39. Beck JD, Offenbacher S, Williams R, Gibbs P, Garcia R. Periodontitis: a risk factor for coronary heart disease? *Ann Periodontol* 1998; 3:127-141.

40. Kinane DF. Periodontal diseases' contributions to cardiovascular disease: an overview of potential mechanisms. *Ann Periodontol* 1998; 3:142-150.

41. Loesche WJ, Lopatin DE. Interactions between periodontal disease, medical diseases and immunity in the older individual. *Periodontol 2000* 1998; 16:80-105.

Table 1. Selected characteristics of study subjects

Variables	Males (n=76)		Females (n=69)		*p* value
	Mean	SD	Mean	SD	
Number of remaining teeth	18.0	8.0	18.1	8.6	0.926
Mean clinical attachment level (mm)	3.7	0.9	3.2	1.0	0.005
Mean probing depth (mm)	2.2	0.5	2.2	0.5	0.366
% of sites with ≥6mm attachment level	11.4	12.9	7.7	12.9	0.093
% with more than 1site with ≥6mm attachment level	88.2		69.6		0.006
% with past or current smoking habit	82.9		3.2		<0.001
% who experienced with dental treatment during past year	36.0		36.2		0.977
Educational level (years)	10.6	2.7	9.5	2.1	0.009
% who use of interdental brushes or dental floss	48.7		53.6		0.552

Table 2. Statistical correlation coefficients and *p* values among renal function, bone metabolism markers, smoking habit and periodontal disease markers

Variables	% of sites with ≥ 6mm attachment level	Creatinine clearance per 24 h (l/day)†	Volume of urine per 24 h (ml/day)	Serum oseocalcin (ng/ml)	Urinary deoxypyridinoline (nM/nM*Cr)	Number of remaining teeth	Smoking habit
% of sites with ≥6mm attachment level							
r	1.00						
p	-						
Creatinine clearance per 24 h (l/day)†							
r	0.30	1.00					
p	<0.001	-					
Volume of urine per 24 h (ml/day)							
r	-0.23	-0.71	1.00				
p	0.006	<0.001	-				
Serum oseocalcin (ng/ml)							
r	-0.29	-0.27	0.11	1.00			
p	0.001	0.001	0.167	-			
Urinary deoxypyridinoline (nM/nM*Cr)							
r	-0.22	0.04	-0.08	0.56	1.00		
p	0.011	0.632	0.344	<0.001	-		
Number of remaining teeth							
r	-0.46	-0.07	0.13	0.06	0.07	1.00	
p	<0.001	0.359	0.090	0.484	0.419	-	
Smoking habit							
r	-0.22	-0.11	-0.01	0.27	0.47	0.02	1.00
p	<0.001	0.174	0.906	0.002	<0.001	0.750	-

†Creatinine(g/day) in urine per 24 h/creatinine(g/l) in serum

Table 3. Renal function, bone metabolism, oral health markers, and social markers of subjects by tertiles of attachment level

	% of sites with ≥6mm attachment level			*p* value
	1st tertile**	2nd tertile**	3rd tertile**	
Mean (SD)	0.2 (0.3)	3.0 (1.5)	21.8 (13.5)	
Mean (SD) creatinine clearance per 24 h (l/day)†	67.7 (24.1)	76.3 (35.7)	87.7 (44.2)	0.017*
Mean (SD) volume of urine per 24 h (ml/day)	1704.6 (477.6)	1676.1 (466.6)	1496.3 (558.0)	0.053*
Mean (SD) serum oseocalcin (ng/ml)	9.1 (3.3)	8.2 (3.5)	7.0 (2.8)***	0.008*
Mean (SD) urinary deoxypyridinoline (nM/nM*Cr)	5.9 (1.5)	5.3 (1.7)	4.9 (1.7)****	0.016*
% with past or current smoking habit	26.1	51.7	62.2	<0.001§
% who experienced with dental treatment during past year	31.4	29.8	37.1	0.455§
Mean (SD) educational level (years)	9.9 (2.3)	10.3 (2.7)	10.3 (2.6)	0.373*
% who use of interdental brushes or dental floss	56.6	52.8	38.3	0.011§

*ANOVA.

§ Chi-square test.

** We categorized the subjects by three tertiles according to the percentage of sites with greater than or equal to 6 mm attachment level. The 1/3, 2/3 percentiles were computed.

