Tokyo, Japan). The signal intensity of each cDNA was quantified with the use of NIH Image (Ver. 1.62), and normalized against that of glyceraldehyde-3-phosphate dehydrogenase (GAPDH).

Tissue distribution of mRNA for the target gene was analyzed by Northern hybridization with adult rat multiple-tissue RNA blots in triplicate (Cat. 7764-1; Clontech, Palo Alto, CA, USA). The [α-^{32}P] dCTP-labeled probe was prepared from a cDNA fragment displaying the greatest difference in mRNA expression between the wounded and healthy pulps. The blots were finally washed with 1 x SSC containing 0.1% SDS at 50°C for 30 min. The hybridization signals were visualized in the BioImaging Analyzer.

Library Screening, Rapid Amplification of cDNA Ends, and Structural Analysis

The probe for Northern analysis was used for the following hybridizations. Five x 10^5 plaques from a rat liver λ ZAP cDNA library (Cat. No. 937507; Stratagene, La Jolla, CA, USA) were screened. Positives were fully sequenced from both 5′ and 3′ ends.

To obtain a full-length cDNA, we performed rapid amplification of cDNA ends (RACE) using a rat liver Marathon-Ready cDNA kit (Cat. 7471-1; Clontech) according to the manufacturer's instructions. Gene-specific primers (GSPs) were designed as described previously (Chenchik *et al.*, 1996). The GSPs and arbitrary primers (APs) are shown in the Appendix. PCR products were cloned into pT7 Blue T-Vector (Novagen, Madison, WI, USA), and sequenced.

The deduced amino acid sequence for the full-length cDNA was analyzed by the SMART program (http://smart.embl-heidelberg.de/), MOTIF (http://motif.genome.jp/), and PROSITE SCAN (http://npsa-pbil.ibcp.fr/cgi-bin/npsa_automat.pl?page=%20/NPSA/npsa%20_proscan.html).

Semi-quantitative Analysis of mRNA

The mRNA accumulation in the wounded and healthy pulps was examined by reverse transcription (RT)-PCR. The PCR mixture (50 μL) contained specific primers designed for the genes isolated as described above or for rat *β-actin*. An independent amplification was performed in duplicate at 36, 38, and 40 cycles. The cDNA (1 ng) prepared from the wounded or healthy pulp was added to all PCR mixtures. After the PCR product (5 μL) underwent electrophoresis on a 2% gel, the intensity of the signal was quantified with NIH Image and normalized against that of *β-actin*.

Tissue Preparation and *in situ* Hybridization

The procedures of tissue preparation and *in situ* hybridization are described in detail in the Appendix. Face and oral cavity tissues were taken from neonatal Wistar rats under deep anesthesia, fixed with 4% paraformaldehyde, and serial sections were made.

In situ hybridization was performed according to a method described previously (Myokai *et al.*, 2004). In brief, the neonatal rat tissue sections and rat embryo sections (Cat. 69159-4; Novagen) were pre-treated and hybridized with either anti-sense or sense riboprobe. The hybridization signal was detected by autoradiography. The plasmids containing the coding region of the target gene were linearized, and they were used as templates to synthesize either anti-sense or sense riboprobes. The riboprobes were prepared with the use of T7 or SP6 polymerases with [α-^{35}S] UTP, and the unincorporated labeled nucleotides were removed.

RESULTS

Histology of Pulp Tissues and Clones Isolated

Neither reparative dentin formation nor apparent disruption of the odontoblast layer was seen 1 wk after the cavity was prepared (Fig. 1A). An inflammatory cell infiltrate, such as neutrophils or lymphocytes, was not observed in relation to the cavity position.

Both WIN and WSP cDNAs were amplified by PCR, and displayed on a gel (Fig. 1C). Forty WIN clones and 30 WSP clones were isolated, and then 23 clones containing cDNA fragments longer than 250 bp were sequenced. They were identified as 13 individual sequence types containing 2 unknown and 6 known genes, and 5 expressed sequence tags (ESTs) (Table).

Table. Clones Isolated by Subtractive Hybridization.

Nomenclature[a]	Length[b]	Identity[c]	Accession[d]	Similarity[e]
WIN-1, 3, 4, 9, 12, 14, 15, 16	357	Cytochrome c	X12553	99% (356/357)
WIN-2	260	EST 9088437	BI285481	100% (260/260)
WIN-5	384	Mitochondrial genome	X14848	98% (381/384)
WIN-6	317	EST 2620273	AI712920	99% (315/317)
WIN-7, 8, 10	278	EST 217162	AI171208	99% (277/278)
WIN-11	350	EST 2708823	AI763748	99% (349/350)
WIN-13	212	Cathepsin B	X82396	97% (207/212)
WSP-1	310	EST 6873738	BF412896	100% (310/310)
WSP-2	441	Unknown 1		NS[f]
WSP-3, 5	362, 353	Ribosomal protein	X53378	99% (361/362), 98% (346/353)
WSP-4	327	Rat cDNNA clone similar to mouse Laminin γ2 chain	AA925420	99% (326/327)
WSP-6	359	Pro-alpha 2 collagen I	AF121217	99% (357/359)
WSP-7	378	Unknown 2		NS[f]

[a] Name of clones examined.
[b] Insert length (base pairs) determined by sequencing.
[c] Gene or DNA sequence similar to each clone with the highest scores.
[d] GenBank accession number of the gene identified.
[e] Percentage of similarity and number of matched sequences with the known gene.
[f] No significant homology (NS, less than 30%) was found in the databases.

Messenger RNA Accumulation of Genes Identified

Reverse Northern hybridization was used to detect 9 kinds of mRNA among 13 kinds of genes in wounded and healthy pulp tissues (Fig. 1D), while little or no signal was detected in the other genes (data not shown). WIN-11 and WSP-6 differed in mRNA expression between the wounded and healthy pulp tissues, with WIN-11 displaying the greatest difference. WIN-11 was expressed in

