Macrophage-Adipocyte Interaction: Marked Interleukin-6 Production by Lipopolysaccharide

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Abstract

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Objective: Recent studies suggested macrophages were integrated in adipose tissues, interacting with adipocytes, thereby exacerbating inflammatory responses. Persistent low-grade infection by gram-negative bacteria appears to promote atherogenesis. We hypothesized a ligand for toll-like receptor 4 (TLR4), bacterial lipopolysaccharide (LPS), would further exaggerate macrophage-adipocyte interaction.

Research Methods and Procedures: RAW264.7 macrophage cell line and differentiated 3T3-L1 preadipocytes were co-cultured using transwell system. As a control, each cell was cultured independently. After incubation of the cells with or without *Escherichia coli* LPS, tumor necrosis factor (TNF)-α and interleukin (IL)-6 production was evaluated.

Results: Co-culture of macrophages and adipocytes with low concentration of *Escherichia coli* LPS (1 ng/mL) markedly up-regulated IL-6 production (nearly 100-fold higher than that of adipocyte culture alone, $p < 0.01$), whereas TNF-α production was not significantly influenced. This

increase was partially inhibited by anti-TNF-α neutralizing antibody. Recombinant TNF-α and LPS synergistically up-regulated IL-6 production in adipocytes. However, this increase did not reach the level of production observed in co-cultures stimulated with LPS.

Discussion: A ligand for TLR-4 stimulates macrophages to produce TNF-α. TNF-α, thus produced, cooperatively up-regulates IL-6 production with other soluble factors secreted either from adipocytes or macrophages in these cells. Markedly up-regulated IL-6 would greatly influence the pathophysiology of diabetes and its vascular complications.

Key words: macrophages, adipocytes, tumor necrosis factor

Introduction

It has been postulated that type 2 diabetes and atherosclerosis are diseases of an innate immunity (1,2). Mild elevation of C-reactive protein (CRP)[1] well predicts the future development of type 2 diabetes and myocardial infarction, suggesting that chronic inflammatory state greatly up-regulates the risk of developing type 2 diabetes and its vascular complications (1,2). The most predominant chronic inflammatory state is known to be obesity. Obese subjects are characterized by increased level of circulating tumor necrosis factor (TNF)-α, interleukin (IL)-6, and, hence, CRP (3). Adipose tissue may be a primary tissue producing TNF-α and IL-6 in obese subjects, although exact cell types responsible for the production of each cytokine are still unclear. Recent studies suggested that macrophages were integrated in adipose tissues, interacting with adipocytes, thereby exacerbating inflammatory responses, insulin resistance, and vascular complications (4). Indeed, co-culturing adipocytes with macrophages has been reported to up-regulate some inflammatory gene expressions, although subsequent protein expression and its effects are still unclear (5).
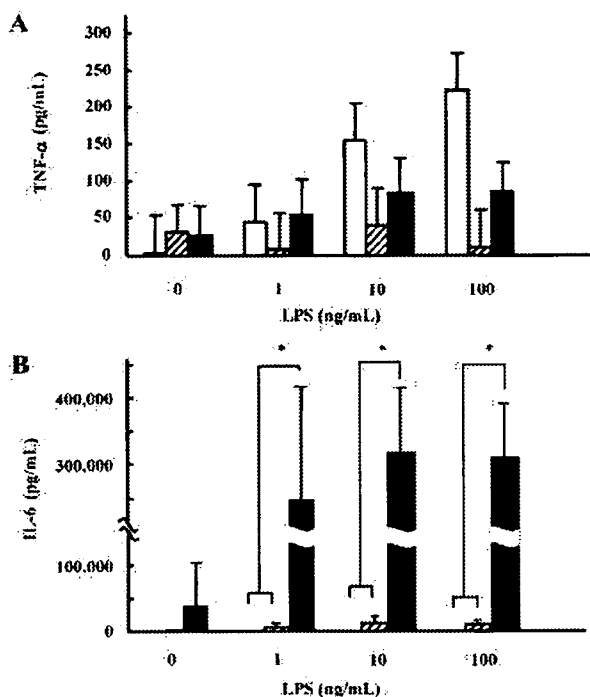
Figure 1: TNF-α (A) and IL-6 (B) production in macrophage culture alone (open box), adipocyte culture alone (shadow box), and macrophage-adipocyte co-cultures (closed box) stimulated with indicated concentration of LPS. Although TNF-α production increased according to the increased concentration of LPS in macrophages and macrophage-adipocyte co-cultures, no significant differences were observed between the two culture conditions. In contrast, IL-6 production was markedly up-regulated by TLR-4 ligand (LPS) in macrophage-adipocyte co-cultures. * $p < 0.01$ by Student's t test.

