*Table 2B.* Relationship between periodontal conditions and decreased adiponectin level by logistic regression analysis

| Model 1 | | | | | |
|---|---|---|---|---|---|
| Independent variables | Adiponectin ≥11.5ng/ml | Adiponectin <11.5ng/ml | $p$[a] | Multivariate OR[b] (95%CI) | $p$ |
| Periodontal condition | | | | | |
| Control | 34 (45.9) | 40 (54.1) | 0.336 | 1 | |
| Periodontitis | 32 (38.1) | 52 (61.9) | | 1.38(0.68-2.80) | 0.374 |
| Sex | | | | | |
| Male | 19 (23.7) | 61 (76.3) | <0.001 | 1 | |
| Female | 47 (60.3) | 31 (39.7) | | 0.21(0.07-0.61) | 0.004 |
| BMI | | | | | |
| <25 | 57 (43.5) | 74 (56.5) | 0.395 | 1 | |
| ≥25 | 9 (33.3) | 18 (66.7) | | 2.21(0.83-5.92) | 0.114 |
| Fasting glucose | | | | | |
| <110mg/dL | 39 (57.6) | 29 (42.6) | 0.001 | 1 | |
| ≥110mg/dL | 27 (30.0) | 63 (70.0) | | 2.57(1.26-5.24) | 0.009 |
| Smoking habit | | | | | |
| No | 48 (55.2) | 39 (44.8) | <0.001 | 1 | |
| Yes | 18 (25.4) | 53 (74.6) | | 1.04(0.36-3.04) | 0.942 |
| Model 2 | | | | | |
| Independent variables | Adiponectin ≥11.5ng/ml | Adiponectin <11.5ng/ml | $p$[a] | Multivariate OR[b] (95%CI) | $p$ |
| Periodontal condition | | | | | |
| Control without bleeding | 27 (45.0) | 33 (55.0) | 0.321 | 1 | |
| Periodontitis with bleeding | 16 (34.0) | 31 (66.0) | | 1.62(0.67-3.92) | 0.290 |
| Sex | | | | | |
| Male | 13 (24.5) | 40 (75.5) | 0.002 | 1 | |
| Female | 30 (55.6) | 24 (44.4) | | 0.25(0.08-0.83) | 0.023 |
| BMI | | | | | |
| <25 | 37 (43.0) | 49 (57.0) | 0.321 | 1 | |
| ≥25 | 6 (28.6) | 15 (71.4) | | 2.20(0.69-7.04) | 0.182 |
| Fasting glucose | | | | | |
| <110mg/dL | 28 (57.1) | 21 (42.9) | 0.001 | 1 | |
| ≥110mg/dL | 15 (25.9) | 43 (74.1) | | 3.11(1.30-7.43) | 0.011 |
| Smoking habit | | | | | |
| No | 31 (50.8) | 30 (49.2) | 0.011 | 1 | |
| Yes | 12 (26.1) | 34 (73.9) | | 1.00(0.31-3.25) | 0.997 |

[a] chi-square test

[b] odds ratio by logistic regression analysis

*Table 3.* Adjusted mean value of serum resistin and adiponectin in the subjects with each periodontal conditions

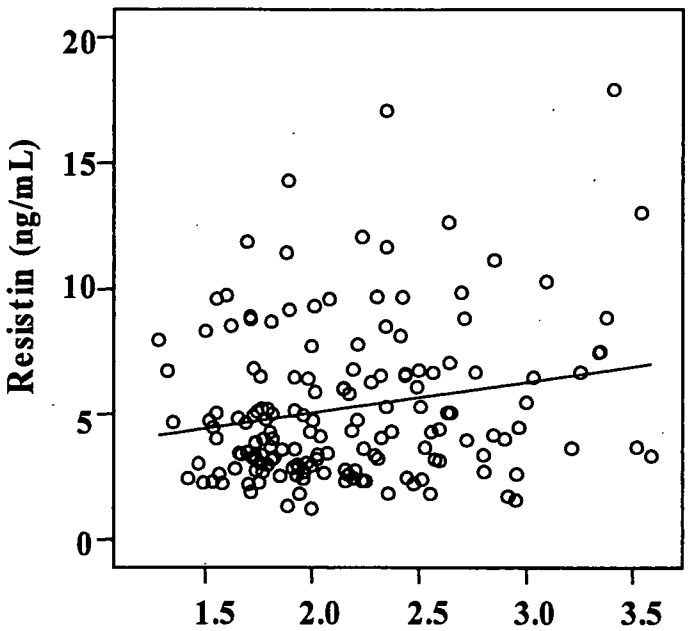
| Periodontal status | Resistin | $p$ [a] | Adiponectin | $p$ [a] |
|---|---|---|---|---|
| Model 1 | | | | |
| Control | 4.86 ± 2.90 | 0.138 | 12.09 ± 6.27 | 0.248 |
| Periodontitis | 5.60 ± 3.23 | | 10.92 ± 4.96 | |
| Model 2 | | | | |
| Control without bleeding | 4.78 ± 2.95 | 0.037 | 11.90 ±6.55 | 0.551 |
| Periodontitis with bleeding | 6.11 ± 3.54 | | 10.85 ±5.62 | |

[a] ANCOVA was performed adjusting for sex, BMI, fasting glucose, and smoking.