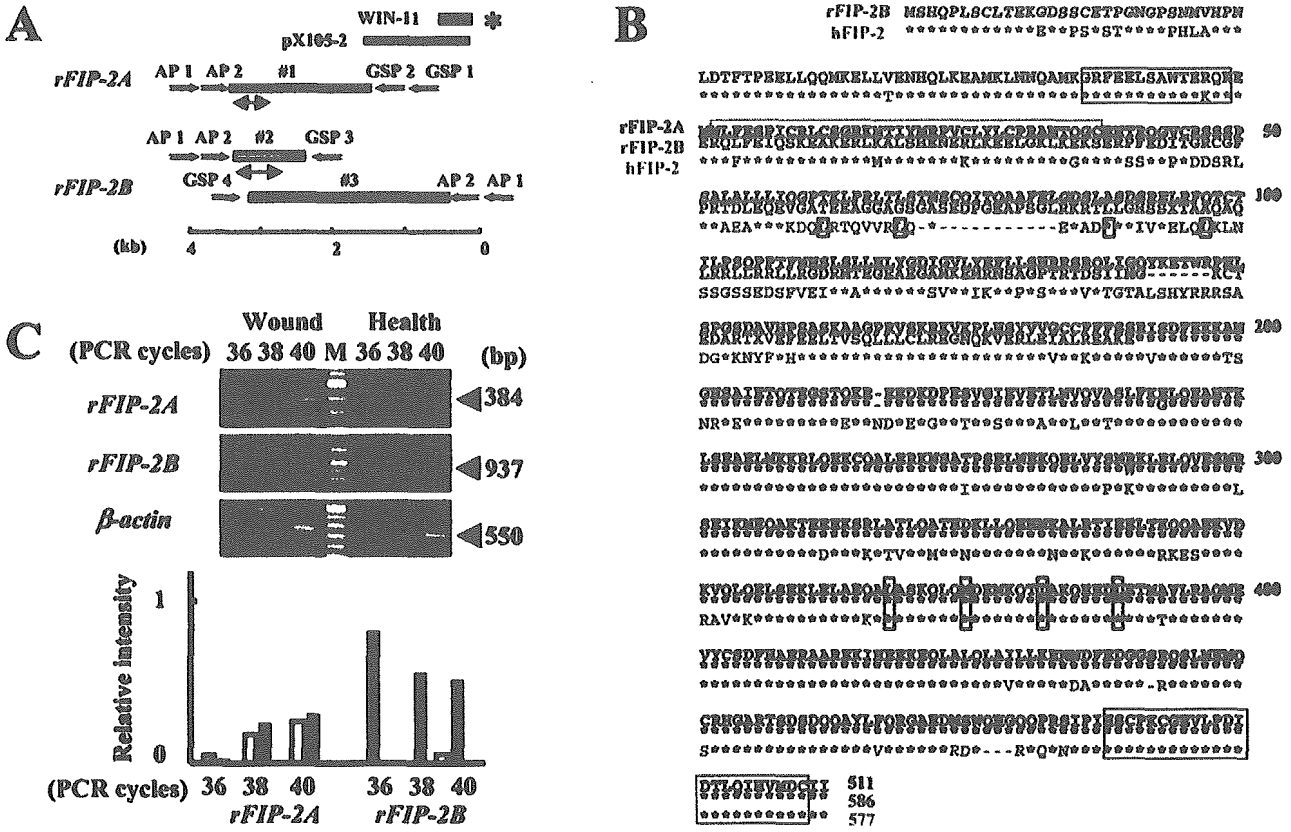

Figure 2. Identification and structure of 2 *FIP*-2s and their expression. **(A)** Clones obtained by cDNA library screening and RACE studies. WIN-11 (0.35 kb), pX105-2 (1.8 kb), and clone #1 (2.2 kb) significantly overlapped; therefore, they have been submitted to DDJB and assigned accession no. AB050777. Clones #2 (0.9 kb) and #3 (3.0 kb) were completely overlapped; therefore, they have been submitted to DDJB and assigned accession no. AB069907. *WIN-11 displaying the greatest difference in mRNA expression between the wounded and healthy pulp tissues by reverse Northern analysis; ▬, common region in *rFIP-2A* and *rFIP-2B*; ▭, region of *rFIP-2B* different from that of *rFIP-2A*. ↔, cDNA containing the specific region for *rFIP-2A* or *rFIP-2B* was cloned and used as a template for riboprobes of *in situ* hybridization. The procedure is described in detail in the Appendix. **(B)** Structure of *rFIP-2s*. Deduced amino acid sequences of rFIP-2s and hFIP-2 are shown. The signal peptide domain is boxed in green, the putative leucine-zipper domains are boxed in black, and the zinc-finger domain is boxed in blue. The putative bZIP motif is boxed in red. *Same amino acid as the sequence above; –, missing amino acid. **(C)** Expression of *rFIP-2* mRNA. Complementary DNA was amplified by PCR with the primers as described below. The PCR products for *rFIP-2A*, *B*, and *β-actin* underwent electrophoresis on a gel. The specific primers were designed: *rFIP-2A* sense, 5′-TGCCCAGCCAGCCTCCTACC-3′; *rFIP-2B* sense, 5′-ATCTCTGTGGCCGGACCTGTTACC-3′; and *rFIP-2A* and *rFIP-2B* antisense, 5′-CCACTTCGATTCCCACACTC-3′. For an internal control, specific primers for rat *β-actin* were designed: sense, 5′-TTGTAACCAACTGGGACGATATGG-3′; and antisense, 5′-GATCTTGATCTTCATGGTGCTAGG-3′. Two independent PCRs were performed, and typical results are shown. Lane M, 100-bp DNA ladder. Relative signal intensity (each mRNA from/*β-actin* mRNA) is shown in the lower panel. ▭, healthy pulp; ▬, wounded pulp.

almost all of the tissues tested, and was expressed strongly in the heart, brain, and liver (Fig. 1E).

Genes Isolated by cDNA Library Screening and RACE

We isolated the pX105-2 by screening the cDNA library using the WIN-11 probe (Fig. 2A). Clone #1 was obtained by RACE with AP 1, AP 2, GSP 1, and GSP 2. Nucleotide sequences of WIN-11, pX105-2, and the clone overlapped significantly. Additional RACE with AP 1, AP 2, and either GSP 3 or GSP 4 gave 2 clones (#2 and #3), and clones overlapped. The results indicated that 2 genes were isolated; however, they shared the same nucleotide sequence in the 3′ region. Moreover, both rat genes had significant homology with human 14.7K-interacting protein (hFIP)-2, and contained a common zinc-finger domain (Fig. 2B). However, *hFIP-2* has 2 putative leucine-zipper domains, while the 2 rat genes had 1, and rat *(r)FIP-2A* was missing a putative basic-leucine zipper motif, whereas both *rFIP-2B* and *hFIP-2* were not.

Messenger RNA Expression of *rFIP-2s*

The RT-PCR analysis with different numbers of cycles allowed for the quantification of the target mRNA in the pulp (Fig. 2C). Up-regulation of mRNA expression by wounding was detected only for *rFIP-2B*, although mRNA for both *FIP-2A* and *B* was detected in the wounded and healthy pulp tissues.

Expression of *rFIP-2s* in the Rat Embryo

The *rFIP-2A* and *B* mRNAs were detected in condensing mesenchymal cells of the palatal process and surrounding Meckel's cartilage during rat embryogenesis, whereas they were absent in the intramembranous chondrogenic cells (Fig. 3B). However, no or very weak mRNA expression for *rFIP-2A* and *B* was found in the tooth germ at cap and early crown stages (Fig. 4, in the Appendix).

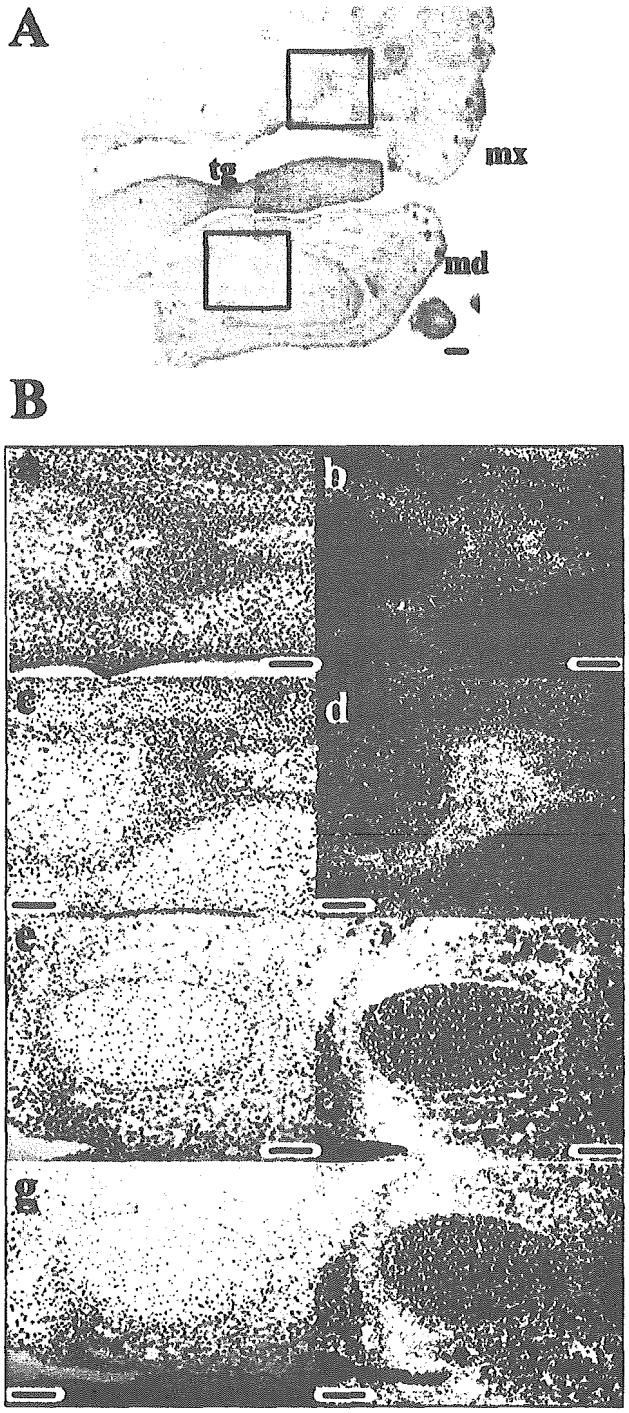

Figure 3. Expression of the 2 *rFIP-2s* during rat embryogenesis. **(A)** Histology of the rat embryo at 17 days. Hematoxylin and eosin staining was performed on the sagittal section from the rat embryo. Bar equals 200 μm. mx, maxilla; md, mandible; tg, tongue. **(B)** *In situ* hybridization in rat embryo at 17 days. Using *rFIP-2A* or *B* anti-sense riboprobe, we observed strong signals for the *rFIP-2A* and *B* mRNA in condensing mesenchymal cells of the palatal process (a,b,c,d) and surrounding Meckel's cartilage (e,f,g,h), while they are absent in the neighboring chondrogenic cells (a to h). The results are shown as bright- (a,c,e,g) and dark-field (b,d,f,h) views. The hybridization signals of *rFIP-2A* (a,b,e,f) and *rFIP-2B* (c,d,g,h) were detected by autoradiography at 1 wk, and similar results were obtained after three-week exposure (data not shown). No significant signal was detected on any sections in the case of sense riboprobe for *rFIP-2A* or *B* (data not shown). Bar equals 50 μm.

DISCUSSION

Sixteen WIN and 7 WSP cDNAs were isolated from wounded pulp tissues, and were identified as 13 individual sequence types containing 6 known and 2 unknown cDNAs, and 5 ESTs (Table). Of the 16 WIN cDNAs, 8 were identified as cytochrome *c*, which is the terminal enzyme of the mitochondrial respiratory chain and regulates both electron transfer and energy transduction. The frequent isolation of cytochrome *c* may reflect a marked response to the wound in pulpal cells. Cathepsin B (catB), a lysosomal cysteine protease, has recently been implicated in apoptosis. The role of catB in the TNF-α-triggered apoptotic cascade has been examined in hepatocytes from $catB^{-/-}$ and $catB^{+/+}$ mice, and apoptosis has been shown to be diminished in the $catB^{-/-}$ cells, suggesting that TNF-α-induced apoptosis was dependent, in part, upon catB activity (Guicciardi *et al.*, 2000). Therefore, catB isolated here may be involved in TNF-α-induced apoptosis in pulpal cells after cavity preparation. Of the 7 WSP cDNAs, 4 were identified as known cDNAs: laminin γ2, type I collagen, and 2 ribosomal proteins. At the cap stage of tooth development in mice, strong staining for the laminin γ2 chain has been shown in the basement membrane in contact with enamel knot cells (Kieffer-Combeau *et al.*, 2001). However, no significant signal for the laminin γ2 chain was detected in either wounded or healthy pulp tissues by reverse Northern hybridization (data not shown). Therefore, the expression of laminin γ2 may be low-level or limited locally in adult rat pulp tissues. Type I collagen distributes in skin, bone, gingiva, periodontal ligament, cementum, and most connective tissues, and is abundant in pulpal cells and odontoblasts in erupted teeth (Garcia *et al.*, 2003). Interestingly, WSP-6 (pro-α 2 collagen I) showed increased expression in the wounded pulp tissues (Fig. 1D). Since type I collagen is composed of 2 α1 chains and 1 α2 chain, increased expression of pro-α-2 collagen I may have an influence on type I collagen synthesis in the wounded pulp. There is no report of the involvement of ribosomal protein in the apoptosis of cells or in dentinogenesis. In spite of the elimination of genomic DNA with our procedure, WIN-5 had high homology with the mitochondrial genome. The extensive amplification of the subtracted cDNA by PCR may account for the detection of trace amounts of small genomic DNA fragments.