The origin of infiltrated macrophages in adipose tissues has been suggested to be peripheral tissues (4). Because previous studies have suggested that persistent low-grade infection by gram-negative bacteria, such as *Chlamydia* infection (6) and periodontal disease (7), may promote atherosclerosis and influence insulin resistance; and because both adipocytes and macrophages have recently been shown to express toll-like receptor 4 (TLR-4) (8), a ligand for lipopolysaccharide (LPS), we hypothesized that bacterial LPS would further exaggerate biological interaction between macrophages and adipocytes. Therefore, we investigated the effects of stimulating TLR-4 by LPS on inflammatory cytokine expression in co-cultured cells.

Research Methods and Procedures

Cells and Cell Culture

Mouse 3T3-L1 preadipocytes and mouse macrophage cell line RAW264.7 were used. Preadipocytes were differentiated into mature adipocytes as described (9). Co-

culture was performed by using transwell system (Corning Inc., Acton, MA) with 0.4-μm porous membrane to separate upper and lower chamber. 1×10^5 of differentiated 3T3-L1 cells were cultured in a lower chamber, while 5×10^4 of RAW cells were cultured in an upper chamber.

Cytokine Assay

The cells were stimulated with indicated concentration of *Escherichia coli* LPS (1 to 100 ng/mL; SIGMA, St. Louis, MO) for 24 hours, and culture supernatant was collected. TNF-α, IL-6, monocyte chemotactic protein-1, and adiponectin concentration in the culture supernatants were measured by using commercial immunoassay (mouse TNF-α, IL-6, monocyte chemotactic protein-1 enzyme-linked immunosorbent assay kits, Endogen Inc., Woburn, MA; mouse adiponectin enzyme-linked immunosorbent assay kit, Otsuka Pharmaceuticals, Inc., Tokyo, Japan). As a control, each cell was cultured independently. In some experiments, the cells were cultured with or without indicated concentration of anti-mouse TNF-α neutralizing antibody (1 to 100 ng/mL; R & D Systems, Minneapolis, MN). To see the synergistic effects of LPS and TNF-α on IL-6 production in adipocytes, differentiated adipocytes were cultured with or without recombinant murine-TNF-α and LPS.

Statistical Analyses

Statistical analyses were performed by using Student's t test.

Results

We first saw the effects of LPS on production of TNF-α and IL-6 according to the different culture conditions. Production of TNF-α was mainly observed in RAW264.7, and LPS dose-dependently up-regulated TNF-α production in RAW264.7 cells. Co-cultures of macrophages and adipocytes did not significantly influence TNF-α production (Figure 1A). As for IL-6, the major source of IL-6 appeared to be adipocytes, and LPS even at low concentration (1 ng/mL) markedly up-regulated IL-6 production in co-cultures (Figure 1B). The amount of IL-6 produced in co-cultures was almost 100-fold higher than that of adipocyte culture alone ($p < 0.01$, Student's t test). In contrast, although monocyte chemotactic protein-1 production was observed in adipocyte culture and co-cultures, the amount was less than that of IL-6 (data not shown). In addition, although adiponectin was detected in adipocyte culture and co-cultures, its concentration did not differ significantly regardless of the LPS concentration, nor did it differ with or without macrophage cultures (data not shown).

