = 2,736)	
Variable	Median (Quartile, Third Quartile)		*P* Value	Median (Quartile, Third Quartile)		*P* Value
Age (years)	42 (37, 52)	51 (40, 58)	<0.001*	41 (37, 51)	48 (40, 57)	<0.001*
Number of teeth	28 (27, 29)	28 (26, 29)	<0.001*	28 (27, 29)	28 (26, 29)	<0.001*
Alcohol consumption (g/day)	6.1 (1.8, 18.8)	7.7 (1.8, 30.6)	<0.001*	6.1 (1.8, 17.9)	7.7 (1.8, 25.5)	<0.001*
CRP (mg/dL)	0.04 (0.02, 0.08)	0.05 (0.03, 0.10)	<0.001*	0.04 (0.02, 0.08)	0.05 (0.03, 0.09)	<0.001*
Female [n (%)]	1,151 (24.1)	326 (19.9)	<0.001†	875 (23.7)	602 (22.0)	0.105
Toothbrushing (times/day) [n (%)]						
≤1	1,315 (27.5)	568 (34.6)	<0.001†	1,040 (28.2)	843 (30.8)	<0.05†
2	2,508 (52.5)	802 (48.9)		1,910 (51.8)	1,400 (51.2)	
≥3	958 (20.0)	270 (16.5)		735 (19.9)	493 (18.0)	
Smoking habit [n (%)]						
Never	3,376 (70.6)	995 (60.7)	<0.001†	2,601 (70.6)	1,770 (64.7)	<0.001†
Former	297 (6.2)	138 (8.4)		228 (6.2)	207 (7.6)	
Current light (<20 pack-years)	765 (16.0)	245 (14.9)		622 (16.9)	388 (14.2)	
Current heavy (≥20 pack-years)	343 (7.2)	262 (16.0)		234 (6.4)	371 (13.6)	
BMI ≥25 kg/m^2	1,073 (22.4)	425 (25.9)	<0.01†	829 (22.5)	669 (24.5)	
Blood pressure (mmHg)						
Systolic ≥85 or diastolic ≥130	1,339 (28.0)	568 (34.6)	<0.001†	1,028 (27.9)	879 (32.1)	<0.001†
Fasting plasma glucose ≥100 mg/dL	1,307 (27.3)	576 (35.1)	<0.001†	990 (26.9)	893 (32.6)	<0.001†
HDL cholesterol (mg/dL)						
<40 for males; <50 for females	418 (8.7)	194 (11.8)	<0.001†	312 (8.5)	300 (11.0)	<0.001†
Triglyceride ≥150 mg/dL	1,016 (21.3)	403 (24.6)	<0.01†	778 (21.1)	641 (23.4)	<0.05†
MetS presence	645 (13.5)	313 (19.1)	<0.001†	491 (13.3)	467 (17.1)	<0.001†

* Mann-Whitney *U* test.
† Mantel-Haenszel χ^2 test.

analyses were used in the multivariate analyses. *P* values <0.05 were deemed to indicate statistical significance. The statistical analyses were performed using a software program.§

RESULTS

Table 1 shows the characteristics of individuals with and without MetS. Individuals with MetS were older; had higher alcohol consumption, BMI, systolic and diastolic blood pressure, fasting plasma glucose, triglyceride, and C-reactive protein (CRP) levels; and had lower HDL cholesterol than individuals without MetS (Table 1). Proportions of males, smokers, individuals who brushed their teeth infrequently, and individuals who had poor periodontal status were higher in individuals with MetS than in individuals without (Table 1). Table 2 shows the characteristics of individuals according to periodontal status. Periodontal status was significantly associated with age, sex, number of teeth, alcohol consumption, CRP level, toothbrushing frequency, smoking habit, each component of MetS, and MetS itself (Table 2).

Table 3 shows the influence of each independent variable, including periodontal parameters, on MetS in univariate and multivariate analyses. Age, sex, alcohol consumption, frequency of toothbrushing, CRP, and each periodontal parameter were significantly associated with MetS in separate multivariate analyses of PD (model 1) and CAL (model 2) (Table 3). We analyzed the combined influence of PD and CAL on

§ SPSS version 17.0, IBM, Tokyo, Japan.

Table 3.