† Creatinine(g/day) in urine per 24 h/Cratinine(g/l) in serum

***: p =0.010 by Scheffe multiple comparison test for 1st tertile as the post-hoc procedure.

****: p =0.016 by Scheffe multiple comparison test for 1st tertile as the post-hoc procedure.

Table 4. Relationship between % of sites with ≥6mm attachment level and renal function markers controlling for confounding factors by multiple regression analysis

	Dependent variable					
	% of sites with ≥6mm attachment level					
Independent variables	Coef.	Std. Err.	*p* value	[95% CFI]		Sta. Coef.*
Number of remaining teeth	-0.75	0.12	<0.001	-1.00	-0.51	-0.46
Creatinine clearance for 24 h (l/day)†	0.09	0.04	0.015	0.02	0.16	0.26
Volume of urine for 24 h (ml/day)	1.90E-04	2.80E-03	0.956	-0.01	0.01	0.01
Smoking habit	2.11	3.08	0.500	-3.98	8.20	0.08
Gender	-4.75	3.05	0.121	-10.78	1.28	-0.17
Use of interdental brushes or dental floss	-0.27	2.02	0.893	-4.26	3.72	-0.01
Constant	15.26	8.48	0.074	-1.52	32.03	
				R^2=0.321, p <0.001		

†Creatinine(g/day) in urine per 24h/creatinine(g/l) in serum.
* Standardized coefficient.

Table 5. Relationship between % of sites with ≥ 6mm attachment level and bone metabolism markers controlling for confounding factors by multiple regression analysis

	Dependent variable: % of sites with ≥6mm attachment level					
Independent variables	Coef.	Std. Err.	*p* value	[95% CFI]		Sta. Coef.*
Number of remaining teeth	-0.74	0.12	<0.001	-0.99	-0.49	-0.47
Serum oseocalcin (ng/ml)	-1.06	0.38	0.006	-1.82	-0.31	-0.27
Urinary deoxypyridinoline (nM/nM*Cr)	-0.34	0.85	0.688	-2.03	1.34	-0.04
Smoking habit	-2.70	3.24	0.406	-9.12	3.72	-0.10
Gender	2.70	3.83	0.481	-4.88	10.28	0.10
Use of interdental brushes or dental floss	-0.37	2.11	0.861	-4.55	3.81	-0.01
Constant	36.98	6.16	<0.001	24.79	49.18	
				R^2=0.316, p <0.001		

* Standardized coefficient.

A. 宛名：分担研究者　宮崎秀夫　殿

B. 指定課題名：地域住民の口腔保健と全身的な健康状態の関係についての総合研究

C. 研究協力課題：
「血清アルブミンレベルと根面う蝕の進行に関する経年調査」

D.研究協力者：葭原明弘 1、高野尚子 2、広富敏伸 2、小川祐司 1、花田信弘 3、宮崎秀夫 1

1 新潟大学大学院医歯学総合研究科
2 新潟大学医歯学総合病院
3 国立保健医療科学院

E. 研究目的：

血清アルブミン・レベルは、高齢者の栄養状態をあらわす標識であって、死亡や基礎疾患に関連するといわれている。本調査は、血清アルブミンレベルと根面う蝕の発症との関連を経年的に評価することを目的としている。

F. 対象および方法

ベースライン時に１本以上の現在歯を持っていて、その後６回の検査をすべて受診した合計 266 人を対象とした。６年間の根面う蝕および歯周病の発症歯数を EVENT で表した。重回帰分析により血清アルブミンレベルとの関連を評価した。従属変数は、血清アルブミン値の６年間の変化量である。独立変数は、根面う蝕の発症歯数、歯周病の発症または進行歯数、ＢＭＩ・IgG の６年間の変化量、性別、ベースラインのう蝕歯面数、ベースラインの 4mm 以上の部位数である。

G. 研究結果および考察

６年間の根面う蝕の発症歯数は６年間の血清アルブミン値の変化量と統計学的に有意な関連が認められ、標準化係数は、-0.148（p=0.024）であった。本調査結果から、血清アルブミンが根面う蝕の発症に対する良い標識であることが確認された。血清アルブミン値は高齢者の栄養状態や基礎疾患の有無を表している。全身的な栄養状態が根面う蝕に関連していることが経年調査からも明らかになった。

H.研究発表論文 ： なし

Longitudinal relationship between root caries and serum albumin

A. Yoshihara[1*], N. Takano[1], T. Hirotomi[1], H. Ogawa[1], N. Hanada[2], and H. Miyazaki[1]

[1]Division of Preventive Dentistry, Department of Oral Health Science, Graduate School of Medical and Dental Sciences, Niigata University, 2-5274 Gakkocho-Dori, Niigata, 951-8514, Japan

Tel: +81 25 227 2858, Fax: +81 25 227 0807, E-mail: akihiro@dent.niigata-u.ac.jp

[2]Department of Oral Science, National Institute of Public Health, 2-3-6 Minami, Wako-shi 351-0197, Japan.