**Figure legends**

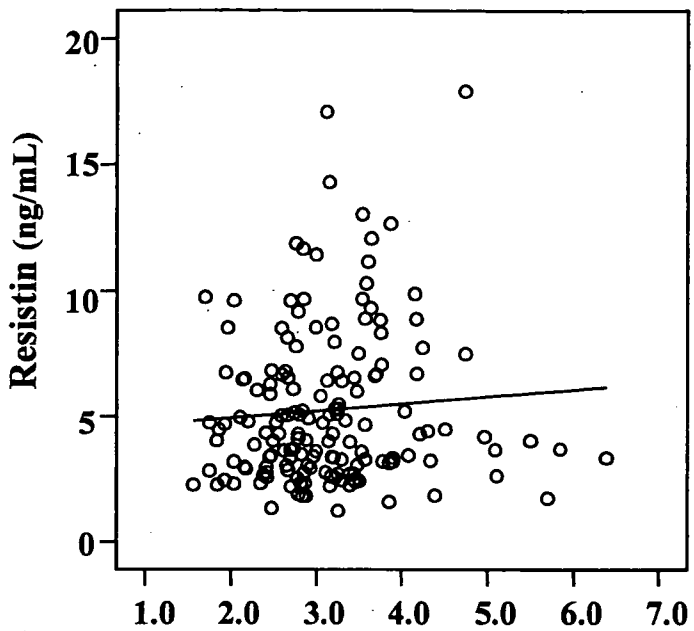
**Fig 1.** Correlations between serum levels of resistin or adiponectin and mean probing depth, mean attachment loss, percentage of bleeding on probing, leukocyte counts. Serum levels of resistin and adiponectin were determined by ELISA. Mean values of probing depth, mean values of attachment loss, percentage of bleeding on probing of each subjects were determined by periodontal examination. Spearman's rank correlation analyses between mean probing depth (A), mean attachment loss (B), percentage of bleeding on probing (C), and leukocyte counts (D) and serum levels of resistin. Spearman's rank correlation analyses between mean probing depth (E), mean attachment loss (F), percentage of bleeding on probing (G), and leukocyte counts (H) and serum levels of adiponectin.