The relationships between genes from different genomes are naturally represented as a system of homologous families that include both orthologs and paralogs. Orthologs are proteins from different species that evolved by vertical descent, and typically retain the same function as the original. In contrast, paralogs are proteins from within a given species that are derived from gene duplication, and new functions may evolve that are related to the original (http://www.ncbi.nlm.nih.gov/Education/BLASTinfo/Orthology.html). Here, 2 *rFIP-2*s were identified: *rFIP-2B* was structurally homologous to *hFIP-2*; however, *rFIP-2A* in the 5′ region had no significant similarity with known genes, while *rFIP-2A* in the C terminus was homologous to *hFIP-2* (Fig. 2B). The findings imply that *rFIP-2B* is orthologous to *hFIP-2*, while *rFIP-2A* is paralogous to *rFIP-2B*.

FIP-2 was originally identified as a novel human tumor necrosis factor α-inducible cellular protein interacting with an adenovirus 14.7-kDa protein, and it is involved in the complex regulation of apoptosis; however, by itself it did not cause cell death (Li *et al.*, 1998). Hattula and Peränen (2000) have reported that the amino-terminal region of *FIP-2* interacts with

the activated form of Rab8, while the carboxy-terminal region of *FIP-2* binds to Huntingtin. Moreover, co-expressed *FIP-2* and Huntingtin enhance the recruitment of Huntingtin to Rab8-positive vesicular structures, and, similarly, *FIP-2* promotes cell polarization to Rab8, suggesting that *FIP-2*, together with Huntingtin and Rab8, is part of a protein network that regulates membrane trafficking and cellular morphogenesis (Hattula and Peränen, 2000). Sahlender *et al.* (2005) reported the role of FIP-2 in Golgi ribbon formation and exocytosis after our latest revision. In this study, *in situ* hybridization analysis revealed that *rFIP-2A* and *B* were expressed strongly in condensing mesenchymal cells of the palatal process and surrounding Meckel's cartilage, but not in the intramembranous chondrogenic cells (Fig. 3B). Moreover, the expression of *rFIP-2B* was up-regulated, although both *rFIP-2A* and *B* were expressed in the wounded pulp tissues (Fig. 2C). These findings suggest that up-regulated *rFIP-2B* expression plays a role in regulating the membrane trafficking or cellular morphogenesis of these embryonic mesenchymal cells and the wounded pulpal cells.

The dentin-pulp complex shows a broad spectrum of responses to caries, which represents a summation of injury, defense, and repair events. The complex interplay among these events will be important in determining the fate of the dentin-pulp complex (Smith, 2002). In this study, the cavities were left exposed to the oral environment; however, no apparent reparative dentin formation was observed in relation to the cavity position (Fig. 1A). In general, reparative dentinogenesis occurs following pulp damage, similar to our experimental pulp wound (Sveen and Hawes, 1968; Taylor and Byers, 1990; Kitamura *et al.*, 2001). It is currently unknown why no apparent reparative dentin formation occurred in our model. However, the high level of *rFIP-2B* expression may be involved in differentiation or proliferation of the wounded pulpal cells, because it expressed strongly in the condensing mesenchymal cells during palatal and mandibular development (Fig. 3B).

In conclusion, *rFIP-2A* and *B* were identified, following reciprocal subtraction, both being structurally homologous to *hFIP-2*, regulating membrane trafficking and cellular morphogenesis. The *rFIP-2B* mRNA was up-regulated in the wounded pulp and expressed strongly in condensing mesenchymal cells of the palatal process and surrounding Meckel's cartilage during rat embryogenesis. These results suggest that up-regulated *rFIP-2B* expression plays a role in regulating the membrane trafficking or cellular morphogenesis of these embryonic mesenchymal cells and wounded pulpal cells.

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A Proposed Model Linking Inflammation to Obesity, Diabetes, and Periodontal Infections

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Background: Obesity is an important risk factor for diabetes, cardiovascular disease, and periodontal disease. Adipocytes appear to secrete proinflammatory cytokines which may be the molecules linking the pathogenesis of these diseases. We evaluated the relationship between obesity, periodontal disease, and diabetes mellitus insulin resistance as well as the plasma levels of tumor necrosis factor alpha (TNFα) and its soluble receptors (sTNFα) to assess the relationship of inflammation to obesity, diabetes, and periodontal infections.

Methods: The relationship between periodontal disease, obesity, and insulin resistance was examined in the Third National Health and Nutrition Examination Survey (NHANES III). In a population of 12,367 non-diabetic subjects, the variable body mass index (BMI) was used as an assessment of obesity and periodontal disease was assessed by mean clinical attachment loss. The plasma levels of TNFα and sTNFα were assessed in subsets of 1,221 adults from Erie County, New York, who represented the highest and lowest quartile of BMI. These subjects had extensive periodontal and medical evaluations.

Results: In the NHANES III portion of the study, BMI was positively related to severity of periodontal attachment loss ($P<0.001$). Weighted multiple logistic regressions showed that this relationship is likely mediated by insulin resistance, since overweight individuals (with BMI ≥27 kg/m^2) with high levels of insulin resistance (IR) exhibited an odds ratio of 1.48 (95% confidence interval 1.13 - 1.93) for severe periodontal disease as compared to overweight subjects with low IR. In the Erie County adult population, the highest levels of TNFα and sTNFα receptors were found in those individuals in the highest quartile of BMI. A positive correlation of TNFα levels with periodontal disease was found only in those in the lowest quartile of BMI.

Conclusions: Obesity is a significant predictor of periodontal disease and insulin resistance appears to mediate this relationship. Furthermore, obesity is associated with high plasma levels of TNFα and its soluble receptors, which in turn may lead to a hyperinflammatory state increasing the risk for periodontal disease and also accounting in part for insulin resistance. Further studies of the molecular basis of insulin resistance and its relationship to diabetes, periodontal disease, and obesity are necessary to fully test the hypothesis that adipocyte production of proinflammatory cytokines is a pathogenic factor linking obesity to diabetes and periodontal infections. *J Periodontol 2005;76:2075-2084.*

KEY WORDS

Diabetes; insulin resistance; obesity; periodontal disease; soluble tumor necrosis factor receptor; TNF-alpha.

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Obesity, one of the most significant health risks of modern society, is now recognized as a chronic disease with a multifactorial etiology. The incidence of obesity and elevated body mass index (BMI) has dramatically increased in the Western world.[1] Although the fundamental mechanisms underlying this increase in obesity are not well understood, it has become clear that genetic and environmental factors and socioeconomic and behavioral influences leading to excess caloric intake, decreased physical activity, and metabolic and endocrine abnormalities are likely important factors. Obesity is associated with increased morbidity and mortality[2,3] and is either an independent or aggravating factor for a number of diseases such as hypertension, coronary heart disease (CHD), osteoarthritis, and type 2 diabetes mellitus.[4] In addition, there is a strong association between obesity and mortality. In the United States (U.S.), deaths attributable to obesity constitute a significant cause of mortality, second only to smoking.[5] The prevalence of obesity is increasing at alarming rates, both in the U.S. and worldwide, reaching epidemic proportions, particularly among children and adolescents.[6] This global epidemic places more of the population at risk for concomitant diseases.

Obesity is a major contributor to the development of type 2 diabetes mellitus,[4] and the prevalence of diabetes mellitus in the U.S. is also increasing at an alarming rate. The number of diagnosed cases of diabetes has increased 30% in less than 10 years, earning the unfortunate distinction of likely becoming the next lifestyle-disease epidemic affecting this population.

Periodontal disease is a complication of diabetes mellitus.[7] The presence of periodontal disease in a diabetic individual is a serious health hazard, for once the disease is established, the chronic nature of this infection contributes to worsening diabetic status leading to more severe diabetes-related complications.[8,9] Conversely, treatment of periodontal infection results in improvement of diabetes metabolic control and a decrease in diabetes treatment requirements.[10]

An association has been reported between obesity and periodontal disease in a cohort of 241 otherwise healthy Japanese subjects.[11] A national survey of older people in Great Britain showed that those with more than 20 teeth are more likely to have a normal BMI, and those with less than 20 natural teeth were, on average, three times more likely to be obese.[12] An analysis of the Third National Health and Nutrition Examination Survey (NHANES III) showed that waist to hip ratio, BMI, fat-free mass, and log sum of subcutaneous fat had significant correlations with periodontal disease, suggesting that abnormal fat metabolism may be an important factor in the pathogenesis of periodontal disease.[13] BMI and periodontal disease were associated in adults, and high waist circumference was associated with periodontal disease in 18- to 34-year-olds.[14] None of the above studies address the nature of the association of obesity and periodontitis, or the relationship of obesity to insulin resistance, a key feature of type 2 diabetes mellitus.