*To whom correspondence and reprint requests should be addressed.

Short title: Root caries and serum albumin

Key words: Root caries, Geriatric dentistry, Serum albumin

Number of words in the abstract: 147
Number of the words in the text: 2370
Number of tables and figures: 4
Number of cited references: 27

ABSTRACT

Serum albumin levels are a practical marker of general health status in the elderly and have been used to determine the severity of an underlying disease and the risk for death. This longitudinal study evaluated the relationship between serum albumin levels and root caries. A total of 266 subjects with at least 1 tooth at baseline underwent a baseline examination and then annual investigations for 6 years. Multiple linear regression analysis was used to assess the relationship between changes in serum albumin levels and the number of root caries over 6 years after controlling for confounding factors. Change in the number of root caries was significantly associated with change in serum albumin concentrations. Standardized coefficient was -0.148 (p=0.024). We can confirm that serum albumin was a good marker for root caries. From these data, we conclude that subjects with hypoalbuminemia are at high risk for root caries.

INTRODUCTION

Serum albumin levels are a practical marker of general health status in the elderly and have been used to determine the severity of an underlying disease and the risk for death (Phillips *et al.*, 1989, Shibata *et al.*, 1991). Many conditions, such as inflammatory states, liver diseases, and renal diseases, lead to decreased serum albumin levels (Herrmann *et al.*, 1992; Rigaud *et al.*, 2000; Walrand *et al.*, 2000). Moreover, malnutrition is monitored by examining serum albumin levels (Don and Kaysen, 2004; Magagnotti *et al.*, 2000; Giordano *et al.*, 2001). Recently, studies have shown that serum albumin levels are associated with general health status among the elderly (Corti *et al.*, 1994; Baumgatner *et al.*, 1996). In this way, hypoalbuminemia occurs in a variety of diseases, and is associated with an increased rate of complications during hospitalization. In addition, serum albumin is a possible index of intrinsic aging (Sibata *et al.*, 1991).

On the other hand, aging is known to lead to an increase in some oral conditions, such as gingival recession and root caries. Several risk factors for the development of root caries have been identified, including past caries, periodontal status, and salivary levels of cariogenic bacteria (Lawrence *et al.*, 1995; Locker *et al.*, 1996; Powell *et al.*, 1998; Scheinin *et al.*, 1994). Furthermore, some reports indicate a

link between general health and dental caries. For example, the composite dental index, which combines caries, periodontitis, and edentulousness, was linked to ischemic events in patients with coronary heart disease (Mattila *et al.*, 1995). Furthermore, it has been shown that an increased number of dental caries may be associated with an increased immune response (Tenovuo *et al.*, 1990).

Previously, we showed an association between serum albumin levels and root caries in a cross-sectional study of elderly patients (Yoshihara *et al.*, 2003). However, because of the cross-sectional design, we could not confirm a clear relationship between serum albumin concentrations and root caries.

This longitudinal study evaluated the relationship between serum albumin concentrations and root caries in elderly patients, after controlling for confounding factors.

MATERIALS & METHODS

Subjects

A longitudinal study was conducted in older adults who reside in Niigata City, Japan. Initially, questionnaires were sent to all 4,542 residents aged 70 years (born in 1927). Of them, 600 people were randomly selected in order to have approximately the same number of each gender for the baseline survey. Participants were asked to sign consent forms regarding the protocol, which was approved by the Ethics Committee of Niigata University School of Dentistry.

Subjects were assessed using TMIG-Index of Competence subscale questionnaires. The TMIG-Index of Competence is used to assess functional capacity in older patients. The ability to perform a given function is indicated by 'Yes' or 'No'. The highest score on the TMIG-Index subscales is 13 (Koyano *et al.*, 1991). The mean score of the TMIG-Index subscales of subjects in this study was 11.9±1.4. The results of this assessment pointed to a high level of competence among participants of this study.