A



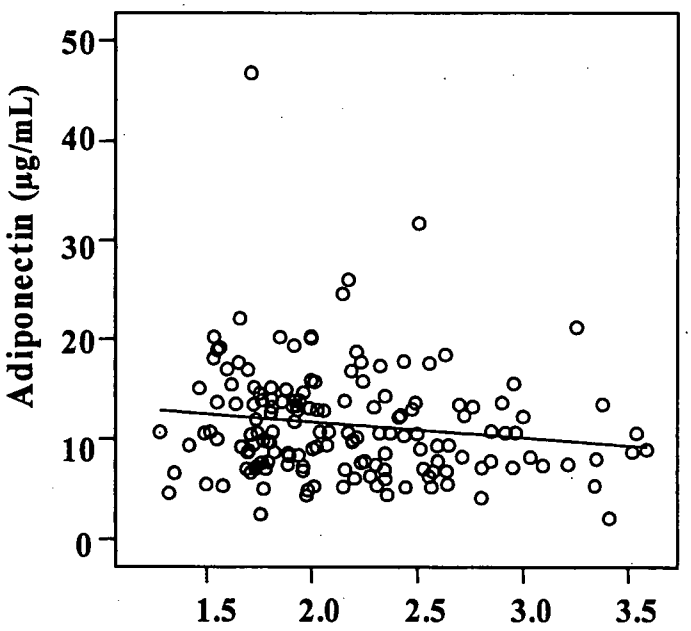

$r_s = 0.149$, $p = 0.062$

B



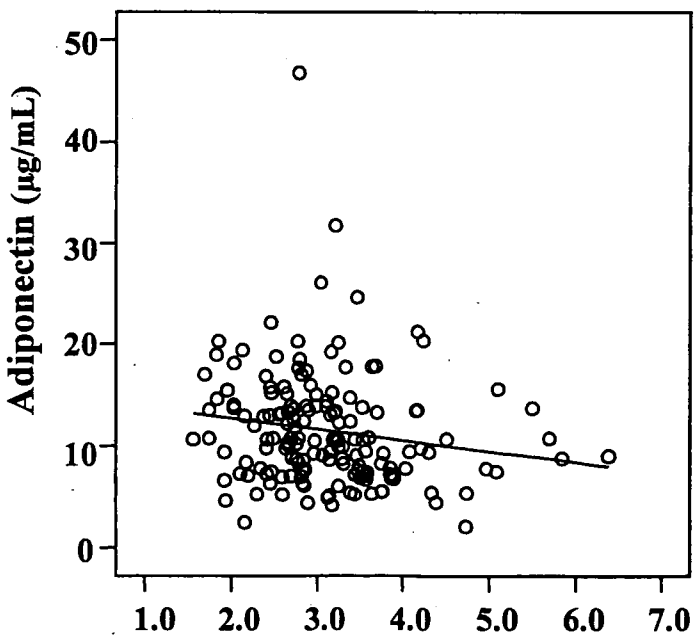

$r_s = 0.089$, $p = 0.266$

E



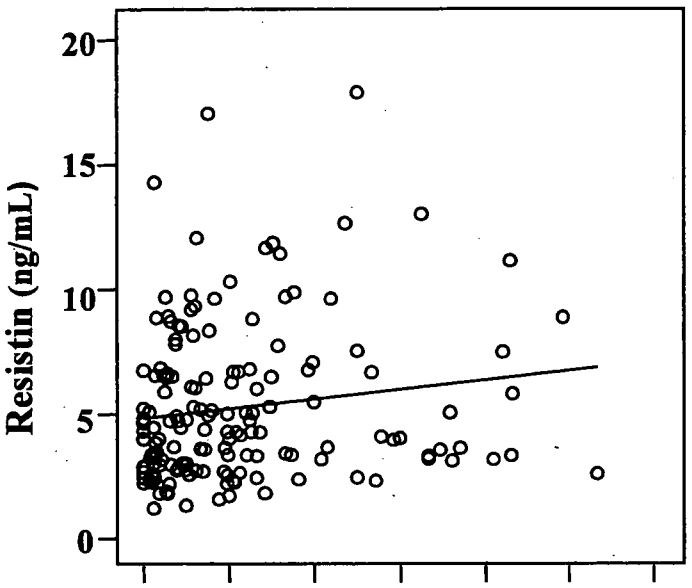

$r_s = -0.154$, $p = 0.053$

F



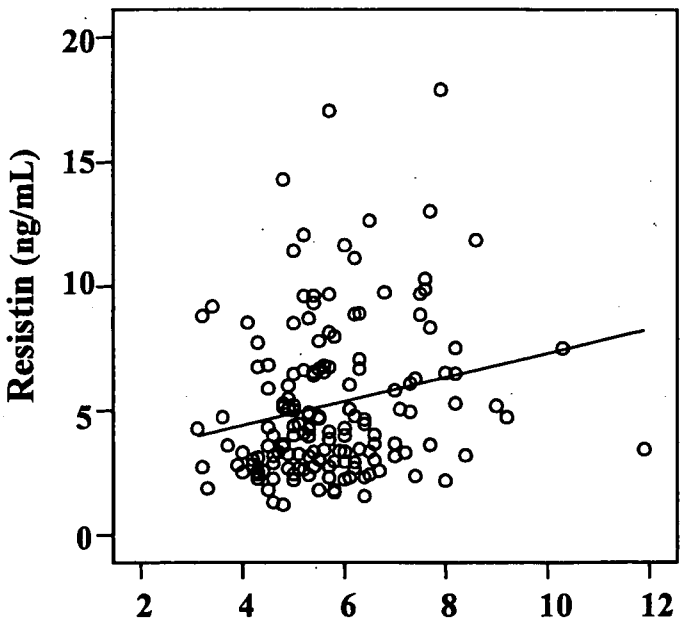

$r_s = -0.212$, $p = 0.007$

C



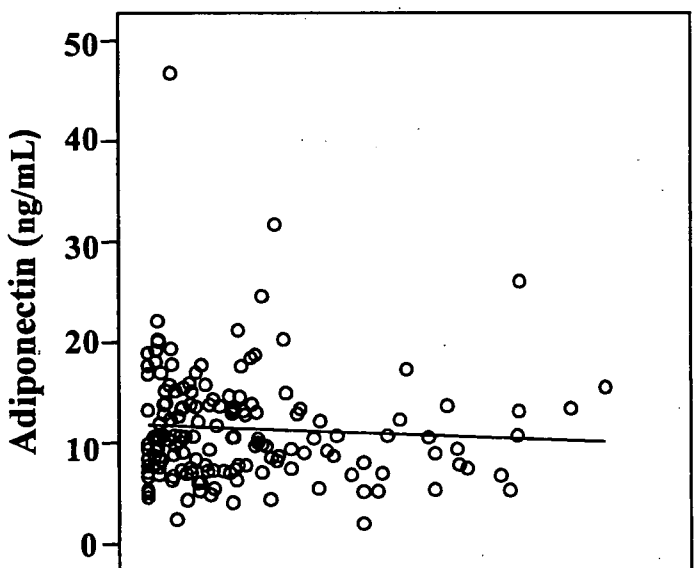

$r_s = 0.198$, $p = 0.013$

D



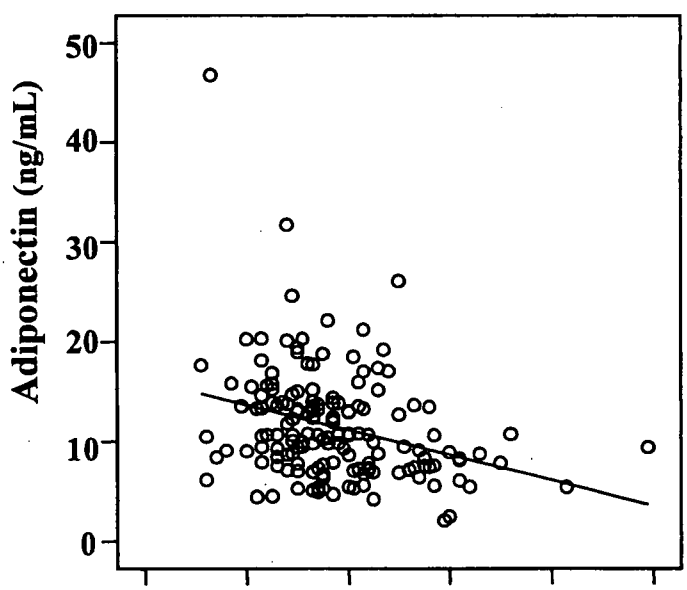

$r_s = 0.233$, $p = 0.003$

G




$r_s = -0.082$, $p = 0.304$

H




$r_s = -0.316$, $p < 0.001$

A. 宛名： 分担研究者 宮﨑秀夫 殿

B. 指定課題名： 平成16年度医療技術評価総合研究事業
「地域住民の口腔健康と全身的な健康状態の関係についての総合的研究」

C. 研究協力課題：
「血清アルブミンと歯周病の関係についての経年的評価」

D. 研究協力者： 岩﨑正則[1], 葭原明弘[1], 廣冨敏伸[1], 小川裕司[1], 花田信弘[2], 宮﨑秀夫[1]
[1]新潟大学大学院医歯学総合研究科
[2]国立保健医療科学院

E. 研究目的：

全身の栄養状態を示す指標の一つとして血清アルブミンがある。近年の疫学的調査結果から，栄養失調，炎症，肝疾患，腎疾患などにより，血清アルブミン濃度が減少するとされている。血清アルブミンの低値により示される栄養不良状態では，免疫機能が低下し，感染症にかかりやすくなる。発展途上国における乳幼児死亡や，先進国においても，高齢者などの栄養障害による感染と免疫機能との関連が明らかにされている。

う蝕や歯周病は口腔における細菌感染症性疾患である。歯周病の病変部では細菌に対する宿主の免疫応答として炎症性反応が起こっている。免疫機能の低下は歯周病を進行させることが知られている。

全身栄養状態の低下により血清アルブミンの低下が生じる。血清アルブミンが低下すると炎症性サイトカインなどのcell mediatorの影響を受けやすくなることが報告されており，それが直接歯周病の発生・進行に関与していることが考えられる。

昨今，歯科疾患と全身的な健康状態との関連を評価する調査が行われてきたが，いずれも横断的研究が多く，経年的に評価した疫学研究はほとんど認められない。

本研究は，全身的な健康状態の指標として血清アルブミンを採用し，歯周病との関連を経年的に評価することを目的とする。

F. 研究方法：

厚生科学研究（高齢者の口腔健康状態と全身健康状態の関係についての総合的研究）において，平成10年度に行われたベースライン調査で対象とした70歳高齢者600名のうち，平成14年までの4年間のすべての調査（5回）に参加し，ベースラインにおいて有歯顎者である者304名（男性164名，女性140名）を本研究対象とした。

歯周組織検査を行い，アタッチメントレベル（LA）を1歯あたり6点について計測した。診査部位各点で前年比3mm以上のLAの増加が認められた場合に歯周病が発生/進行したも