The relationship between obesity and proinflammatory cytokines has been extensively studied. For example, Vendrell et al.[15] found elevations of soluble tumor necrosis factor receptor 1 and 2 (sTNF-αRI and sTNF-αRII) in obese patients. It has been proposed that adipocytes produce several proinflammatory cytokines including TNF, leptin, and interleukin-1, leading to a proinflammatory state associated with obesity.[16] Evaluation of proinflammatory cytokines also occurs in chronic infections. For example, Nishimura and coworkers showed that serum TNF-α concentrations were elevated in periodontitis patients as compared to periodontally healthy subjects. Those periodontal patients with elevated TNF-α concentrations had reduced levels after periodontal therapy.[17,18]

The purpose of the present study was to examine the relationship between obesity and periodontal disease, and to evaluate to what extent insulin resistance and associated systemic TNF-α levels and sTNF-α receptors may account for this relationship.

MATERIALS AND METHODS

Data and Study Sample

Data from the Third National Health and Nutrition Examination Survey (NHANES III) were used for a portion of this study.[19] NHANES III was conducted from 1988 to 1994 using a multistage stratified sampling design. Detailed information on sample design, operation of NHANES III, blood specimen collection, and laboratory procedures utilized to analyze blood samples has been described.[20] Blood specimens were collected and immediately stored under appropriate conditions until they were shipped to analytical laboratories for testing. Fasting insulin was measured by radioimmunoassay, and fasting glucose was assessed using a chemistry system.‖ Serum cholesterol was also measured.¶ Serum triglycerides were measured enzymatically after hydrolization to glycerol using the same analyzer. Glycated hemoglobin was measured by ion-exchange high-performance liquid chromatography.# C-reactive protein (CRP) was measured using latex-enhanced nephelometry.

Height was measured with a stadiometer to the nearest 0.1 cm. Weight was measured with a Toledo

‖ Cobas Mira Chemistry System, Roche Diagnostic Systems, Montclair, NJ.
¶ Hitachi 704 Analyzer, Boehringer Mannheim Diagnostics, Indianapolis, IN.
# DIAMAT Glycated Hemoglobin Analyzer System, BioRad Laboratories, Hercules, CA.

self-zeroing weight scale and recorded to the nearest 0.01 kg. From these two measurements, the body mass index (weight in kilograms divided by height in meters squared) was calculated.

Periodontal assessments included measurements of gingival bleeding, calculus, probing depth, and attachment level carried out at two sites (buccal and mesio-buccal) of two randomly selected quadrants, one upper and one lower. Individual subject mean attachment levels (AL) were calculated in millimeters. We utilized mean AL ≥1.5 mm to define a case of periodontal disease. This case definition has been utilized previously to analyze data from NHANES III to determine the risk for periodontal disease associated with serum levels of specific nutrients and inflammatory mediators.[21,22]

Demographic variables included gender, race, and ethnicity (non-Hispanic white, non-Hispanic black, Mexican, and other), number of years of education completed, and age at examination. Smoking status was categorized as never, former, or current cigarette smoker. For former and current smokers, overall exposure to tobacco was calculated as packyears; i.e., number of cigarettes smoked per day × number of years smoked.

The analyses were carried out on participants of both genders aged 20 to 90 years, with no clinical diagnosis of diabetes mellitus. Specifically, participants responding that they had previously been told by a physician that they had diabetes, or who had fasting blood glucose levels of >126 mg/dl were considered to have previously diagnosed diabetes and were excluded from this analysis. In order to improve the reliability of periodontal assessment, individuals included in this analysis were required to have at least six natural teeth.

Statistical Analysis of the NHANES III Data

Descriptive statistics including means, standard deviations, and percentages were used to summarize the demographic variables and health-related behaviors of the study sample. An index of insulin resistance (IR) was constructed from the product of fasting insulin × fasting glucose. The sample was stratified by BMI into overweight and non-overweight (BMI ≥27 and <27 kg/m^2) and in quartiles of insulin resistance. Mean values of total cholesterol, triglycerides, C-reactive protein, glucose, insulin, and glycated hemoglobin (HbA_{1c}) were calculated for all quartiles of insulin resistance. Comparisons were made for all dependent variables and quartiles of IR, with the lowest quartile of IR as the reference group.

Multiple logistic regression analyses were used to examine the association between obesity and periodontal disease. Age, gender, education, race and ethnicity, and smoking were utilized as covariates and as such were adjusted for in the final model. To obtain estimates representative of the entire U.S. sampling frame, weighting of the sample data was done.[23] Analyses were performed using a statistical software program incorporating the sampling weights.**

Plasma Levels of TNF-α, sTNF-αRI, and sTNF-αRII

A subset of the University at Buffalo myocardial infarction in periodontal disease case control study[24] was used. In this study, 1,221 adult controls with no history of myocardial infarction were assessed by extensive periodontal and medical examinations as well as laboratory studies. A subset of individuals (305 subjects) in the highest quartile of BMI, (≥30.8 kg/m^2) was selected. Of these, 41 had periodontal disease as evidenced by having two or more teeth with attachment loss ≥6 mm and one or more teeth with probing depth ≥5 mm. Two hundred sixty-four (264) were identified in the highest BMI quartile as having little or no periodontal disease. In the lowest quartile for BMI (<24.6 kg/m^2), 305 subjects were assessed. Of these, 35 (11.5%) had periodontal disease based on the same criteria, while 270 subjects had little or no periodontal disease.

Test subjects selected from the highest quartile of BMI included the 41 with periodontal disease, and 50 randomly selected from the 264 with little or no periodontal disease. From the lowest quartile of BMI, the 35 with periodontal disease and 50 randomly selected from the 270 with little or no periodontal disease were selected. This resulted in four groups for analysis of systemic cytokines: A: high BMI with periodontal disease (41); B: high BMI with little or no periodontal disease (50); C: low BMI with periodontal disease (35); and low BMI with little or no periodontal disease (50).

Samples Analyzed

Ethylenediamine tetracetic acid (EDTA) plasma was frozen at -86°F. Samples were coded and kept frozen until assay. About 5% of the samples were analyzed in duplicate as a quality control. Assessment of TNF-α and soluble TNF receptor levels was carried out as described by Nishimura and coworkers.[17]

Statistical analyses of TNF-α and sTNF-α receptors were carried out using analysis of variance (ANOVA), with *P* values expressed as the result of a *t* test. The correlation coefficients were calculated to measure the linear relationship of clinical attachment loss to plasma levels of TNF-α and sTNF-α receptors.

RESULTS

A total of 12,367 non-diabetic individuals 20 to 90 years old participated in the dental section of the NHANES III study. Of these 53.1% were men and 46.9% women; 38.7% were whites, 27.7% were

** Westvar PC, Version 2.1, WESTAT, Inc., Rockville, MD.

blacks, 29.4% were Mexican Americans, and 4.2% were of other racial and ethnic groups; and 43.1% were overweight (BMI ≥27 kg/m^2) (Table 1). Overweight individuals were slightly older, less educated, and had a lower income compared to non-overweight individuals. A greater proportion of females, non-Hispanic blacks, and Mexican Americans were overweight compared to those non-overweight. A greater level of attachment loss (P<0.01) and more periodontal disease (P <0.05) were seen in the overweight group (Table 1).

The distribution of the sample by quartiles of IR is shown in Table 2. Increasing age was significantly associated with IR (P <0.05). Significantly greater (P<0.05) proportions of non-Hispanic blacks, Mexican Americans, and other racial groups were in the upper quartiles of IR compared to white Americans (Table 2). Likewise, significantly more individuals with less than 12 years of education, lower income levels, and smokers were in the highest quartile of IR compared to those in the lowest IR quartile (Table 2). There was no significant difference in gender distribution among those in different quartiles based on insulin resistance.

Table 2 also shows that the severity of periodontal attachment loss increased proportionally with increasing IR (P <0.05). Individuals in the highest IR quartile exhibited greater mean attachment loss compared to those in the lowest quartile. Following a similar trend, the number of teeth lost increased significantly (P <0.05) with increasing levels of IR. On average, individuals in the highest IR quartile had lost 1.1 more teeth compared to individuals in the lowest IR quartile (Table 2).

A significant (P<0.05) proportional increase in BMI was seen with increasing levels of IR (data not shown). Most individuals in the IR highest quartile can be considered obese, as they exhibited a mean BMI of 31.8 kg/m^2 (data not shown). Individuals in the highest quartile of IR had significantly elevated (P<0.05) levels of total cholesterol and triglycerides, mean 208.2 mg/dl and 187.2 mg/dl, respectively, compared to 193.2 mg/dl and 96.6 mg/dl in quartile 1 (Table 3). Fasting glucose levels in the highest IR group were significantly elevated (P<0.05) compared to the lowest quartile of IR (Table 3). Fasting levels of insulin were more than 4 times greater in the highest quartile compared to the lowest quartile (Table 3). Levels of glycated hemoglobin (HbA_{1c}) were also significantly elevated in the highest IR quartile group compared to the lowest, 5.5% versus 5.1% (Table 3). Table 3 also shows that C-reactive protein levels were higher in the two highest quartiles of IR as compared to the lowest quartiles.

Multivariate analyses revealed that BMI is positively and significantly related to severity of attachment loss (P<0.001; Fig. 1). A weighted multiple logistic regression showed that this

Table 1.