As IL-6 production was extremely enhanced in co-cultures when stimulated with LPS, we wondered if any solu-
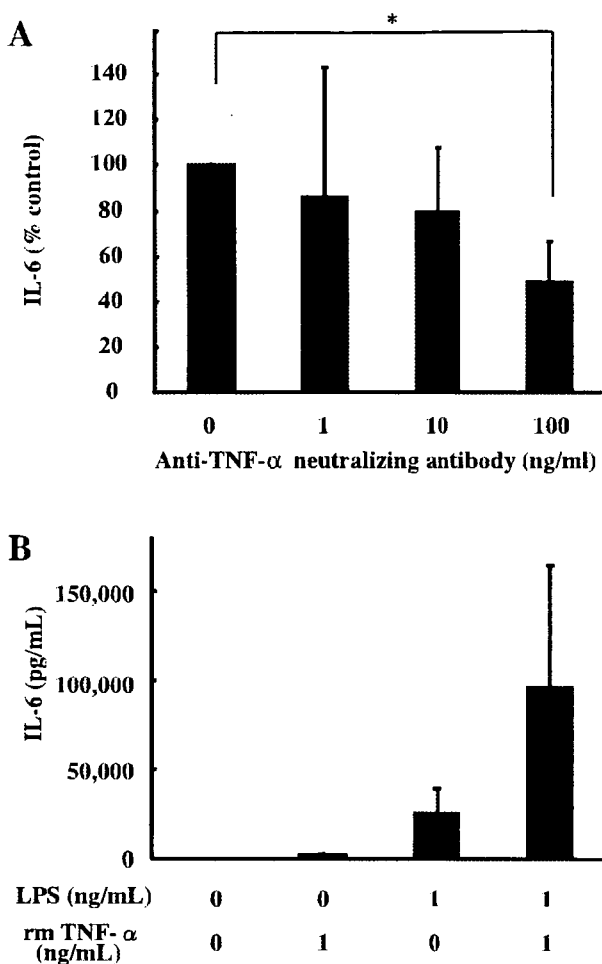
Figure 2: Effects of anti-TNF-α neutralizing antibody on the production of IL-6 in macrophage-adipocyte co-cultures stimulated with 1 ng/mL of LPS (A), and the effects of bacterial LPS and TNF-α on the production of IL-6 in adipocytes (B). Elevated IL-6 production was partially (~50% inhibition with 100 ng/mL of neutralizing antibodies) blocked by anti-TNF-α neutralizing antibody. Data are % control (IL-6 production without antibody). In addition, although bacterial LPS and recombinant murine-TNF-α synergistically up-regulated IL-6 production in adipocytes, the amount did not reach the level that was observed in co-cultures in the presence of LPS. rmTNF, recombinant murine TNF. * $p < 0.01$ by Student's t test.

ble molecule was responsible for this marked up-regulation. As TNF-α production from macrophages increased by LPS, the effects of anti-TNF-α neutralizing antibody was examined (Figure 2A). Anti-TNF-α neutralizing antibody partially suppressed IL-6 production in co-cultures (~50% inhibition with 100 ng/mL of neutralizing antibody, $p <$ 0.01). To see if TNF-α is actually involved in the synergistic up-regulation of IL-6 production in adipocytes, IL-6 production in adipocytes cultured with or without LPS and

recombinant murine-TNF-α was investigated (Figure 2B). Although TNF-α and LPS synergistically up-regulated IL-6 production in adipocytes, the increase was not compatible with the level of that seen in co-cultures (up to 30% of co-cultures).

Discussion

A ligand for TLR-4 greatly enhanced IL-6 production in co-cultures of macrophages and adipocytes at protein level. It was suggested that IL-6 acts as an insulin-resistance-inducing molecule (10) like TNF-α. Interestingly, IL-6 appears to induce insulin resistance selectively in hepatocytes (10). Adipose tissue-derived IL-6 may easily accumulate in the liver via portal vein. Additionally, IL-6 is known to be a major inducer of CRP in hepatocytes (11). Mild elevation of CRP well predicts the future development of myocardial infarction (2). Furthermore, a recent study indicated that CRP is not merely a sensitive marker of inflammation but positively acts as atherosclerosis-promoting factors via several distinct mechanisms, such as inducing cell surface expression of adhesion molecules (12). Taken together, markedly enhanced IL-6 production in macrophage-adipocyte co-cultures stimulated with TLR-4 ligand may promote both diabetes and its vascular complications.

Neutralizing TNF-α action by specific antibodies partially suppressed markedly up-regulated IL-6 production in co-cultured cells. As TNF-α production in 3T3-L1 cells was very low, the major source of TNF-α appeared to be macrophages. In contrast, the major source of IL-6 appeared to be adipocytes, as IL-6 production in 3T3-L1 cells was far exceeding of that observed in RAW cells. Therefore, TLR-4 ligand primarily stimulates macrophages to produce TNF-α. TNF-α, in turn, stimulates adipocytes to produce higher amounts of IL-6 in co-operation with LPS. However, exogenously added TNF-α and LPS was not enough to reproduce the high level of IL-6 production seen in co-cultures, indicating other numerous cytokines and adipocytokines, soluble adhesion molecules, and/or yet unknown molecules secreted either from adipocytes or macrophages also played important roles in markedly enhanced IL-6 production. Further study is necessary to elucidate the molecular mechanisms behind this important interaction.