のと定義した。一度進行が認められた歯については次年度以降，評価対象歯から外した。4年間で歯周病が発生/進行した歯の累計を歯周病進行経験歯数として対象者ごとに算定し，歯周病の発生/進行の評価基準として用いた。血清アルブミンはBCG法により測定し，その他，血液生化学検査により，GOT，GPT，γ-GTP，IgG，総タンパク，カルシウムを測定した。

ベースライン時の血清アルブミン濃度により2群（≤4.0g/dl，>4.0g/dl）に分け，歯周病経験歯数との関係を評価した。さらに関連要因を加え，歯周病進行経験歯数を従属変数とする重回帰分析を行った。また，ベースライン時から4年間（5回）の血清アルブミン濃度の平均値の高い群と低い群に分け（≤4.0g/dl，>4.0g/dl），歯周病進行経験歯数を比較した。4年間全5回の血清アルブミンの濃度の記録がある者284名のみを対象とした。

Effect modificationを評価するため全ての検定は対象者を喫煙群139名，非喫煙群165名に分け行った。ベースライン時に行った質問から一度でも喫煙の経験のある者を喫煙群とした。

G. 研究結果および考察：

非喫煙群において，平均歯周病進行経験歯数はベースライン時の血清アルブミン濃度の低い群（≤4g/dl, N=20）で10.5±7.3本，濃度の高い群（>4g/dl, N=145）で6.7±4.8本であり，血清アルブミン濃度の低い群で平均歯周病進行経験歯数が多く，その差は統計学的に有意であった（Student's $t$-test, $p$ =0.0024）（Fig. 1）。

また，性別，BMI，現在歯数，LA最大値，血圧（最大、最小），GOT，GPT，γ-GTP，IgG，総タンパク，カルシウムの違いによる平均歯周病進行経験歯数をそれぞれ比較したところ，男性の方が歯周病進行経験歯数が多く（$p$ =0.0155），その他では現在歯数20-32の者（$p$ <0.0001），LA最大値6mm以上の者（$p$ =0.0003）が歯周病進行経験歯数が多く，それぞれ統計的に有意であった（Table 1）。

さらに歯周病進行経験歯数と血清アルブミン濃度，性別，現在歯数，LA最大値との関連について重回帰分析を用いて評価したところ，歯周病進行経験歯数と血清アルブミン濃度の間に有意な相関が認められた（standardized coefficient =-0.16, $R^2$=0.3005, $p$ <0.001）（Table 2）。

また，ベースライン時から4年間の血清アルブミン濃度の平均値の低い群（≤4g/dl, N=19）の平均歯周病進行経験歯数は10.4±7.5本，血清アルブミン濃度の平均値の高い群（>4g/dl, N=133）は6.8±4.8本であり，血清アルブミン濃度の平均値の低い群の平均歯周病進行経験歯数が有意に多いことがわかった（Student's $t$-test, $p$ =0.0049）（Fig. 2）。

一方，喫煙群において平均歯周病進行経験歯数と血清アルブミン濃度の間に統計学的に有意な関連は認められなかった（Figs 1 & 2）。

以上より，非喫煙群において，血清アルブミンの低値で示される全身の栄養状態の低下が歯周病の発生に関連していることが示唆された。

H. 結論：

本研究の結果から，喫煙経験のない高齢者において，血清アルブミン値の低下が歯周病発生の有力なリスクプレディクターであることが示された。

I. 研究発表論文：

Iwasaki M, Yoshihara A, Hirotomi T, Ogawa H, Hanada N, Miyazaki H: Longitudinal relationship between serum albumin and periodontal disease. *J Clin Periodontol*, in press, 2008.