Dental examinations were carried out at baseline and once a year for 6 years (1998-2004), that is, 7 times in 6 years.

Measurements

Root caries events

Four trained and experienced dentists assessed dental caries, including root caries. The examinations were conducted using mirrors and ball-pointed periodontal probes under artificial light, without bite-wing radiographs. Root caries was diagnosed using the criteria of the World Health Organization (1997). First, it was determined whether a given surface was exposed or not. An exposed root surface was defined as at least 1 mm of visible root surface between the gingival crest and the cement-enamel junction or the restoration margin. All exposed root surfaces were examined and recorded. Root decay was defined as a lesion detected on an exposed root surface that felt soft or leathery to probing. For a single decay affecting both the crown and the root, the likely site of origin of the lesion was recorded as "decayed". When it was not possible to judge the site of origin, both the crown and the root were recorded as "decayed".

We tracked root caries incidence only on surfaces that were neither decayed nor filled at baseline examination. Whenever root decay was detected on a root surface that had previously been sound or non-exposed, it was counted as a disease event. Disease events were counted each year. Surfaces where disease events occurred once were excluded from additional-year evaluations. Finally, the number of surfaces on

which a disease event occurred over the 6 years was converted into the number of teeth on which a disease event occurred in a given subject.

Interexaminer reliability for surfaces was assessed for the 4 examiners using 18 volunteer patients in the University Hospital before and during the survey. We calculated a kappa score using 5 codes (Sound, Filled, Decayed, Filled [with decay], and Bridge abutment: Special crown or Veneer/implant). The kappa values between each pair of examiners were 0.84-0.97.

Periodontal disease events

The periodontal examination included the assessment of attachment level at 6 sites around each tooth. Probing was performed using a pressure constant probe (Vivacare TPS Probe®, Schaan, Liechtenstein) and a probing force of 20 g. The periodontal examination was carried out by 4 trained dentists under sufficient illumination using artificial light. At first, the difference between attachment level at baseline and at follow-up for each site was calculated using site-level data. If the difference was ≥3 mm, it was counted as a periodontal disease event. Surfaces where disease events occurred once were excluded from additional-year assessments. Data were rounded from site-level to tooth-level. Finally, the number of teeth with an event

per person was calculated.

Interexaminer reliability for attachment was assessed for the 4 examiners using 18 volunteer patients in the University Hospital before and during the survey. As determined by replicate examinations on attachment level, the percent agreement (± 1 mm) ranged from 70.0% to 100%. The kappa (± 1 mm) ranged from 0.62 to 1.00.

Composition and Blood Measurements

Anthropometric evaluation included measurements of weight and height for the calculation of body mass index (BMI). BMI is defined as the individual's body weight divided by the square of his/her height. In addition, serum albumin and immunoglobulin G (IgG) concentrations were measured at a commercial laboratory (BML, Inc., Tokyo, Japan). Serum albumin concentration ≤4.0g/dl was defined as low according to a previous report (Phillips *et al.*, 1989).

Statistical Analysis

For descriptive data (BMI, serum IgG levels, and the number of periodontal disease events), statistical differences between the number of root caries events were evaluated by analysis of variance (ANOVA) and Scheffe multiple comparison test for

root caries event (0) as the post-hoc procedures. Means and standard deviations were used to characterize continuous variables. In addition, we compared the number of root caries events over 6 years between subjects with serum albumin concentrations ≤4.0g/dl at baseline and those of subjects with serum albumin concentrations >4.0g/dl at baseline using the student's *t* test with two-sided *p*-values. Afterwards, we selected subjects with serum albumin concentrations >4.0g/dl at baseline and divided them into 2 groups: those with serum albumin concentrations ≤4.0g/dl after 6 years and those with serum albumin concentrations >4.0g/dl after 6 years. We then compared the number of root caries events between these 2 groups.

Finally, multiple linear regression analysis was performed to assess the relationship between changes in serum albumin concentrations and the number of root caries event over 6 years after controlling for periodontal disease events over 6 years, changes in BMI over 6 years, changes in serum IgG concentrations over 6 years, gender, the number of teeth at baseline, the number of sites with ≥4mm attachment level at baseline, and the number of decayed and filled surfaces at baseline. The level of significance was set at $p<0.05$ for these tests. All calculations and statistical analyses were performed using the STATA® software package (Stata Corp., Texas, USA).