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Relationship of periodontal infection to serum antibody levels to periodontopathic bacteria and inflammatory markers in periodontitis patients with coronary heart disease

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Summary

Several reports have demonstrated a possible association of periodontal infections with coronary heart disease (CHD) by elevated antibody titre to periodontopathic bacteria in CHD patients compared with non-diseased controls. Although each periodontopathic bacterium may vary in virulence for periodontitis and atherosclerosis, antibody response to multiple bacteria in CHD patients has not been understood fully. Therefore, serum levels of antibody to 12 periodontopathic bacteria together with other atherosclerotic risk markers were compared among 51 patients with CHD, 55 patients with moderate to severe chronic periodontitis and 37 healthy individuals. The antibody response was the most prevalent for Porphyromonas gingivalis, a major causative organism, in CHD as well as periodontitis patients. However, antibody positivity was different between CHD and periodontitis if the response was analysed for two different strains of P. gingivalis, namely FDC381 and Su63. While periodontitis patients were positive for both P. gingivalis FDC381 and Su63, a high frequency of antibody positivity for P. gingivalis Su63 but not for FDC381 was observed in CHD patients. The results indicate that the presence of particular periodontopathic bacteria with high virulence may affect atherogenesis. Identifying the virulence factors of P. gingivalis Su63 may gain insight into the new therapeutic modality for infection-induced deterioration of atherosclerosis.

Keywords: CHD, periodontitis, Porphyromonas gingivalis, serum antibody

Introduction

Coronary heart disease (CHD) is the leading cause of death in Japan as well as other developed countries. The main underlying pathological pathway for the disease is atherosclerosis. Although hypertension, elevated serum cholesterol, smoking, diabetes and obesity are classical risk factors for atherosclerosis [1], a substantial proportion of patients have no such traditional risk factors. The general

hypothesis that chronic infections can contribute to the development of atherosclerosis has come from (i) direct effects of infectious agents on cellular components of the vessel wall; (ii) increased expression of cytokines, chemokines and cellular adhesion molecules resulting in local endothelial dysfunction; and (iii) immune responses targeted to self-proteins located in the vessel wall mediated by molecular mimicry [2]. Recent epidemiological studies have suggested a link between atherosclerosis and infection/inflammation.

Associations have been reported with *Chlamydia pneumoniae*, *Helicobacter pylori*, cytomegalovirus [3,4] and dental infections; in particular, those associated with periodontal disease [5]. With respect to inflammation, serum high-sensitivity C-reactive protein (hs-CRP) has been used as a risk marker for CHD [6] and a number of reports have demonstrated that hs-CRP is also elevated in periodontitis patients [7–13]. However, other systemic inflammatory markers such as tumour necrosis factor (TNF)-α and interleukin (IL)-6 showed inconsistent results [8,14].

In vitro studies have suggested that *Porphyromonas gingivalis* may have a relation to atherogenesis, because this bacterium can invade endothelial cells [15]; lipopolysaccharide induces cell adhesion molecules and cytokine production in endothelial cells [16]; and autoimmune or cross-reactive response to heat shock protein 60 may also be involved in both periodontitis and CHD [17]. The association of this bacterium to atherosclerotic disease is documented by higher antibody titres in patients compared with non-diseased controls [18]. The apparent specificity of the antibody to *P. gingivalis* for incident CHD supports the hypothesis that infection with, or the host response to, this particular bacterium is particularly deleterious in terms of atherosclerotic complications [19].

Not all subjects infected with these infectious agents necessarily develop CHD. It is important to recognize that the results from these studies identify only an association, not causation, between periodontitis and CHD. In response to infection and inflammation, certain individuals may exhibit greater expression of local and systemic mediators, and consequently be at increased risk for atherosclerosis [20].

Because pathogens in periodontitis comprise several genetically and serologically heterogeneous bacterial species, it can be speculated that a single or a few species may be of particular importance in the development and progression of atherosclerosis due to having the relevant virulence to the pathogenesis. The aim of the present study, therefore, was to investigate whether particular periodontal pathogens are associated with CHD by measuring the serum antibody levels to various periodontopathic bacteria. The difference of systemic inflammatory conditions and serum lipid profiles among patients with both CHD and periodontitis, with periodontitis and normally healthy subjects, was also compared.