Association of Demographic Variables and Periodontal Parameters With MetS in Logistic Regression Models (n = 6,421)

Independent Variable	Absence of MetS (n = 5,463)	Presence of MetS (n = 958)	Crude OR (95% CI)	Dependent Variable: MetS (Absence = 0, Presence = 1) Adjusted OR (95% CI) Model 1 (including PD)	Model 2 (including CAL)
Age			1.02 (1.01 to 1.03)‡	1.02 (1.01 to 1.02)‡	1.02 (1.01 to 1.02)‡
Sex					
Females	1,405	72	1.00	1.00	1.00
Males	4,058	886	4.26 (3.33 to 5.46)‡	3.46 (2.64 to 4.55)‡	3.46 (2.64 to 4.55)‡
Smoking habit					
Never	3,791	580	1.00	1.00	1.00
Former	344	91	1.73 (1.35 to 2.21)‡	1.17 (0.91 to 1.51)	1.19 (0.92 to 1.53)
Current light (<20 pack-years)	856	154	1.18 (0.97 to 1.43)	0.94 (0.77 to 1.16)	0.95 (0.77 to 1.17)
Current heavy (≥20 pack-years)	472	133	1.84 (1.49 to 2.28)‡	1.03 (0.82 to 1.29)	1.04 (0.83 to 1.30)
Alcohol consumption (g/day)					
0	1,188	145	1.00	1.00	1.00
0.1 to 14.0	2,515	383	1.25 (1.02 to 1.53)*	0.93 (0.75 to 1.15)	0.93 (0.75 to 1.16)
14.1 to 28.0	694	136	1.61 (1.25 to 2.07)‡	1.00 (0.77 to 1.31)	1.01 (0.77 to 1.31)
>28.0	1,066	294	2.26 (1.82 to 2.80)‡	1.29 (1.02 to 1.63)*	1.29 (1.02 to 1.63)*
Toothbrushing (times/day)					
≤1	1,477	406	1.00	1.00	1.00
2	2,865	445	0.57 (0.49 to 0.66)‡	0.67 (0.57 to 0.78)‡	0.66 (0.57 to 0.77)‡
≥3	1,121	107	0.35 (0.28 to 0.44)‡	0.50 (0.40 to 0.64)‡	0.50 (0.39 to 0.63)‡
CRP (mg/dL)			1.32 (1.11 to 1.57)†	1.26 (1.06 to 1.50)†	1.27 (1.07 to 1.50)†
Number of teeth			0.97 (0.94 to 1.00)*	0.98 (0.95 to 1.01)	0.98 (0.95 to 1.01)
Periodontal PD (mm)					
None/mild (≤3)	4,136	645	1.00	1.00	
Moderate (4 to 5)	994	223	1.44 (1.22 to 1.70)‡	1.25 (1.05 to 1.49)*	
Severe (≥6)	333	90	1.73 (1.35 to 2.22)‡	1.32 (1.01 to 1.71)*	
CAL (mm)					
None/mild (≤3)	3,194	491	1.00		1.00
Moderate (4 to 5)	1,566	298	1.24 (1.06 to 1.45)†		1.11 (0.95 to 1.31)
Severe (≥6)	703	169	1.56 (1.29 to 1.90)‡		1.28 (1.04 to 1.57)*

* $P<0.05$.
† $P<0.01$.
‡ $P<0.001$.

MetS. Individuals with severe PD and severe CAL and individuals with moderate PD and moderate CAL had significantly higher ORs for MetS (Table 4). However, ORs for MetS in individuals with severe CAL but without severe PD were not significant (Table 4).

DISCUSSION

The present study shows that having severe PD and severe CAL or having moderate PD and CAL were significantly related to MetS, but severe CAL without severe PD was not. The presence of deep PD implies the existence of current local inflammation in periodontal tissue. In contrast, the presence of CAL suggests the accumulation of periodontal tissue destruction attributable to periodontitis but does not necessarily correspond to current periodontal inflammation. Because existing PD at the same level as CAL is suspected to represent untreated periodontal

Table 4.

Risk of MetS by Various Combinations of Periodontal PD and CAL* (N = 6,414)

	CAL		
PD	None/Mild	Moderate	Severe
None/mild			
n	3,663	869	249
MetS	485 (13.2%)	119 (13.7%)	41 (16.5%)
OR (95% CI)	1.00 (reference)	0.98 (0.79 to 1.23)	1.24 (0.86 to 1.78)
Moderate			
n	20	990	207
MetS	6 (30.0%)	179 (18.1%)	38 (18.4%)
OR (95% CI)	2.23 (0.84 to 5.93)	1.25 (1.03 to 1.52)†	1.22 (0.84 to 1.79)
Severe			
n	2‡	5‡	416
MetS			90 (21.6%)
OR (95% CI)			1.35 (1.03 to 1.77)†

* Adjusted for age, sex, smoking habit, alcohol consumption, toothbrushing, CRP, and number of teeth.
† $P<0.05$.
‡ The individuals were omitted from analysis because the numbers were too low to include in analysis.

inflammation, one may reasonably assume that poor periodontal status accompanied by deep PD affects MetS or that MetS develops in parallel with periodontitis. Lipopolysaccharide derived from periodontal pathogens, such as *Porphyromonas gingivalis* existing in deep PD, increases circulating tumor necrosis factor-α (TNF-α),[20] which induces insulin-resistant and atheromatous change.[21,22] This may be a possible reason for the relationship between poor periodontal status and MetS.