Demographics, Periodontal Status, Serum Glucose, and Lipid Parameters of Obese (BMI ≥ 27 kg/m^2) and Non-Obese (BMI < 27 kg/m^2) Individuals

Demographic	Overall	Body Mass Index <27 kg/m^2	Body Mass Index ≥27 kg/m^2
N	12,367	7,041	5,326
Prevalence (%)	NA	56.9	43.1
Age in years (mean ± SE)	43.5 ± 0.2	42.2 ± 0.2	45.2 ± 0.2
Periodontal disease (%)*	25.4	24.3	26.9
Attachment loss in mm (mean ± SE)†	1.1 ± 0.1	1.1 ± 0.1	1.2 ± 0.1
Gender (%)			
Female	46.9	51.7	55.0
Male	53.1	48.3	45.0
Race and ethnicity (%)*			
Non-Hispanic white	38.7	42.6	33.6
Non-Hispanic black	27.7	25.8	30.3
Mexican American	29.4	26.9	32.7
Other	4.2	4.7	3.4
Education (%)*			
<7 years	14.8	12.9	17.3
8 to 11 years	20.6	20.1	21.1
12 years	32.4	31.5	33.6
>12 years	32.2	35.5	28.0
Annual household income (%)*			
<US$30,000	61.7	60.8	63.0
≥US$30,000	38.3	39.2	37.0
Serum parameters (mean ± SE)			
Fasting glucose (mg/dl)*	93.3 ± 0.1	91.6 ± 0.1	95.4 ± 0.1
Serum insulin (pmol/l)*	67.3 ± 0.5	50.0 ± 0.4	90.2 ± 1.0
Hemoglobin A_{1c} (%)*	5.3 ± 0.1	5.2 ± 0.1	5.4 ± 0.1
White blood cell count*	7.2 ± 0.1	7.0 ± 0.1	7.4 ± 0.1
Cholesterol (mg/dl)*	202.1 ± 0.4	196.8 ± 0.5	209.0 ± 0.6
Triglyceride (mg/dl)*	135.1 ± 0.9	115.7 ± 1.0	160.6 ± 1.6
C-reactive protein (mg/dl)*	0.4 ± 0.1	0.4 ± 0.1	0.5 ± 0.1

* Statistically significant when comparing those overweight to those of normal weight (P<0.05).
† Statistically significant when comparing those overweight with those of normal weight (P<0.01).

Table 2.

Demographics, Periodontal Status, and Smoking History by Quartiles of Insulin Resistance

Characteristic	Insulin Resistance			
	Q1 (Lowest)	Q2	Q3	Q4
Age in years (mean ± SE)	40.7 ± 0.3	43.3 ± 0.3†	45.3 ± 0.3†	45.1 ± 0.3†
Prevalence of periodontal disease (%)	5.8	6.6	7.2	5.8
Attachment loss in mm (mean ± SE)	1.0 ± 0.1	1.1 ± 0.1	1.2 ± 0.1†	1.2 ± 0.1†
Remaining teeth (mean ± SE)	24.0 ± 0.1	23.7 ± 0.1†	22.8 ± 0.1†	22.9 ± 0.1†
Gender (%)				
Female	53.9	52.9	52.5	53.5
Male	46.1	47.1	47.5	46.5
Race and ethnicity (%)*				
Non-Hispanic white	45.3	43.2	35.6	28.0
Non-Hispanic black	25.2	26.4	28.0	31.9
Mexican American	26.1	26.1	32.2	35.1
Other	3.4	4.3	4.2	5.0
Education (%)*				
<7 years	11.7	12.4	16.5	20.5
8 to 11 years	18.8	19.7	21.2	23.3
12 years	31.3	32.8	33.4	31.8
>12 years	38.2	35.1	28.9	24.4
Annual household income (%)*				
<US$30,000	58.6	59.0	63.1	67.5
≥US$30,000	41.4	41.0	36.9	32.5
Smoking (packyear, mean ± SE)	7.0 ± 0.3	7.2 ± 0.3	8.2 ± 0.3†	8.2 ± 0.4†

* Significant association with insulin resistance (P <0.05, chi square).
† Significantly different from Q1 (P <0.05).

relationship is likely mediated by insulin resistance. In fact, overweight individuals with IR in the highest quartile exhibited an odds ratio (OR) of 1.48 (95% CI 1.13 -1.93) for severe attachment loss, whereas this association was not significant for subjects with high BMI and low IR. The significant association between BMI and periodontal disease remained unchanged after adjusting for age, gender, income, education, race and ethnicity, and smoking (Fig. 1). BMI was a significant predictor of periodontal disease independent of the effects of all of the above confounders, in addition to cholesterol, triglycerides, and C-reactive protein, OR 1.45 (95% CI 1.09 - 1.93) (Fig. 1).

Plasma, TNF-α, and sTNF-α Receptor Levels

Table 4 shows TNF-α, sTNF-αRI, and sTNF-αRII levels in plasma analyzed by age, gender, smoking status, BMI, and periodontal status. Age was related to TNF-α levels, with higher levels seen in individuals over 50 years of age (4.29 ± 0.16 pg/ml), compared to 3.47 ± 0.16 pg/ml in those under age 50 (P ≤0.05). There were no differences between males and females or between current smokers and never or former smokers in levels of TNF-α or sTNF-α receptors. There was, however, a highly statistically significant elevation of TNF-α and sTNF-α RI and RII in those individuals with BMI >30.8 kg/m^2 compared to those with BMI <24.6 kg/m^2.

With respect to periodontal status, although those with severe periodontal disease had a tendency to higher levels of especially TNF-α and sTNF-αR2, these failed to reach statistical significance (Table 4). Table 5 shows a further analysis of the correlation between TNF-α and soluble TNF-α receptor levels and clinical attachment level as a measure of severity of periodontal disease. As can be seen in Table 4, among those in the quartile with the lowest BMI, there was a modest, but statistically significant positive correlation of sTNF-αRI and sTNF-αRII levels and increasing attachment level.

DISCUSSION

Results from analysis of the national representative sample indicate that obesity is a significant predictor for periodontal disease independent of the effects of age, gender, race and ethnicity, and smoking. Furthermore, analysis of this national sample suggests that insulin resistance mediates the relationship between obesity and periodontal disease.

Obesity is likely an independent risk factor for hypertension, coronary heart disease, osteoarthritis, and, in particular, type 2 diabetes.[3] As BMI increases, so does the risk and prevalence of these co-morbidities.[25] BMI was the most important independent predictor of the risk of diabetes mellitus in the Nurses Health Study.[26] The risk of diabetes in women increased 5-fold for those with BMI of 25 kg/m^2, 28-fold for those of BMI of 30 kg/m^2, and 93-fold for those of BMI >35 kg/m^2 compared to women with BMI

Table 3.

Measures of Glucose Metabolism, Serum Lipids, and C-Reactive Protein by Quartiles of Insulin Resistance (mean ± SE)

	Insulin Resistance			
Measure	Q1	Q2	Q3	Q4
Fasting glucose (mg/dl)	87.2 ± 0.1	91.9 ± 0.1*	95.6 ± 0.2*	100.0 ± 0.2*
Serum insulin (pmol/l)	30.0 ± 0.1	46.4 ± 0.1*	68.7 ± 0.2*	142.1 ± 1.8*
Hemoglobin A_{1c} (%)	5.1 ± 0.1	5.2 ± 0.1*	5.3 ± 0.1*	5.5 ± 0.1*
Cholesterol (mg/dl)	193.2 ± 0.7	202.3 ± 0.7*	206.1 ± 0.7*	208.2 ± 0.9*
Triglyceride (mg/dl)	96.6 ± 1.0	121.6 ± 1.5*	147.5 ± 1.8*	187.2 ± 2.6*
C-reactive protein (mg/dl)	0.4 ± 0.1	0.4 ± 0.1	0.5 ± 0.1*	0.6 ± 0.1*

* Significantly different from Q1 (P <0.05).

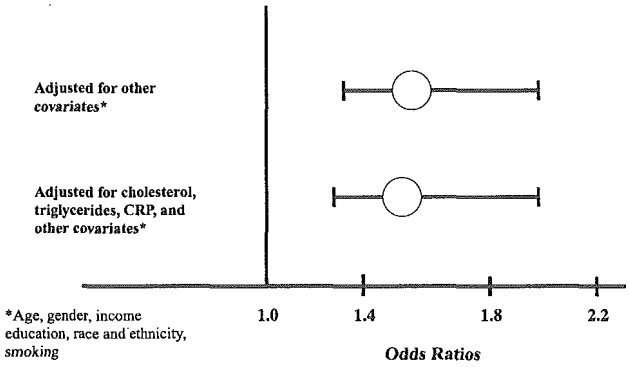

Figure 1.
Association of periodontal disease and BMI. Individuals with BMI ≥27 kg/m^2 and upper quartile of IR have increased risk for severe attachment loss, adjusted OR 1.48 (95% CI: 1.13 - 1.93), compared to those with BMI <27 kg/m^2. This increased risk did not vary after adjusting for additional covariates of cholesterol, triglycerides, and CRP: OR 1.45 (95% CI: 1.09 - 1.93).

of ≤21.[26] The distribution of fat tissue is also an independent predictor of diabetes mellitus. Abdominal obesity (waist circumference of >40 inches) increases the risk of diabetes 3.5-fold after controlling for BMI.[27] The risk of periodontitis increased 3-fold in Japanese individuals with BMI 25 to 29.9 kg/m^2 and 8.6 for those with BMI ≥ 30 kg/m^2 compared to those with BMI ≤ 20 kg/m^2 after adjustment for age, gender, oral hygiene status, and smoking history.[11] In a manner similar to the risk for diabetes mellitus, the increased risk for periodontal disease was especially significant in individuals with upper body obesity; i.e. high waist-hip ratios.[11]

A similar finding from a large survey was recently reported in which high waist circumference was associated with periodontal disease in 18- to 34-year-olds, but not in older adults.[14] Why an increase in periodontal disease was not seen in older individuals is unclear.