Materials and methods

Patients

We studied 51 CHD patients who underwent percutaneous coronary intervention for chronic stable angina (CSA; $n = 17$) or acute coronary syndrome (ACS; $n = 34$) at the Coronary Care Unit of Niigata City General Hospital, and 55 patients with chronic periodontitis admitted to the Periodontal Clinic of Niigata University Medical and Dental

Hospital. ACS and CSA were grouped together for biochemical and immunological analyses. Although all CHD patients demonstrated clinical signs of periodontitis, both the degree and extent of the disease were variable. As a control, 37 healthy individuals selected from the staff members of the university were included. The study protocol was approved by the review boards of both institutions. Written informed consent was obtained from each patient and control subject prior to entry into the study. The periodontal status of each of the subjects was assessed as described previously [21]. Briefly, the clinical attachment level and probing pocket depth were measured at six sites per tooth, and the alveolar bone levels were examined radiographically. Smoking status was defined as 'ever smoker' and 'never smoker'. Fasting serum was obtained from periodontitis patients and control subjects. Sera of CHD patients were obtained after operations. The cholesterol and triglyceride profiles in terms of serum lipoproteins were analysed at Skylight Biotech Inc. (Akita, Japan).

None of the periodontitis patients or healthy control individuals had self-reported overt atherosclerotic disease at their most recent regular medical check.

Serum IgG antibody titres to periodontopathic bacteria and *Chlamydia pneumoniae*

Antibody responses to antigens of periodontopathic bacteria were assessed by enzyme-linked immunosorbent assay (ELISA) and evaluated according to the method as described previously [22]. Values ≥ 1 represent more than 2 standard deviations (s.d.) of the mean in controls and is considered to be antibody positive. Absolute measures of serum antibody were categorized into positive or negative groups. Serum IgG antibodies to *C. pneumoniae* was determined by enzyme immunoassay (SRL Inc., Tokyo, Japan).

Measurement of CRP

Serum high-sensitivity CRP (hs-CRP) was measured with nephelometry, a latex particle-enhanced immunoassay (NA Latex CRP kit; Dade Behring, Tokyo, Japan) on a commercial basis (SRL Inc.). Only one sample from a control subject demonstrated a value lower than the limit of the assay (50 ng/ml). Undetectable CRP values were recorded as 25 ng/ml, halfway between zero and the threshold of detection.

Measurement of serum interleukin (IL)-6 and tumour necrosis factor (TNF)-α

Serum levels of IL-6 and TNF-α were determined by sensitive ELISA using commercial kits (R&D Systems Inc., Minneapolis, MN, USA), according to the manufacturer's instructions. The lower limit of detection was 0·016 pg/ml for IL-6 and 0·06 pg/ml for TNF-α.

Statistical analysis

Clinical and biochemical parameters were compared using unpaired t-test and Mann–Whitney U-tests, respectively. A value of $P < 0.05$ was considered significantly different.

For anti-bacterial antibodies, the association of antibody positivity and disease type, e.g. periodontitis, or CHD with periodontitis, was determined by χ^2 and adjusted further for multiple comparisons using Bonferroni's correction, where the significance was accepted at $P < 0.025$. A logistic regression analysis was utilized to assess the relationship between antibody positivity and disease status while adjusting for potential confounding factors. We carried out this analysis with CHD patients with periodontitis versus periodontitis patients without CHD as dependent variable and age, gender, smoking and antibody positivity as independent variables. Odds ratios (OR) were calculated with 95% confidence intervals (CI). Correlation coefficient was analysed for antibody levels between either C. pneumonia and P. gingivalis FDC381 or C. pneumonia and P. gingivalis Su63 in each serum sample from CHD patients. Statistical analyses were performed by using the standard statistical software (StatView J-4·5 application program; SAS Institute Inc., Cary, NC, USA). Significance was set at 5% ($P < 0.05$).

Results

Clinical status of the patients

The clinical profile of the study population is shown in Table 1. The mean age of the CHD patients was higher than the periodontitis patients and control. The percentages of having ever smokers were 77·8% for the CHD patients and 34·5% for the periodontitis patients, whereas none of the controls had ever been smokers. Seventeen of 51 CHD patients were taking atorvastatin calcium. Although the CHD patients manifested apparent symptom of periodontitis, the severity of the disease was significantly greater than that of control subjects but significantly less than periodontitis patients. However, CHD patients had significantly less

teeth than periodontitis patients, suggesting that CHD patients have had severe periodontitis previously and several teeth had been extracted due to the disease. Because the severely involved teeth had been extracted and the periodontal status of remaining teeth is less severe than in the periodontitis patients, overall periodontal infection in CHD patients is considered to be more serious than in periodontitis patients. P. gingivalis was detected in the dental plaque samples obtained from all CHD patients by using polymerase chain reaction (PCR); however, the strains could not be differentiated (data not shown).