Elevated serum CRP level suggesting systemic inflammatory status enhances the risk of cardiovascular disease[23-25] and is associated with MetS.[26] In contrast, although periodontal disease is characterized by the local inflammation of periodontal tissue, some studies have reported that serum CRP level was positively associated with the degree of periodontitis,[27-29] and one study of Japanese patients with type 2 diabetes showed that CRP is well correlated with periodontal infection among individuals with BMI <27 kg/m^2.[30] The present study also shows a significantly positive relationship between CRP and MetS, and multivariate analysis demonstrated that periodontal status was significantly associated with MetS independent of CRP. These data suggest that not only systemic inflammatory status but also local periodontal inflammation influences MetS. In the present study, the number of individuals with severe PD without severe CAL is extremely small. In contrast, many individuals had severe CAL without severe PD, and they could have received some kind of periodontal treatment. Periodontal treatment has been reported to be effective in reducing TNF-α and CRP levels.[31-34] Therefore, the provision of adequate periodontal treatment and maintenance therapy to patients with periodontitis may minimize the effect of the periodontal health on MetS. Although the data led to the formulation of these hypotheses, they could not be tested in this cross-sectional study.

This study shows that individuals who frequently brushed their teeth had a significantly lower risk of MetS. Because the main purpose of toothbrushing is the disturbance of the biofilm and bacterial colonies as well as removal of dental plaque to prevent caries and periodontal disease, toothbrushing frequency is associated with periodontal disease.[35,36] One cohort study based on the Scottish Health Survey reported that low toothbrushing frequency was significantly associated with cardiovascular disease events and low-grade systemic inflammation evaluated by CRP and fibrinogen levels.[37] However, that study did not examine periodontal health status. Although the present study has a cross-sectional design, multivariate analysis indicated that individuals who frequently brushed their teeth had a significantly lower risk of MetS independent of periodontal status. Toothbrushing is a daily lifestyle habit, and individuals who brush their teeth frequently have been reported to generally have healthier lifestyles.[38,39] Thus, individuals who brush their teeth frequently may have a lower risk of MetS because of heightened interest in their general health.

Some studies have reported a significant relationship between smoking and MetS.[40,41] In contrast, results regarding the relationship between alcohol

intake and MetS are inconsistent.[40,42,43] In this study, both smoking habit and alcohol consumption are significantly associated with MetS in univariate analyses, but the significance of smoking habit disappeared after adjustment for other factors, including periodontal status. Although smoking is a well-known risk factor for periodontal disease,[44,45] the multivariate model in the present study shows no significant relationship between smoking habit and MetS after the removal of periodontal parameters from the independent variables (data not shown). Therefore, the lack of association between smoking habit and MetS was not likely to be attributable to the confounding influence of periodontal parameters.

The modified NCEP ATP III definition of MetS was used because abdominal obesity is not a required factor for MetS,[19] compared to the definition of the International Diabetes Federation, which places emphasis on abdominal obesity as a required factor.[46] Although the need for modified criteria of waist circumference for Asian people, including Japanese, was considered in previous statements and studies,[46-48] the present study uses BMI as a substitute for waist circumference. Therefore, if we evaluate waist circumference as abdominal obesity, some influences on the relationship between periodontal health and MetS may exist.

This study has several limitations. First, the cross-sectional study design prevented us from confirming causality or identifying the mechanisms underlying the relationship between periodontal health and MetS. Many confounding and disease-related factors to MetS are believed to exist, and one recent cross-sectional study reported that MetS was only weakly associated with periodontal disease as a result of the significant effects of confounding factors.[9] Because we were unable to adjust for all possible confounding factors, other unexamined factors might have affected the study results. Because the assessment of periodontal status was based on a partial periodontal examination, a resulting underestimation of periodontal disease might have affected the evaluation of the relationship between periodontal status and MetS.[49]

CONCLUSIONS

The data of this study suggest that periodontal status, particularly in individuals suspected to have untreated periodontitis accompanied by ≥4 mm PD, is significantly associated with MetS. However, additional longitudinal studies are required to clarify the relationship between periodontal health status and MetS. Also, interventional studies accompanied by periodontal treatment in patients with advanced periodontitis would likely increase our understanding of the effect of periodontal status on MetS.

ACKNOWLEDGMENTS

This work was supported by Grant-in-Aids of Scientific Research 22390401, 22406034, and 23390483 from the Ministry of Education, Science, Sports, and Culture of Japan, Tokyo, Japan, and by the department budget of the Kyushu University, Fukuoka, Japan. Drs. Fukui and Shimazaki contributed equally to this work. The authors report no conflicts of interest related to this study.