RESULTS

In this study, 334 subjects dropped out during the study. Serum albumin concentrations at baseline were 4.3±0.2 g/dl for study subjects and 4.3±0.3 g/dl for the group who dropped out during the study. There was no significant difference between the two groups (p=0.168; student's t test). In addition, 36 people died during the study. Serum albumin concentrations at baseline for these subjects were 4.1±0.3 g/dl. The difference in serum albumin concentrations at baseline between study subjects and subjects who died during the study was statistically significant (p<0.001; student's t test).

Of 600 participants, 266 subjects who had at least 1 tooth at baseline and participated in all annual investigations (7 times in total) from baseline to 6 years were included in the analysis. Table 1 shows that the baseline characteristics, and the distribution of root caries events and the association with changes in BMI, serum IgG concentrations, and periodontal disease events over 6 years. Root caries developed in 52.3% of the subjects over the 6-year study. Serum IgG concentrations and periodontal disease events significantly showed a high value with increase of root caries events by ANOVA (p=0.013 for serum IgG; p=0.007 for periodontal disease events). However, they were no significant by Scheffe multiple comparison test for

root caries event (0) as the post-hoc procedures.

In addition, subjects with lower serum albumin concentrations (≤4.0g/dl) at baseline had a significantly higher number of root caries events over 6 years compared with subjects with high serum albumin concentrations (>4.0g/dl) at baseline (1.8±2.2 vs 1.1±1.6, respectively; p=0.031, student's t test) (Fig. 1). We divided subjects with serum albumin concentrations >4.0g/dl at baseline into 2 groups: those with serum albumin concentrations ≤4.0g/dl after 6 years and those with serum albumin concentrations >4.0g/dl after 6 years. The mean number of root caries events for 6 years was 1.6±2.1 for the subjects with serum albumin concentrations ≤4.0g/dl after 6 years compared with 1.0±1.4 for those with serum albumin concentrations >4.0g/dl after 6 years (p=0.009, student's t test) (Fig. 2).

Table 2 shows the results of multiple regression analysis. The number of root caries events, the change in BMI, serum IgG concentrations over 6 years, gender, and the number of sites with ≥4mm attachment level at baseline were significantly associated with the change in serum albumin concentrations over 6 years.

DISCUSSION

There was no significant difference in serum albumin concentration at baseline between the study subjects and the subjects who dropped out. Therefore, we thought that the subjects in this study were representative of the community. In addition, serum albumin concentrations ≤4.0g/dl were defined as low according to Phillips's report (Phillips *et al.*, 1989). In the report, serum albumin concentrations were divided into six categories (<4.0, 4.0-, 4.2-, 4.4-, 4.6-, 4.8-) and mortality rate. There was a gradual increase in mortality rate with decreasing serum albumin concentrations. Subjects with serum albumin levels <4.0g/dl had a crude all-cause mortality rate six times that of subjects with a serum albumin of 4.8g/dl or higher. Therefore, we designated serum albumin concentrations as low (≤ 4.0g/dl) and high (> 4.0 g/dl) in this study.

To our knowledge, this is the first longitudinal study to clarify the relationship between root caries and serum albumin levels in elderly patients. In this study, the number of root caries events over 6 years was significantly associated with the change in serum albumin concentrations over 6 years after controlling for confounding factors by multiple regression analysis. The standardized coefficient of the number of root

caries events was -0.148 (p=0.024). We can confirm that serum albumin concentration was a good marker for root caries events. Accordingly, these longitudinal findings support a previous cross-sectional study indicating an association between oral health status and serum albumin levels (Yoshihara *et al.*, 2003).

Serum albumin levels provide an index of the severity of an underlying disease. Many conditions, such as malnutrition, inflammatory disorders, liver disease, and renal diseases, reduce serum albumin levels. In these cases, subjects with hypoalbuminemia and malnutrition are likely to have decreased immunocompetence with an increased risk of infection (Botros *et al.*, 1996).

In our study, the root caries events showed a tendency to increase with increasing levels of IgG. In addition, a statistically significant association was found between IgG and serum albumin. Serum albumin concentrations fall with a variety of infections. However, in inflammatory states, the activity of macrophages and other cells of the immune system are enhanced, adversely (Conlon *et al.*, 2004). Therefore, the both root caries and IgG levels increased even if the subjects had a lower immunocompetence and a low serum albumin level, as shown in our study.