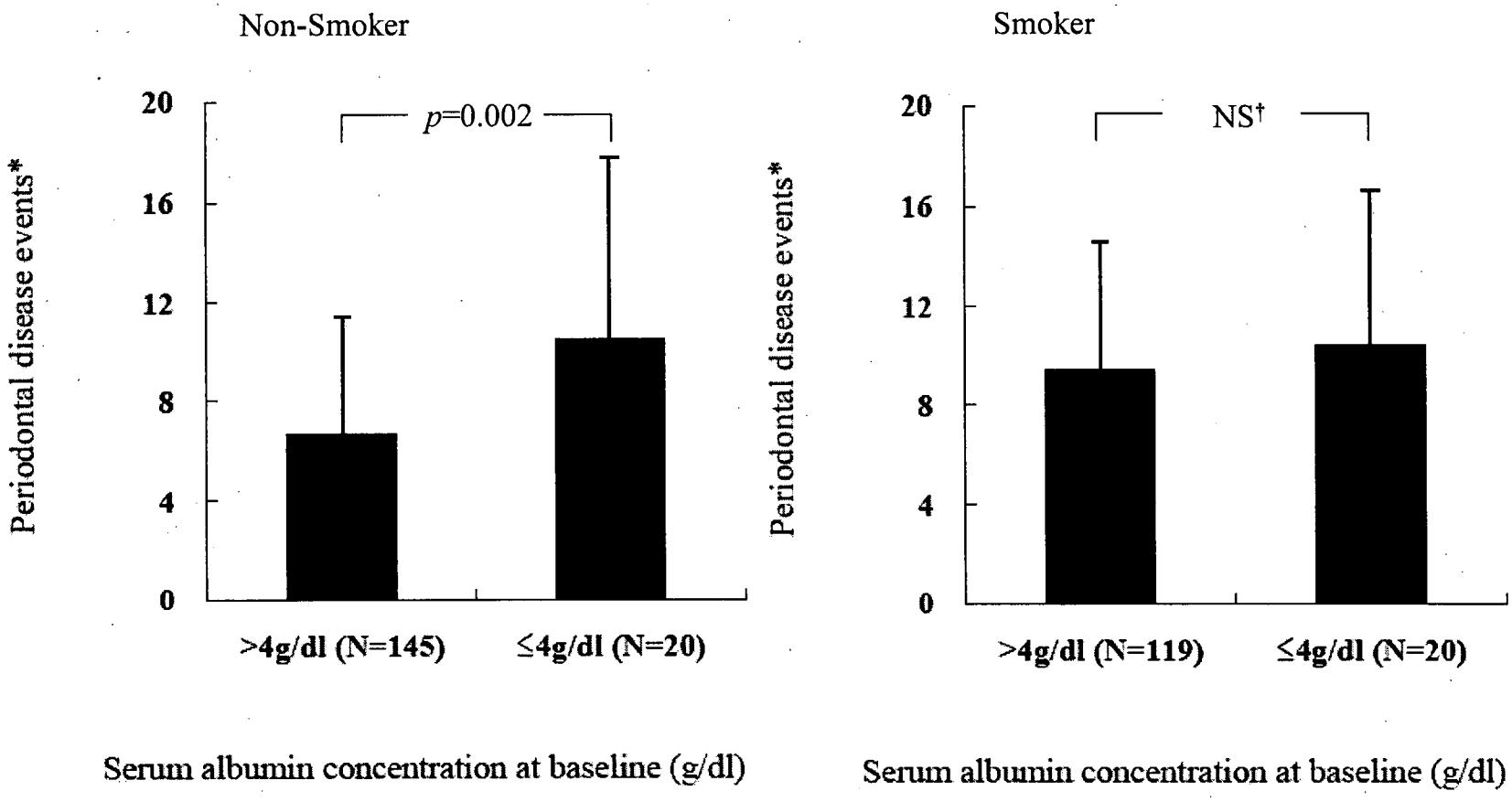



***Fig. 1.* Relationship between periodontal disease events and serum albumin concentration at baseline, stratified by smoking status .**
*** Number of teeth with periodontal disease progression during 4years.**
**†Not significant**