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Submitted October 11, 2011; accepted for publication December 26, 2011.

Osteoporosis Japan

2012年10月31日発行　vol. 20　no. 4　別刷

〔略号：*Osteoporosis Jpn*〕

全国的データベースを用いた骨粗鬆症性骨折の予防と治療に関する研究

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平成23年度骨粗鬆症財団研究助成－①

Osteoporosis Japan

全国的データベースを用いた骨粗鬆症性骨折の予防と治療に関する研究

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1 研究の背景

高齢者における骨折は疼痛や変形によって日常生活活動度（ADL）を低下させ，生活の質（QOL）を悪化させる，いわゆる「寝たきり」の主要な原因のひとつである。さらに，高齢者の骨折は生命予後にも影響を与える重大な疾患である。高齢者の骨折で頻度の高いものとして，椎体骨折，前腕骨遠位端骨折，上腕近位部骨折，大腿骨近位部骨折などがあげられるが，これらを予防するためには，骨粗鬆症対策が欠かせない。骨粗鬆症は「骨強度の低下を特徴とし，骨折のリスクが増大しやすくなる骨格疾患」と定義され[1]，脆弱性骨折は本疾患の合併症として位置付けられる。

骨粗鬆症診療に関する全国的データの収集・解析を行うことにより，実際の診療現場での診断や治療の成果を解析することが欠かせない。このことを通じて，既存ガイドラインの客観的評価に役立つことも期待される。現在 1500～1600 億円ともいわれている骨粗鬆症治療薬に対する医療費の適正化に資する臨床研究は，社会的ニーズに即したものと考えられる。さらに骨折に関連する医療・介護費としては，薬剤費以外にも腰痛に対する外来・入院治療費，手術関連の医療費，リハビリテーションの費用，さらに長期療養にかかる費用も考えなければならず，これらの総額は 1 兆円にものぼることが推定されている。また，骨折や転倒予防に対する介入は全身の健康づくりにも寄与するものであることを考え合わせると，日常診療に基づくデータベータを用いた研究は骨折予防の総合的対策立案に重要な情報をもたらし，国民の保健・医療・福祉の全般的な向上にも結びつくことが期待される。

世界保健機構（WHO）が作成した fracture risk assessment tool（FRAX®）は，前向き 10 年間の骨折発生確率（主要骨粗鬆症性骨折と大腿骨近位部骨折について）を算定するツールである[2]。これは地域住民に関する疫学データをもとに作成されたものであり，その臨床的意義を検証する研究が求められている。

2 研究目的

本研究では日常の骨粗鬆症診療におけるデータを全国規模で収集し，骨粗鬆症性骨折の発症要因，骨粗鬆症治療薬の選択に及ぼす因子，骨粗鬆症の薬物治療による骨折予防効果などについて検討することを目的とする。

3 研究計画・方法

1）研究の概要

平成 18 年から 20 年の厚生科学研究長寿科学総合研究で構築された骨粗鬆症診療の全国的データベースを用いる[3]。データベース研究は前向きコホート研究であり，原発性骨粗鬆症または骨量減少の女性を対象とする。2 年おき経過情報

[1] 国立長寿医療研究センター臨床研究推進部，[2] パブリックヘルスリサーチセンター，[3] 産業医科大学整形外科，[4] 成人病診療研究所，[5] 国際医療福祉大学，[6] 国立長寿医療研究センター，[7] 東京都健康長寿医療センター，[8] 東京大学公共健康科学，[9] 公益財団法人骨粗鬆症財団；研究協力者は論文末に記載

表1　登録情報

- 登録番号
- 研究者名
- 登録データ入力年月日
- 生年月日
- 身長，体重
- 疾患名
- 脆弱性骨折
- 椎体部位・グレード
- 非椎体：大腿骨近位部，上腕近位，上腕遠位，骨盤，肋骨，その他
- 骨密度：測定日，部位，機種，測定値，単位，Tスコア，Zスコア
- マーカー：測定日，種別，キット名，測定値，単位，依頼測定機関
- 臨床検査：測定日，Ca，P，ALP，ALB，uc-OC，i-PTH，25OHVD
- 合併症：RA，糖尿病，高血圧，高脂血症，虚血性心疾患，脳血管障害，悪性腫瘍，認知症，パーキンソン病など神経疾患，不眠症，うつ病
- アンケート：喫煙，飲酒，納豆・牛乳の摂取，日常生活活動，骨折の家族歴，ステロイド服用，腰背部痛，月経，身長低下
- 介護度
- 骨粗鬆症に関する薬剤名