Obesity in general has been known to lower insulin sensitivity. In addition, distribution of body fat influences glucose metabolism through independent and additive mechanisms. Abdominal obesity is especially associated with an increase in the glucose and insulin response to an oral glucose challenge.[3] Upper body obesity is associated with a decrease in the uptake of insulin by the liver, increased hepatic gluconeogenesis, systemic dyslipidemia, and insulin resistance. Abdominal adipocytes contribute to increased release of free fatty acids (FFA), resulting in elevation of triglycerides.[28] Increased plasma FFAs lead to further increase in hepatic gluconeogenesis and increased peripheral insulin resistance with downregulation of insulin receptors. Links between dyslipidemia and periodontal disease have been proposed by investigators who propose that there is a link between elevated triglycerides and inflammatory heparin responsiveness which results in enhanced periodontal disease.[29-31]

Sustained compensatory hyperinsulinemia and insulin resistance further compounds the dyslipidemia associated with obesity, resulting in the classical abnormal lipid profile; i.e., elevated plasma fasting triglyceride, cholesterol, and low-density lipoprotein cholesterol.[32] Elevated FFA have also been shown to induce apoptosis of B-cells of the pancreas via *de novo* ceramide formation and increased nitric oxide production.[33]

Data from the Framingham study revealed that for every 10% increase in relative weight, there was an increase in plasma cholesterol of 12 mg/dl, an increase in systolic blood pressure of 6.5 mm/Hg, and an increase in fasting blood sugar of 2 mg/dl (reviewed in 34).[34] Our results support these results. Overweight individuals in our study (BMI > 27 kg/m^2) exhibited an increase in plasma cholesterol of 12.2 mg/dl, in triglycerides of 44.9 mg/dl, in fasting blood sugar of 3.8 mg/dl, in fasting serum insulin of 40.2 pmol/l, and in HbA1c of 0.4% compared to those non-overweight (Table 1). Our study also demonstrated an increase in cholesterol, triglycerides, measures of glucose metabolism, and C-reactive protein proportional to increasing quartiles of IR (Table 3). These findings provide additional evidence that both obesity and insulin resistance are

Table 4.

TNF-α, sTNF-αRI, and sTNF-αRII Plasma Levels

	Mean Concentration (pg/ml ± SE)			
Variable	N (168)	TNF-α (N = 168)	sTNF-αRI (N = 157)	sTNF-αRII (N = 168)
Age				
<50 years	49	3.47 ± 0.16*	1346.9 ± 79.3	2760.7 ± 126.3
>50 years	119	4.29 ± 0.16	1527.7 ± 57.7	3067.7 ± 121.2
Gender				
Male	70	4.22 ± 0.19	1568.4 ± 85.5	3141.9 ± 179.9
Female	98	3.93 ± 0.16	1404.9 ± 52.7	2859.8 ± 95.6
Smoking status				
Never/former	148	4.02 ± 0.13	1461.2 ± 49.9	2965.2 ± 104.2
Current	20	4.24 ± 0.28	1549.1 ± 147.1	3063.6 ± 164.0
BMI				
Low BMI (<24.6 kg/m^2)	84	3.76 ± 0.17*	1276.8 ± 43.0†	2771.9 ± 97.5*
High BMI (≥30.8 kg/m^2)	84	4.34 ± 0.17	1661.4 ± 77.6	3182.3 ± 157.3
Periodontal status				
Low periodontal disease (<2 teeth with ≥6 mm AL, and <1 tooth with ≥5 mm PD)	100	3.98 ± 0.17	1466.4 ± 56.8	2900.2 ± 101.5
High periodontal disease (≥2 teeth with ≥6 mm AL, and ≥1 tooth with ≥5 mm PD)	68	4.15 ± 0.18	1481.4 ± 81.5	3087.9 ± 175.8

* *P* value ≤0.05.
† *P* value ≤0.001.

Table 5.

Correlation of TNF-α, sTNF-αRI, and sTNF-αRII Levels and Attachment Levels

	Correlation Coefficient (*P* value)		
	TNF-α	sTNF-αRI	sTNF-αRII
Overall	0.096 (0.22)	0.061 (0.45)	0.103 (0.19)
Low BMI <24.6 kg/m^2	0.073 (0.51)	0.225* (0.05)	0.250* (0.02)
High BMI ≥30.8 kg/m^2	0.121 (0.27)	−0.025 (0.83)	0.009 (0.93)

* *P* ≤0.05.

associated with parameters of abnormal lipid and glucose metabolism.

It is important to note that as BMI and quartiles of IR increased, so did the severity of periodontal attachment loss. Our study supports the concept that insulin resistance appears to mediate the relationship between obesity and periodontal disease. Several experimental approaches support this epidemiological observation. For example, severe insulin resistance was experimentally induced in rat models following infusion with bacterial LPS.[35,36] TNF-α mediated insulin resistance may occur in infection-related increase in plasma TNF-α by suppressing insulin-induced tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1), thus blocking translocation of glucose transporting proteins (GLUT-4) and impairing insulin action.[37,38] Chronic upregulation of TNF-α in response to lipopolysaccharides from periodontal organisms in subgingival plaque[39] has been proposed as a contributing factor aggravating the state of insulin resistance.[8]

In the present study, a highly statistically significant elevation of plasma TNF-α levels as well as plasma levels of sTNF-αRI and RII were observed in those with the highest quartile of BMI compared to those in the lowest quartile. This is consistent with the elevated levels of TNF-α reported in individuals with abdominal obesity compared to those with peripheral obesity.[40] In addition, adipocytes from obese diabetic individuals with severe insulin resistance secreted high levels of TNF-α.[41] Elevated levels of serum TNF-α have been reported in obese non-diabetic individuals, which declined following weight loss.[42]

Although in our study the absolute levels of TNF-α and its soluble receptors were not statistically significantly elevated in those with severe periodontal

disease as compared to those with little periodontal disease in the whole population, there was a modest, but statistically significant, correlation of sTNF-αR levels with increasing severity of periodontal disease only in the low BMI group. These results suggest that the effect of periodontal infection in increasing sTNF-α receptors is possibly masked by the effect of the elevation of TNFα and its receptors associated with obesity. Only when the effect of BMI on sTNF-α receptors is minimal (at low BMI), does one see increased sTNF-α receptor levels in plasma associated with periodontal disease. It is reasonable then to propose that chronic stimulation and secretion of proinflammatory cytokines associated with periodontal infection occurs and could contribute to insulin resistance,[43] leading to more severe insulin resistance and greater levels of glycated hemoglobin and more dyslipidemia and other metabolic and pathologic consequences of diabetes mellitus. This is consistent with our recent findings that diabetics with periodontal disease have greater mortality from diabetic complications such as cardiovascular disease and diabetic nephropathy than diabetics with little or no periodontal disease.[44]

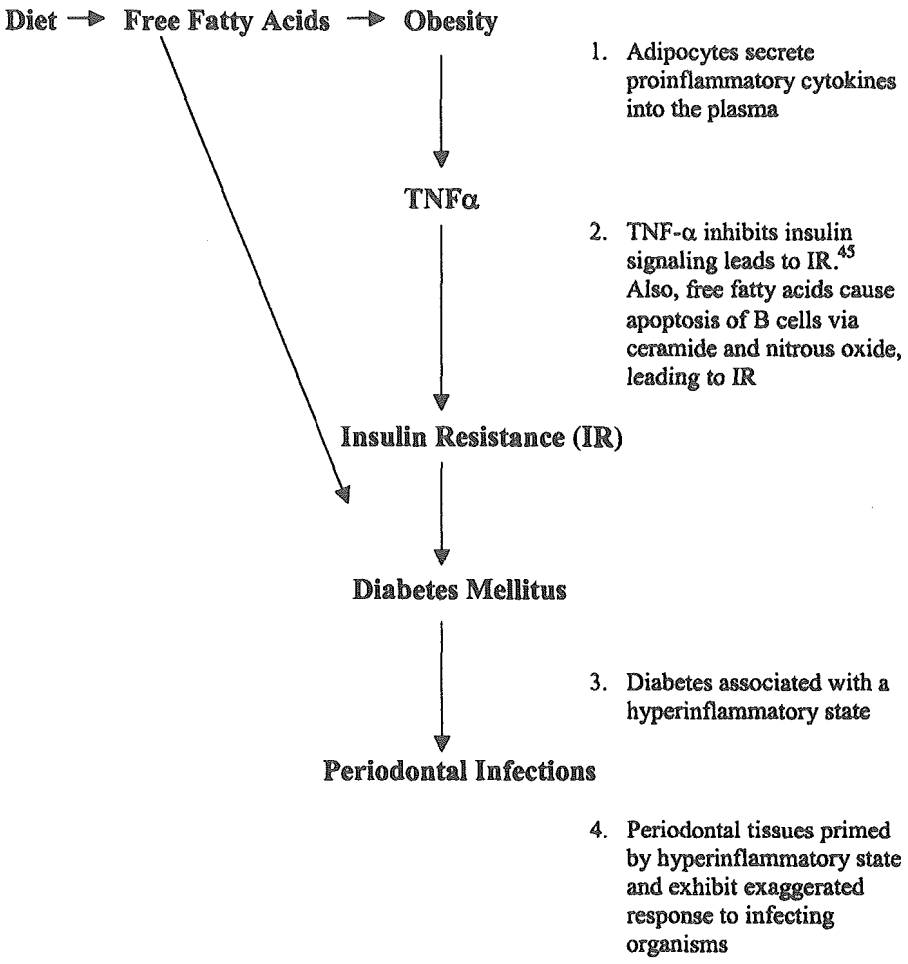

Figure 2.
A proposed model linking inflammation to obesity, diabetes, and periodontal infections.