*Table 1.* Relationship between subject characteristics, dental status, blood pressure levels, serum blood parameters for nutritional and biochemical values, serum disease markers and periodonatal disease events

| | Non-Smokers (N=165) | | | | Smokers (N=139) | | | |
|---|---|---|---|---|---|---|---|---|
| | No. of subjects | Periodontal disease events† | | | No. of subjects | Periodontal disease events† | | |
| | | Mean | SD | *p*-value | | Mean | SD | *p*-value |
| Gender | | | | | | | | |
| Male | 35 | 9.03 | 5.72 | 0.0155 | 129 | 9.74 | 5.51 | NS* |
| Female | 130 | 6.60 | 5.07 | | 10 | 6.90 | 1.79 | |
| BMI‡ | | | | | | | | |
| <20 | 37 | 7.27 | 5.78 | NS* | 33 | 10.61 | 4.92 | NS* |
| ≥20 | 128 | 7.07 | 5.17 | | 106 | 9.20 | 5.49 | |
| No. of teeth present | | | | | | | | |
| 1-9 | 29 | 2.62 | 2.43 | <0.0001 | 16 | 4.19 | 2.07 | <0.0001 |
| 10-19 | 36 | 5.75 | 3.37 | | 44 | 8.23 | 3.26 | |
| 20-32 | 100 | 8.91 | 5.56 | | 79 | 11.34 | 5.86 | |
| Highest CAL§ (mm) | | | | | | | | |
| <6 | 79 | 5.57 | 4.67 | 0.0003 | 29 | 7.17 | 6.18 | 0.0074 |
| ≥6 | 86 | 8.53 | 5.46 | | 110 | 10.15 | 4.99 | |
| High blood pressure | | | | | | | | |
| ≤140 | 115 | 7.15 | 4.95 | NS* | 80 | 9.76 | 5.24 | NS* |
| >140 | 50 | 7.04 | 6.05 | | 59 | 9.22 | 5.58 | |
| Low blood pressure | | | | | | | | |
| ≤90 | 160 | 7.11 | 5.33 | NS* | 128 | 9.51 | 5.38 | NS* |
| >90 | 5 | 7.20 | 4.32 | | 11 | 9.82 | 5.56 | |
| GOT | | | | | | | | |
| ≤40 | 162 | 7.14 | 5.32 | NS* | 136 | 9.59 | 5.38 | NS* |
| >40 | 3 | 6.00 | 3.61 | | 3 | 7.00 | 5.29 | |
| GPT | | | | | | | | |
| ≤35 | 158 | 7.15 | 5.33 | NS* | 133 | 9.51 | 5.31 | NS* |
| >35 | 7 | 6.29 | 4.54 | | 6 | 10.00 | 7.32 | |
| γ-GTP | | | | | | | | |
| <60 | 163 | 7.17 | 5.30 | NS* | 127 | 9.57 | 5.39 | NS* |
| ≥60 | 2 | 3.00 | 1.41 | | 12 | 9.17 | 5.39 | |
| IgG (mg/dl) | | | | | | | | |
| <1000 | 3 | 12.33 | 8.08 | NS* | 9 | 10.67 | 4.00 | NS* |
| 1000-1900 | 144 | 6.94 | 5.24 | | 121 | 9.45 | 5.48 | |
| >1900 | 18 | 7.61 | 5.17 | | 9 | 9.44 | 5.46 | |
| Total protein (g/dl) | | | | | | | | |
| <6.5 | 2 | 8.00 | 4.24 | NS* | 5 | 8.60 | 5.18 | NS* |
| ≥6.5 | 163 | 7.10 | 5.31 | | 134 | 9.57 | 5.40 | |
| Calcium (mEg/l) | | | | | | | | |
| <6.5 | 55 | 7.82 | 5.54 | NS* | 67 | 9.63 | 5.91 | NS* |
| ≥6.5 | 110 | 6.76 | 5.16 | | 72 | 9.44 | 4.86 | |

†Number of teeth with periodontal disease progression during 4 years.

‡Body mass index.

§Clinical attachment level.

*Not significant.