を取集し，骨折の発生等をイベントとして登録する。

研究分担者による症例登録に加えて日本骨粗鬆症学会の下部組織である骨粗鬆症至適療法研究会（A-TOP研究会）に参加している医療機関にも研究協力者として積極的に参加を呼びかける。

2）調査対象

登録の対象は医療機関を受診した女性の原発性骨粗鬆症もしくは骨量減少の患者であり，かつ研究に関する文書同意を取得した患者とする。

3）調査項目

調査担当医師は登録時の情報および2年後との定期観察時に情報をデータベースに登録するとともに，イベント（骨折）の発生時に，情報を追加登録する（表1）。

①登録時の収集情報

生年月日・体格：身長，体重・既存骨折の状況・骨密度・骨代謝マーカー・合併症の有無・患者アンケート（生活習慣，介護度など）・血液検査（Ca, P, ALP, ALB, Uc-OC, i-PTH, 25OHVDのうち，施設で測定が実施されているもの）・治療薬剤

②定期観察時の収集情報

来院継続・脱落の区分・死亡の有無・治療薬剤：骨粗鬆症治療の継続・切替状況，コンプライアンス，副作用・骨密度検査・骨代謝マーカー・介護度の評価：非該当，要支援1・2，要介護1・2・3・4・5度の区分

③イベント（新規脆弱性骨折）発生時

椎体骨折の場合：部位およびグレード

非椎体骨折の場合：部位および発生年月

④対象の追跡

2年おきの調査時に再来院のない対象患者は，電話にて調査担当医師により来院を依頼する。その上で来院のない患者は調査から除外する。

4）データベースへの登録方法

専用の登録システム（Satellite®：電助システムズ社）が組み込まれたUSBを用いて登録を行う。

5）倫理面の配慮

本研究は疫学研究に関する倫理指針およびヘルシンキ宣言に準拠して実施する。対象者には書面による説明と同意を得た。研究内容は国立長寿医療研究センターの倫理・利益相反委員会で審議され承認された。

図1　登録地域と参加施設名

表2　背景情報：年齢，BMI，BMD

	Mean±SD	n
年齢（歳）	72.8±9.3	1482
身長（cm）	149.0±6.8	1472
体重（kg）	48.2±7.5	1470
BMI（kg/m²）	21.7±3.2	1470
BMD：T-score	−2.58±1.16	1079
BMD：Z-score	−0.45±1.19	1079

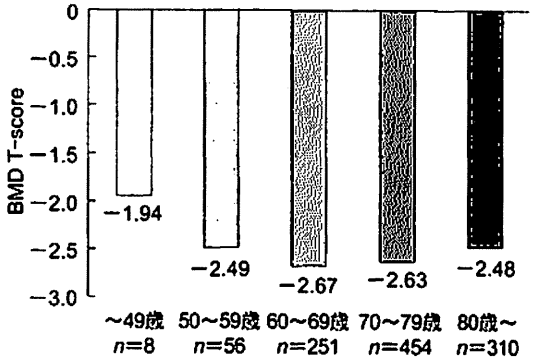

図2　背景情報：年齢とBMD（T-score）

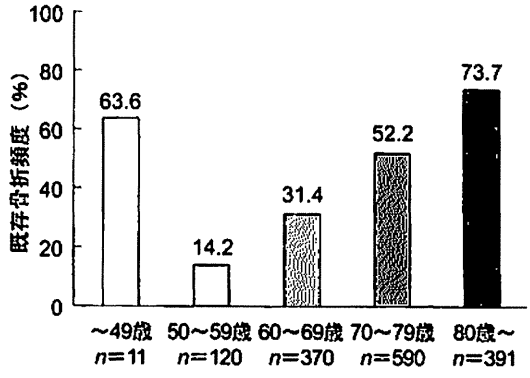

図3　背景情報：年齢と既存脆弱性骨折

4　研究結果

1）登録地域と例数

全国の18医療機関が研究に参加し総登録数は1482例であった（図1）。

2）年齢と骨密度の分布

登録症例の平均年齢は72.8歳であった。身長は149±6.8cm，体重は48.2±7.5kg，BMIは21.7±3.2であった（表2）。骨密度（BMD）の平均値はTスコアで−2.58±1.16，Zスコアで−0.45±1.19であり，Tスコアの年齢分布は図2に示すとおり，年齢依存性の差異は認めなかった。49歳以下の症例は8例ときわめて少なかった。

3）既存骨折の頻度と種類

脆弱性骨折をすでに有する者の割合は年齢依存性に増加する傾向が認められた（図3）。ただし49歳以下の集団では約64%に達しており，若年者における骨粗鬆症の薬物治療例は既存骨折