A proposed model linking inflammation to obesity, diabetes, and periodontal infection is presented in Figure 2. Dietary free fatty acids contribute to obesity, as well as to insulin resistance by enhancing apoptosis of β-cells of the pancreas. Adipocytes produce proinflammatory cytokines such as TNF-α, which in turn appear to contribute to insulin resistance by inhibiting insulin signaling.[45] Insulin resistance is a pathologic process which is a critical feature of type 2 diabetes mellitus. Diabetes also contributes to a hyperinflammatory state through production of advanced glycation end products (AGE) of proteins which trigger monocyte/macrophage and cytokine production through interaction with receptors for AGE. This higher inflammatory state then sets the stage for increased levels of periodontal disease triggered by oral pathogens. The precise nature of the molecular interactions of inflammatory cytokines with obesity, diabetes, and infections such as periodontal disease is not clear. However, it is hoped that this and other models suggest experimental approaches to clarify these mechanisms.

Results from our study suggesting periodontal disease as another co-morbidity associated with obesity is of potential public health relevance. Evidence is rapidly mounting supporting periodontal disease as an independent risk for CHD and as an aggravating factor for diabetes mellitus and cardiovascular and nephropathy complications of diabetics.[8,42,44,46-49] The presence of periodontal infection in obese individuals may be an important factor precipitating the clinical outcome of type 2 diabetes and its complications, as well as CHD in non-diabetics. Further studies of the role of insulin resistance, plasma lipids, leptin, resistin, adiponectin, and proinflammatory cytokines are urgently needed to fully unravel the molecular basis of these relationships. Intervention and preventive approaches

may ultimately lead to amelioration of the significant health burden associated with these diseases.

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【原著】

歯学部 1、2 年生における口腔微生物学に対する意識調査

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要　旨

口腔微生物学未履修の歯学部学生1、2 年生、111 名(平均年齢 19.5 歳)に対して、口腔微生物学に関する意識調査を行った。結果、① 学生の 89 名 (80.2 %) は、口腔微生物学で特に関心があった。② 学生が口腔微生物学で最も学びたい領域は、「口腔内微生物と全身疾患の関係」43 名 (37.7 %) であった。③ 歯科医師の専門資格の一つである感染制御医師 (Infection Control Doctor、ICD) に関心のある学生は 89 名 (80.2 %) であった。学生の口腔微生物学に対する関心が高く、また、感染防御などの専門知識と技術を身につけたい学生も多いことが判明した。

今後、関連分野共に導入教育の充実や感染防止教育、ICD 専門教育など、学生と社会が求める歯科医師養成に対応できる教育体制を絶えず確立していく必要がある。

キーワード：口腔微生物学、インフェクションコントロールドクター (ICD)、意識調査、歯学部学生、歯学教育

目　的

口腔微生物学は、口腔内における様々な微生物について学び、細菌学、ウイルス学、免疫学、遺伝学など幅広い学問にまたがる。また、臨床系と共に口腔内疾患および全身疾患の制圧、院内感染防止などにも寄与し、歯科医師として必須の知識と技術を数多く教授するものである。必須の知識と技術は数多く[1)]、教授する側は適量かつ的確な教育指導を行わなければならない。

今回、口腔微生物学未履修の歯学部 1 年生および 2 年生を対象に口腔微生物学に対する関心についての意識調査を行い、彼らの関心度を把握することにより、今後の口腔微生物学教育の可能性を考察した。

対象および方法

1. 対象および実施日

対象は、平成 17 年度口腔微生物学分野教科(基礎微生物学、微生物学、基礎微生物学実習、免疫学、ウイルス学、感染症学) 未履修の歯学部 1 年生 57 名および 2 年生 57 名の合計 114 名であった。実施前に個人情報保護法の説明および回答内容による個人評価を行わない点等を説明し、無記名方式で平成 17 年 7 月に実施した。

2. 質問内容

質問は、8 項目であり、質問 ① - ④ は口腔微生物学、質問 ⑤ - ⑧ は インフェクションコントロールドクター (ICD、感染制御医師) に関する内容で、表 1 に示した。

結果と考察

1. 回答者データ

回答者は、1 年生 55 名(男性 29 名、女性 25 名、無回答 1 名：平均年齢 18.9 歳)、2 年生 56 名 (男性 30 名、女性 26 名：平均 20.1 歳) の合計 111 名であり、回収率は 97.4 % であった。

表1　質問項目

① 口腔微生物学は、口腔内における様々な微生物の研究や免疫学、遺伝学、全身疾患との関連研究など幅広い学問です。口腔微生物学に関心がありますか？

関心がある　・　どちらかといえば関心がある
どちらかといえば関心がない　・　関心がない

② 質問 ① で「関心がある」、「どちらかといえば関心がある」と回答された方へ質問します。口腔微生物学のどのような点に関心がありますか？（自由記述回答）

③ 質問 ① で「どちらかといえば関心がない」、「関心がない」と回答された方へ質問します。口腔微生物学のどのような点に関心がありませんか？（自由記述回答）

④ あなたは、口腔微生物学のどのような点を特に学んでみたいですか？（自由記述回答）

⑤ 歯科医師の専門職の一つに、院内感染防止や様々な感染防御を専門的に取り扱う「インフェクション・コントロール・ドクター（Infection Control Doctor；ICD）（以下、ICD）」という資格があります。ICD の資格に関心がありますか？

関心がある　・　どちらかといえば関心がある
どちらかといえば関心がない　・　関心がない

⑥ ICD の資格取得には、大学院で学位（博士号）取得後、専門学会での口頭・論文発表等を行い、資格授与組織（ICD 制度協議会）の審査に合格しなければなりません。歯科医師の専門職の一つとして ICD の資格を取得したいと思いますか？

取得したい　・　どちらかといえば取得したい
どちらかといえば取得したくない　・　取得したくない

⑦ 質問⑥で「取得したい」、「どちらかといえば取得したい」と回答された方へ質問します。なぜ ICD の資格を取得したいと思ったのですか？（自由記述回答）

⑧ 質問⑥で「どちらかといえば取得したくない」、「取得したくない」と回答された方へ質問します。なぜ ICD の資格を取得したくないと思ったのですか？（自由記述回答）

2. 質問回答結果

図 1-8 に示す結果が得られた。

口腔微生物学に対する関心は、「関心がある」、「どちらかといえば関心がある」をあわせて 89 名（80.2 %）と高く、また、口腔微生物学において特に学んでみたい分野では、「口腔微生物と全身疾患の関係」43 名（37.7 %）が最も多かった。これは、口腔内微生物と全身疾患との関係についての研究が盛んに行われてきており[2]、これらに対する関心の高さに起因するのかもし

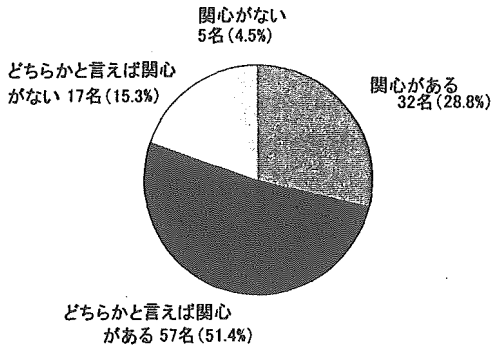

図1　質問①「口腔微生物学への関心」(N=111)

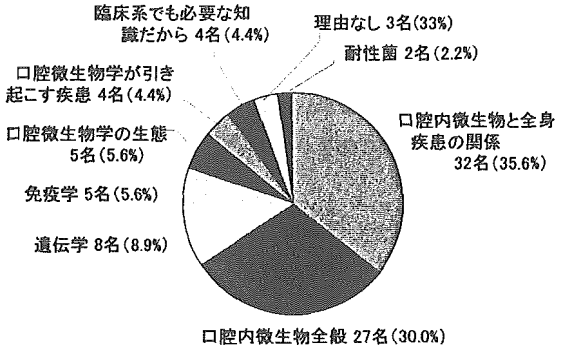

図2　質問②「口腔微生物学に関心のある学生の関心事項
(複数回答)」(N=89, TA=90)

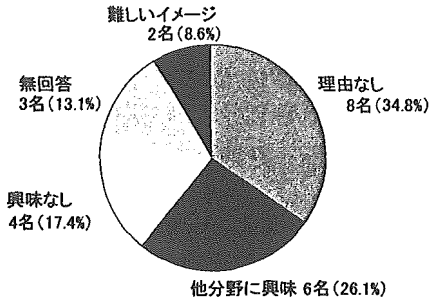

図3　質問③「口腔微生物学に関心のない学生の無関心事項
(複数回答)」(N=22, TA=23)

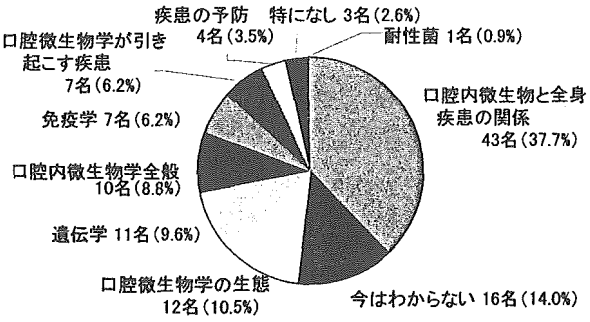

図4　質問④「口腔微生物学で特に学んでみたい点(複数回答)」
(N=111, TA=227)