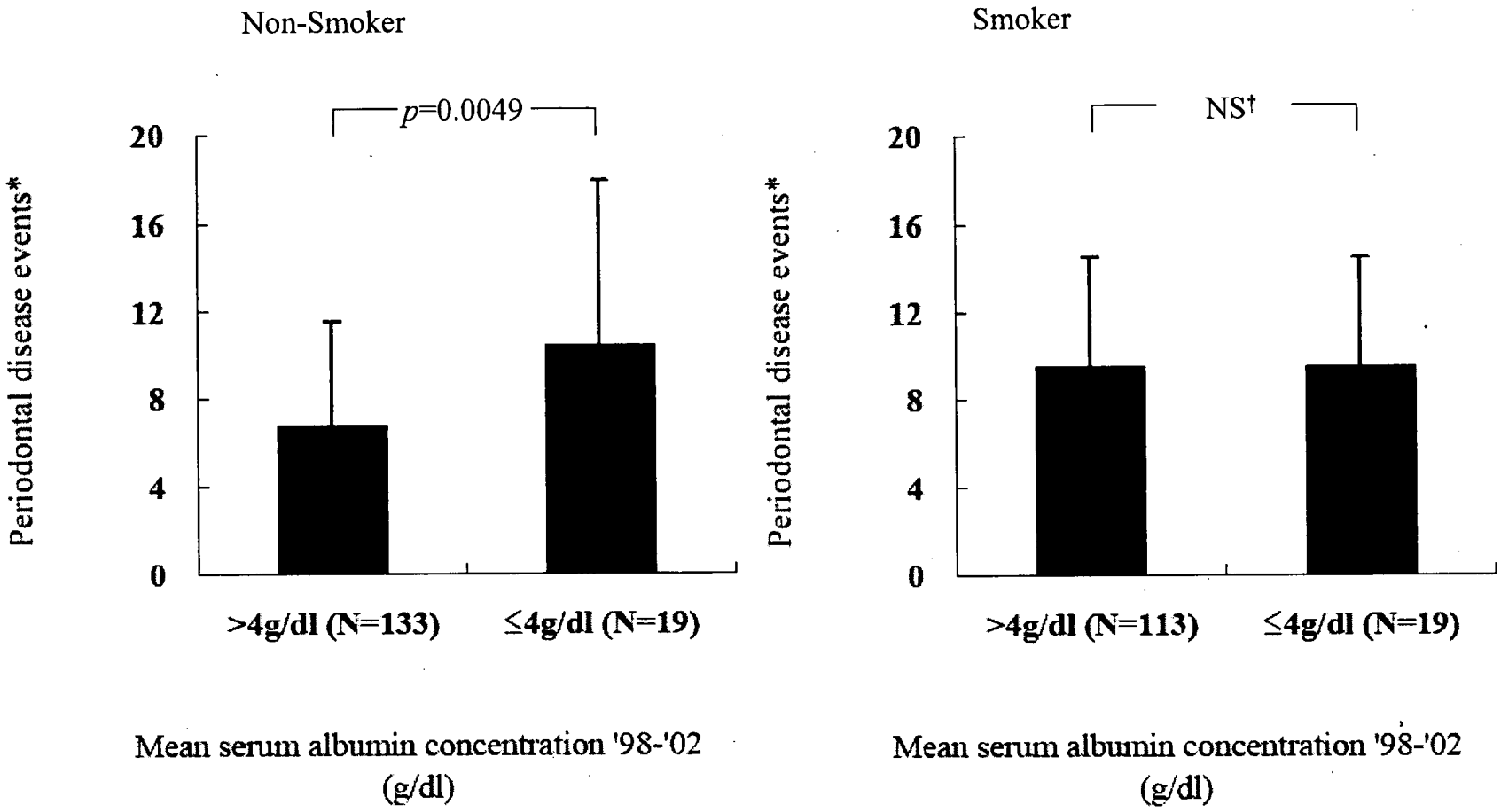



***Fig. 2.* Relationship between periodontal disease events and the mean serum albumin concentration during 4 years, stratified by smoking status .**
*** Number of teeth with periodontal disease progression during 4 years.**
**†Not significant**

*Table 2.* Multiple linear regression and associated *p* values

| Non-Smokers | | | | | | |
|---|---|---|---|---|---|---|
| | Dependent variable | | | | | |
| | Periodontal disease events[†] | | | | | |
| Independent variables | coefficient | standard error | *p*-value | 95% CI[‡] | | Std. Coef[§] |
| Serum albumin (g/dl) | -3.54 | 1.46 | 0.017 | -6.42 | -0.65 | -0.16 |
| Gender | 0.77 | 0.88 | 0.385 | -0.97 | 2.50 | 0.06 |
| No. of teeth present | 0.28 | 0.04 | <0.001 | 0.19 | 0.36 | 0.43 |
| Highest CAL[¶] | 0.60 | 0.17 | 0.001 | 0.26 | 0.93 | 0.23 |
| Constant | 13.31 | 6.64 | 0.047 | 0.21 | 26.42 | |
| | | | | | | $R^2$=0.3005, $p$<0.001 |

| Smokers | | | | | | |
|---|---|---|---|---|---|---|
| | Dependent variable | | | | | |
| | Periodontal disease events[†] | | | | | |
| Independent variables | coefficient | standard error | *p*-value | 95% CI[‡] | | Std. Coef[§] |
| Serum albumin (g/dl) | -1.08 | 1.63 | 0.51 | -4.31 | 2.15 | -0.05 |
| Gender | 0.91 | 1.57 | 0.563 | -2.20 | 4.02 | 0.04 |
| No. of teeth present | 0.34 | 0.06 | <0.001 | 0.23 | 0.45 | 0.47 |
| Highest CAL[¶] | 0.71 | 0.19 | <0.001 | 0.34 | 1.08 | 0.29 |
| Constant | 1.19 | 7.48 | 0.874 | -13.60 | 15.98 | |

[†]Number of teeth with periodontal disease progression during 4 years. $R^2$=0.2538, $p$<0.001

[‡]Confidence interval.

[§]Standardized coefficients.

[¶]Clinical attachment level.

# Longitudinal study on the relationship between serum albumin and periodontal disease

**Masanori Iwasaki[1*], Akihiro Yoshihara[1], Toshinobu Hirotomi[1], Hiroshi Ogawa[1], Nobuhiro Hanada[2], and Hideo 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, Chuo-Ku, Niigata, 951-8514, Japan

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

[*]To whom correspondence and reprint requests should be addressed:

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

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**Key words:** Serum albumin, Periodontal disease, Nutrition, Longitudinal study, Elderly

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Tables and figures: 4

References: 25

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## Abstract

**Aim:** The purpose of this study was to evaluate the relationship between periodontal disease and general health status in community-dwelling elderly using the serum albumin concentration as a criterion index of the severity of underlying disease and nutrition.

**Methods:** 600 subjects aged 70 years underwent a baseline examination. Dental examinations were carried out at baseline and once a year for 4 years. Periodontal conditions were estimated for subjects with at least one remaining tooth. Clinical attachment levels at six sites of all teeth present were measured. A change in loss of attachment of 3mm or greater in 1 year at each site was defined as periodontal disease progression. The serum level of albumin was measured by the bromcresol green albumin method. Data were analyzed in subjects for whom data were available for 4 years.