表3　背景情報：既存骨折

骨折区分	例数	頻度
脆弱性骨折あり	736/1482	49.7%
椎体	727/1482	49.1%
大腿骨近位部	8/1482	0.5%
上腕近位	6/1482	0.4%
上腕遠位	1/1482	0.1%
骨盤	1/1482	0.1%
その他	11/1482	0.7%

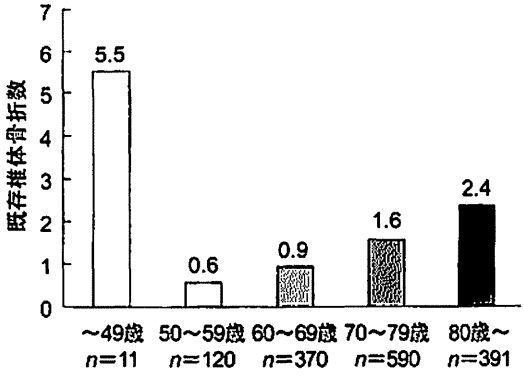

図4　背景情報：年齢と既存椎体骨折数

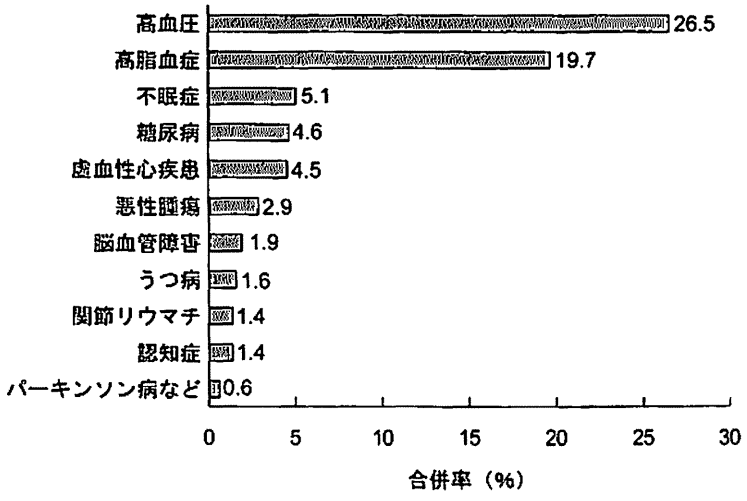

図5　背景情報：合併症

を有する割合が多く，骨折リスクが高いことがより注目されている結果であった。対象者全体での既存骨折の頻度は 49.7%であり，ほとんどが椎体骨折であった（表3）。椎体骨折の個数は年齢とともに増加する傾向がみられた（図4）。

4）併発症の頻度と既存骨折との関連

高血圧の併発率が 26.5%，高脂血症の併発率が 19.7%と，他の疾患に比べて高かった（図5）。併発症の有無で既存骨折の頻度を比較したところ，糖尿病と高血圧を有する場合と有さない場合との間で統計的な有意差を認めた（Student の t 検定）（表4）。認知症の有無についても統計的には有意差があったものの，認知症の症例数は極めて少なく，今回は臨床的意義を見出しかねるものと判断された。

5）骨粗鬆症治療薬の選択状況

対象者に対する薬物治療は，ビスホスホネート単独が最も多く，それにビスホスホネートと活性型ビタミン D の併用，SERM 単独，SERM と活性型ビタミン D の併用，活性型ビタミン D 単独，と続いた（図6）。それぞれの薬剤について既存骨折を有する者の割合を比較したところ，ビスホスホネート単独とビスホスホネートと活性型ビタミン D の併用群では既存骨折を有する者が上回っていた。一方，SERM においてはこの関係は逆転していた（図7）。

治療開始薬と FRAX®による 10 年間の主要骨粗鬆症性骨折発生確率との関連をみると，ビス

表4　背景情報：合併症有無別の脆弱性骨折頻度

種類	区分	脆弱性骨折			p
		無	有	%	
RA	無	737	724	49.5	0.490
	有	9	12	57.1	
糖尿病	無	722	692	48.9	0.011
	有	24	44	64.7	
高血圧	無	586	503	46.2	<0.001
	有	160	233	59.3	
高脂血症	無	598	592	49.8	0.895
	有	148	144	49.3	
虚血性心疾患	無	716	700	49.4	0.417
	有	30	36	54.6	
脳血管障害	無	737	717	49.3	0.052
	有	9	19	67.9	
認知症	無	742	720	49.3	0.006
	有	4	16	80.0	
うつ病	無	736	723	49.6	0.507
	有	19	13	56.5	