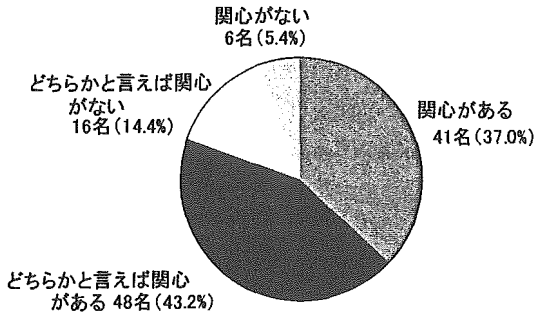

図5　質問⑤「ICDへの関心について」(N=111)

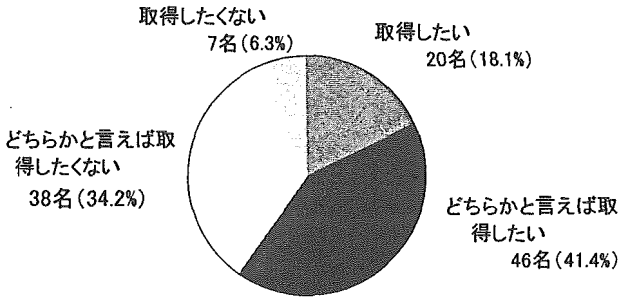

図6　質問⑥「ICDの取得」(N=111)

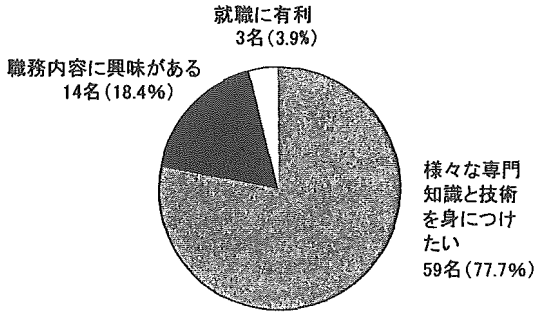

図7　質問⑦「ICD資格を取得したい学生の理由(複数回答)」
(N=66, TA=76)

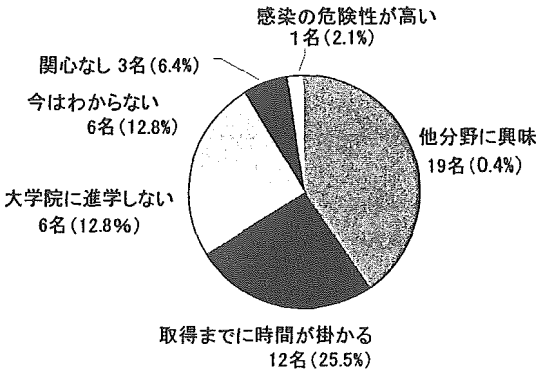

図8　質問⑧「ICD資格を取得したくない学生の理由
(複数回答)」(N=45, TA=47)

れない。この点において、口腔微生物学の導入教育として、「口腔微生物と全身疾患」等のカリキュラムを設け、口腔微生物学および関連分野への学生の関心を高める施策などが考えられる。

また、口腔微生物学に「どちらかといえば関心がない」、「関心がない」を合わせて22名（19.8 %）であった。理由として「特に理由はない」8名（34.8 %）が最も多く、その詳細理由は記入がないため不明だが、仮に「興味がない」とすれば、「興味がない」と回答した4名（17.4 %）とあわせて関心のない最も多い理由となる。また、「他分野に関心がある」と回答した学生も多く、「他分野」とはすべて臨床系分野であった。前述したように口腔微生物学は臨床系分野、他の基礎系分野とも関係が深く、いわば相関関係を成している。臨床系分野においても、また他の基礎系分野においても口腔微生物学が必要であることを低学年から教育することも口腔微生物学の重要性を認識させる一つの方法であると考える。また、幅広い分野にまたがる以上、様々な教科で重複して教えられることも確かである。これは反復して教えることによるメリットもあるが、逆に「ここは口腔微生物学で習います」と済ませてしまう危険性もある。これは分野間の連携が求められる点であり、例えば歯科保存学の齲蝕学習の際に口腔微生物学分野の教員が共同で教育に参画するなどの研究室（講座）を超えた教育方法も一つの方法として考えられる。

次に、ICDに関しては、ICDは医師、歯科医師の中から感染制御の専門知識を有する医師に与えられ、歯科医療を行う上でも必要不可欠な知識と技術を習得することができる資格の一つである。ICDに対する関心は高く、「関心がある」、「どちらかといえば関心がある」をあわせて89名（80.2 %）であった。また、ICDの取得に関しては、「取得したい」、「どちらかといえば取得したい」をあわせて66名（59.5 %）であった。関心度の高さから実際に取得したいと思う学生数は減ったが、その内容は「他分野に関心がある」19名（40.4 %）が多く、「他分野」はすべて臨床系分野であった。臨床系においても感染制御などのICDに関する知識と技術は医療行為上必要不可欠なものである。また、取得したい理由で一番多かった理由は「様々な専門知識と技術を身につけたい」が59名（77.7 %）と最も多かった。この両者の意見を考えるならば、臨床系に進んだ学生（歯科医師）において、基礎系に位置されている口腔微生物学がICDに関する知識と技術を教授し、臨床系専門資格取得あるいは臨床経験を積むと同時にICD資格を取得できるカリキュラムを行うことも一つの方法であると考える。これにより、様々な専門知識と技術を習得したい学生のニーズに対応できる点と高い感染制御の専門能力と臨床能力を兼ね備えた臨床家を養成することができると考える。

急速かつ多様化する歯学教育において、口腔微生物学の役割は多い。今後、更なる検討を行い、学生および社会が求める歯科医師養成の一翼を担える教育体制の確立を絶えず行うことが求められていると考える。

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A Survey of Student's Consciousness of Oral Microbiology in a School of Dentistry.

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Summary

We conducted a survey of consciousness of oral microbiology in 111 dental school students (freshmen and sophomores) who had not yet major in the oral microbiology.

The results were as follows:

1. 89 students (80.2 %) were interested in oral microbiology.
2. 43 students (37.7 %) wanted to learn about "oral microbiology particularly its relationship to whole body diseases" as deeply as possible.
3. 89 students (80.2 %) were interested in Infection Control Doctor (ICD) which is one of the specialized qualification of a dentist.

The results of the present study showed that the student's interest in oral microbiology was high and that many students wanted to learn technical knowledge about infection prevention and treatment modalities.

It is necessary to conduct comprehensive ICD professional training as well as an introductory teaching program on oral microbiology and its related fields. Further efforts are needed to establish an education system that can provide good dentists who better meet the needs of both dental students and society.

Key words: oral microbiology, Infection Control Doctor (ICD), consciousness survey, dental student, dental education.

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【原著】

歯学部臨床実習生における「感染制御医師」に対する意識調査

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（受付：平成17年 9月30日）
（受理：平成17年10月31日）

要　旨

歯学部臨床実習中の 6 年生 56 名（平均年齢 25.3 歳）の学生に対して、感染制御医師（Infection Control Doctor、ICD）の意識調査を行った。調査の結果、38 名（67.9 %）の学生が ICD に関心があった。しかし、実際に ICD の資格を取得したい学生は、22 名（39.3 %）であり、多くの学生が他の専門分野に関心を持っていた（主に臨床歯学系）。

歯科医師は、多くの感染症に感染する可能性のある職業である。その為、感染防御の知識と技術は必要不可欠である。今回の意識調査において、歯学部臨床実習生の ICD に対する関心が判明した。今後、臨床実習生に成る前の段階において、実践的な感染防御の教育と専門医制度などの教育カリキュラムを充実していく必要があると考える。

キーワード：感染制御学、感染制御医師（ICD）、意識調査、歯学部生、歯学教育

目　的

歯科医師は、その職務から様々な感染症に感染する危険性のある職業であり、感染防御や院内感染防止などの様々な専門知識と技術を持つことは非常に重要かつ、必要不可欠である[1)]。

今回、感染制御医師（Infection Control Doctor（以下、ICD）についての意識調査を臨床実習中の歯学部 6 年生に対して行った。彼らの ICD への関心を知ることにより今後の感染制御学教育への構築に寄与することを目的とする。

対象および方法

1. 対象および実施日

対象は、臨床実習中の歯学部 6 年生 59 名である。実施前に個人情報保護法の説明及び回答内容による個人評価を行わない点等を説明し、無記名方式にて実施した（平成 17 年 8 月）。

2. 質問内容

質問は 5 項目である（括弧内は回答方法）。

質問 ①「あなたは、歯科医師の専門職の一つとして、院内感染防止や様々な感染症を専門的に取り扱う「感染制御医師（Infection Control Doctor；ICD）（以下、ICD）」という資格があることを知っていますか？」（はい・いいえ）。

質問 ②「ICD は、院内感染防止や様々な感染症を専門的に取り扱う専門資格です。あなたは、歯科医師の専門職の一つとして、ICD の資格に関心がありますか？」（関心がある・どちらかといえば関心がある・どちらかといえば関心がない・関心がない）。

質問 ③「ICD の資格取得には、大学院で学位取得後、専門学会での口頭・論文発表等を行い、資格授与組織の審査に合格しなければなりません。あなたは、歯科医師の専門職の一つとして ICD の資格を取得したいと思いますか？」（取得したい・どちらかといえば取得したい・どちらかといえば取得したくない・取得したくない）。