**Results:** Serum albumin concentration at baseline ranged from 3.4 to 5.0 g/dl with a mean of 4.3± 0.2. Using multiple regression analysis, we found that serum albumin concentration had a significant effect on periodontal disease progression (standardized regression coefficient = -0.10; $p$=0.032).

**Conclusions:** The findings of the present study suggest that serum albumin concentration is a significant risk predictor of periodontal disease progression.

**Clinical Relevance**

*Scientific rationale for the study:* Investigating the relationship between serum albumin and periodontal disease is important to understand the association between inflammation, nutrition and serum albumin level.

*Principal findings:* According to the results of multiple regression models, we observed an inverse independent relationship between serum albumin concentration and periodontal disease.

*Practical implications:* Serum albumin concentration is a significant risk predictor of periodontal disease progression, especially in the elderly who may be at higher risk of developing inflammatory conditions or disorders.

## Introduction

Serum albumin level is a practical marker of the general health status as it demonstrates the severity of an underlying disease and mortality in elderly (Shibata et al. 1991). Several studies have demonstrated that serum albumin concentrations are associated with general health status among the elderly (Corti et al. 1994; Baumgartner et al. 1996). Moreover, malnutrition also may be monitored by means of serum albumin concentration (Don & Kaysen 2004). Serum albumin is the main protein synthesized by the liver.

Inflammation and malnutrition both reduce albumin concentration by decreasing its rate of synthesis. Chronic diseases are associated with inflammation and the release of inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor α, which cause a decrease in serum albumin (Schalk et al. 2004). Albumin concentration is associated with nutrition and inflammation (Kaysen et al. 2002).

On the other hand, periodontitis is defined as an inflammatory condition of the gingival tissues, characterized by loss of attachment of the periodontal ligament and the bony support of the tooth (Genco 1990). Moreover, periodontitis has been implicated as a risk factor for systemic diseases such as cardiovascular diseases and diabetes mellitus (D'Aiuto et al. 2004; Taylor 2001). In periodontal diseases, bacteria trigger inflammatory host responses which cause destruction of the alveolar bone

and periodontal connective tissue. The individual characteristics that diminish the efficiency of host response may include systemic factors such as malnutrition, which consistently impairs the innate and adaptive defenses of the host, including phagocytic function, cell-mediated immunity, complement system, secretory antibody, and cytokine production and function. Therefore, malnutrition can intensify the severity of periodontal diseases and may lead to their evolution into life-threatening diseases (Enwonwu et al. 2002).

Consequently, it is very important to study the association between periodontal disease and serum albumin levels, which reflect the general health status, in the elderly, who may be at higher risk of developing inflammatory conditions or disorders. However, few studies have demonstrated an important relationship between serum albumin concentration and periodontal diseases. Therefore, we adopted the serum albumin concentration as a criterion, which indicates the general health condition, including nutrition status, and designed this longitudinal study on the relationship between serum albumin and periodontal diseases.

## Materials and methods

### Subjects

Initially, 4542 (2099 men and 2443 women) Niigata citizens, 70 years old,

were sent a written request to participate in the survey and were informed of the purpose of this survey. After two requests, 81.4% (3695) responded positively to participate in the survey. Considering the availability of resources, examination appointments could be arranged for 600 individuals. The final study sample was randomly recruited from several areas of Niigata in order to have an approximately equal number of men (306) and women (294). All subjects agreed and signed informed consent forms regarding the protocol, which was reviewed and approved by the Ethics Committee of the Faculty of Dentistry, Niigata University.

None of the subjects was hospitalized or institutionalized. They did not require special care for their daily activities, and had high scores of reliability and validity in a multidimensional 13-item index of competence (TMIG index of competence) (Koyano et al. 1991). The mean score of the TMIG-index subscales of the subjects was 11.9± 1.4. The subjects were recalled and re-examined once a year from 1998 to 2002.

**Measurements**

Dental examinations were carried out at baseline and once a year for 4 years (1998-2002), that is, 5 times in 4 years. The periodontal conditions were estimated for subjects with at least one remaining tooth.

Four dentists carried out intra-oral examinations under sufficient illumination using artificial light. The periodontal condition, measured as

the clinical attachment level (CAL), was recorded using mouth mirrors and a specially designed pressure-sensitive Vivacare, TPS Probe® (Vivacare, Schaan, Liechtenstein). Teeth were probed at six sites per tooth for all teeth present, and the measurements were recorded approximately to the nearest whole millimeter.

The examiners were calibrated both before and during the survey using 18 volunteer patients in the University Hospital. As determined by replicate examinations of the attachment level, each percent agreement (± 1mm) ranged from 70.0% to 100% among 4 examiners. The kappa values ranged from 0.62 to 1.00.

In the longitudinal study, a change in the loss of attchment of 3mm or greater in 1 year at each site was counted as a periodontal disease event (Brown et al. 1994). Teeth with one disease event were excluded form additional-year assessments. Finally, the numbers of teeth with events over 4 years per person were calculated.

An interview was conducted to obtain information regarding gender and smoking habit. Anthropometric evaluation included measurements of weight and height to calculate body mass index (BMI). In addition, biochemical values, such as total protein, calcium, and immunoglobulin G (IgG), were also evaluated, while the serum level of albumin was measured by the bromcresol green albumin (BCG) method.