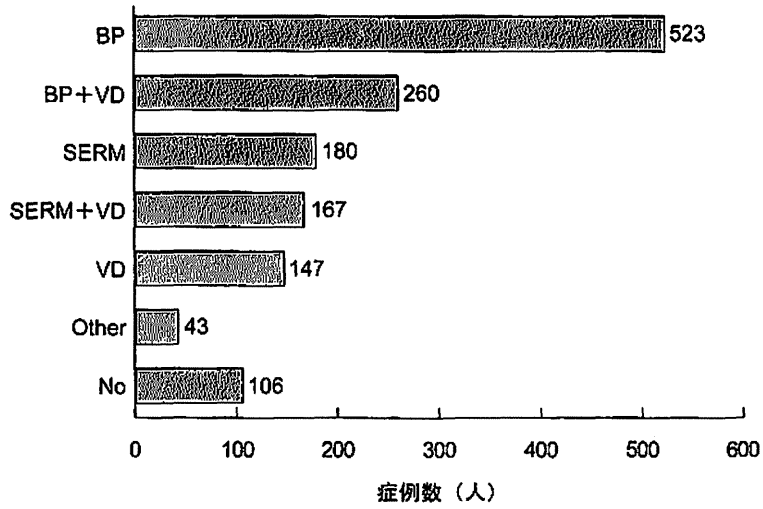

図6　薬物治療

ホスホネート単独，ビスホスホネートと活性型ビタミンDの併用，活性型ビタミンD単独の3群については，主要骨粗鬆症性骨折の確率，大腿骨近位部骨折の確率ともほぼ同等であった（図8）。

治療薬の選択と年齢との関連をみると，高齢者ほどビスホスホネート単独または併用群，活性型ビタミンD単独群が増加し，SERM単独または併用群が減少する傾向が観察された（図9）。

6）新規骨折の発生状況

2年間の経過を終え，現時点でデータが回収された1031例について新規骨折の発生状況を検討したところ，1031例中124例（12%）で新規骨折の発生が認められた（表5）。椎体骨折が多く

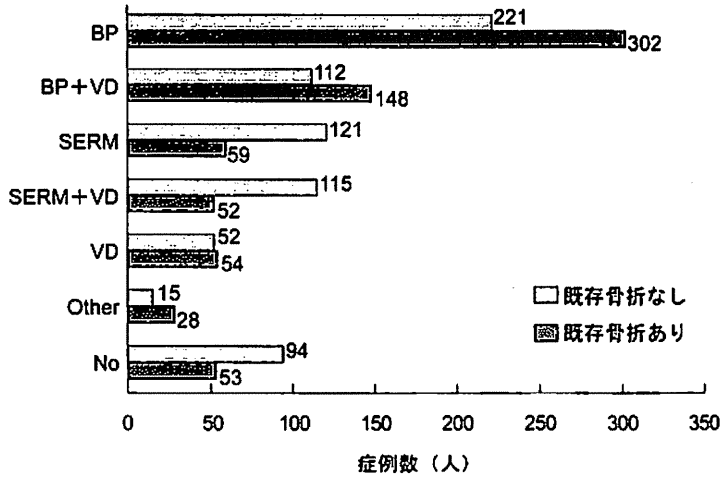

図7　既存骨折と薬物治療

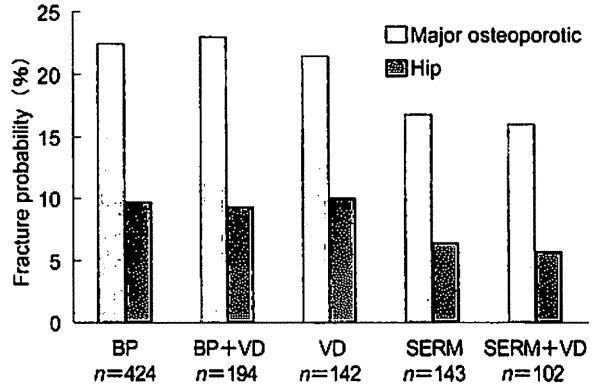

図8　治療開始薬とFRAX®

の部分を占め，四肢の骨折は3例のみだった。

新規脆弱性骨折の発生頻度は加齢とともに上昇した（図10）。一方，登録時の既存脆弱性骨折の有無は新規骨折の発生に大きな影響を及ぼしていることがうかがわれた（図11）。

7）新規骨折の発生頻度と治療薬との関連

今回の集計においては年齢や骨折危険因子などによる補正などを行っていないが，治療薬別の新規骨折発生頻度を比較した（データ未公表）。ビスホスホネートやSERMに対する活性型ビタミンDの併用効果が示唆された。

5　考　　察

今回の参加施設は日本骨粗鬆症学会のA-TOP研究会の参加施設でもあり，骨粗鬆症の診療に積極的に取り組まれている施設であると考えられる。研究デザインはこれらの施設における日常診療の結果を追跡するものであり，薬物の選択についてもそれぞれの担当医の判断に委ねられたものである。これらのことを踏まえると，このたび得られた結果は，わが国における骨粗鬆症診療に関する情報を十分に得ている担当医のプラクティスの現状を反映したものであると考えられる。このため，この結果をわが国の骨粗鬆症診療全体に外挿することには注意を払う必要がある。

ベースラインデータにおいては年齢依存性に既存脆弱性骨折の頻度や椎体骨折の数が上昇す

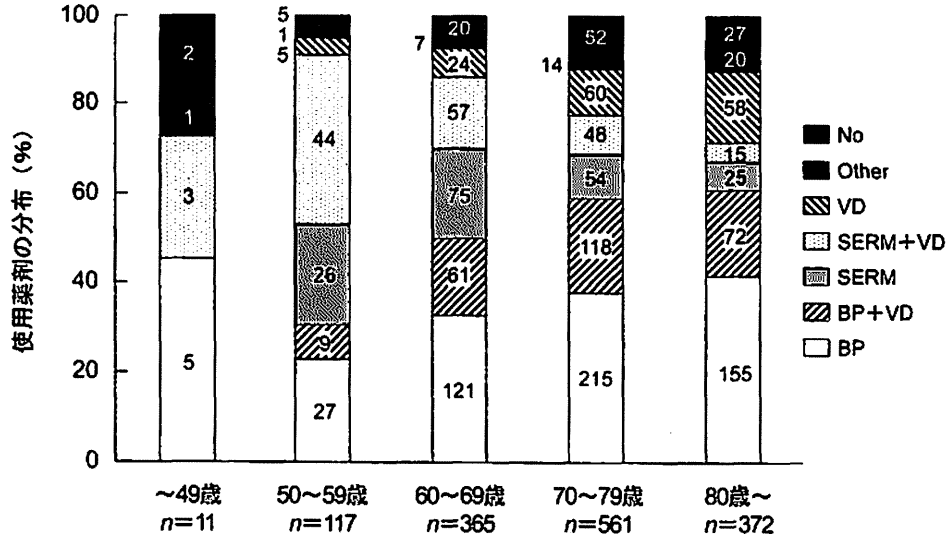

図9　年齢と薬物治療

表5　2年間の観察期間中の新規骨折の発生状況

脆弱性骨折あり	124/1031	12.0%
発生部位（既に収集されたもの）		
・椎体	92例	
・左大腿骨転子部	1例	
・左脛骨近位端	1例	
・脊骨	1例	
・大腿骨近位部	1例	
・椎体－肋骨	1例	
・肋骨	1例	

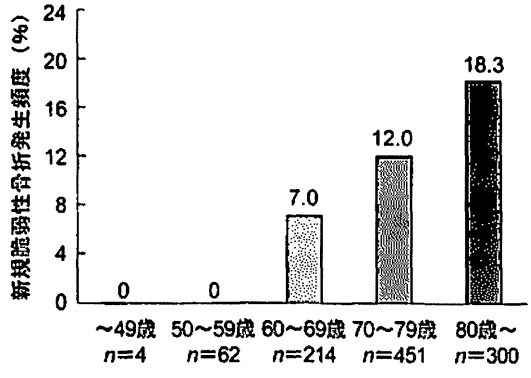

図10　年齢と新規脆弱性骨折

ることが認められ，対象者の集団が日本人骨粗鬆症集団を代表している面を有していることがうかがわれた。一方，49歳以下の集団は症例数が少なかったために他の年齢群とは直接的な比較は困難ではあるものの，特殊な背景を備えている可能性が示唆された。

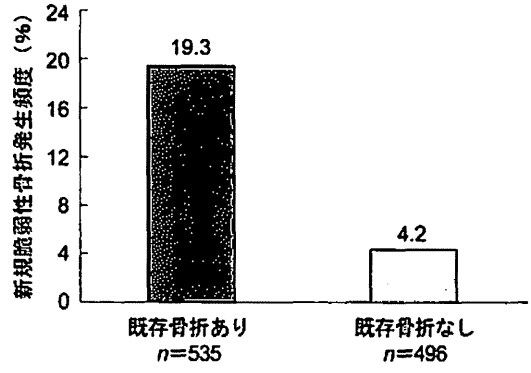

図11　既存骨折の有無と新規脆弱性骨折

近年，生活習慣病による骨折リスクの上昇が注目されているが[4]，本研究においても糖尿病や高血圧の存在が骨粗鬆症性骨折と関連することが示唆され興味深い。

骨粗鬆症治療薬の選択においては，既存骨折の有無や骨折リスクの高さ，年齢などが考慮されていることがうかがわれた。骨折リスクの上昇において年齢は大きく寄与するものであり，薬剤選択における他の要因との関連をさらに検討すべきであろう。「骨粗鬆症の予防と治療ガイドライン2011年版」[5]では，骨粗鬆症の薬物治