The high density lipoprotein (HDL) cholesterol and triglyceride levels of CHD patients were significantly lower than those of periodontitis patients and controls ($P < 0.0001$). The HDL cholesterol level of periodontitis patients was also significantly lower than that of controls ($P = 0.024$). However, the total cholesterol level of periodontitis patients and controls were significantly higher than that of CHD patients ($P = 0.0007$ for periodontitis versus CHD; $P < 0.0001$ control versus CHD). The very low density lipoprotein (VLDL) level of CHD patients was significantly lower than that of periodontitis patients and controls ($P = 0.0002$ and $P < 0.0001$, respectively). No difference was observed for the low density lipoprotein (LDL) level (Table 2).

Serum antibody levels

Serum IgG positivity to 12 periodontal pathogens is shown in Fig. 1. The prevalence of antibody positivity for P. gingivalis FDC381 and P. gingivalis Su63 was higher than the other bacteria. Furthermore, the antibody positivities for these bacteria were higher in periodontitis patients compared with control subjects. These two strains of P. gingivalis are serologically different but are isolated more frequently from Japanese periodontitis patients than the other strains, such as W50 and W83 [23]. There was no difference of antibody positivity to these two pathogens within periodontitis patients. In addition, no difference was observed for any other pathogens tested between these two patients. In CHD

Table 1. Study population and periodontal disease status.

	CHD ($n = 51$)	Periodontitis ($n = 55$)	Control ($n = 37$)
Age	62·4 ± 1·7[1,a]	47·2 ± 1·7	48·6 ± 1·5
Male/female	46/5	24/31	18/19
Smoking status (never smoker/ever smoker)	10/35[5]	36/19	37/0
PD[2] (mm)	2·8 ± 0·1[b]	3·8 ± 0·1[c]	2·0 ± 0·0
CAL[3] (mm)	3·4 ± 0·2[d]	4·5 ± 0·2[e]	2·1 ± 0·1
Mean bone loss (%)	34·7 ± 2·5	40·0 ± 2·0	n.d.[4]
Number of teeth	19·6 ± 1·4	24·5 ± 0·7[f]	27·9 ± 0·4[g,h]

[1]Data are expressed as mean ± s.e.; [2]PD: pocket depth; [3]CAL: clinical attachment level; [4]n.d.: not determined; [5]smoking status of some of the patients was not checked. [a]$P < 0.0001$ versus periodontitis and controls; [b]$P < 0.0001$ versus controls; [c]$P < 0.0001$ versus coronary heart disease (CHD) and controls; [d]$P < 0.0001$ versus controls; [e]$P < 0.0001$ versus CHD and controls; [f]$P = 0.0011$ versus CHD; [g]$P < 0.0001$ versus CHD; [h]$P = 0.0002$ versus periodontitis.

Table 2. Serum lipid profiles of the study population.

	CHD ($n = 51$)	Periodontitis ($n = 55$)	Control ($n = 37$)
Total cholesterol (mg/dl)	158·9 ± 4·8	180·8 ± 4·6[a]	198·2 ± 5·7[b]
HDL cholesterol (mg/dl)	38·2 ± 1·9	57·5 ± 1·9[c]	63·9 ± 1·9[c,d]
LDL cholesterol (mg/dl)	96·1 ± 3·7	89·3 ± 2·9	94·2 ± 4·0
VLDL cholesterol (mg/dl)	24·4 ± 1·5	33·5 ± 1·8[e]	39·6 ± 2·7[f]
Triglyceride (mg/dl)	36·1 ± 2·0	113·5 ± 9·0[g]	96·9 ± 9·2[h]

[a]$P = 0.0007$ versus coronary heart disease (CHD); [b]$P < 0.0001$ versus CHD; [c]$P < 0.0001$ versus CHD; [d]$P = 0.024$ versus periodontitis; [e]$P = 0.0002$ versus CHD; [f]$P < 0.0001$ versus CHD; [g]$P < 0.0001$ versus CHD. HDL: high density lipoprotein; LDL: low density lipoprotein; VLDL: very low density lipoprotein.

patients, on the other hand, a significant antibody response was observed only for *P. gingivalis* Su63 and not for *P. gingivalis* FDC381. As the characteristic response was observed for *P. gingivalis* Su63 and *P. gingivalis* FDC381, the antibody positivity to these strains was analysed further. The prevalence of antibody positive subjects for both strains in CHD patients and periodontitis patients was 13·7% and 50·9%, respectively. The prevalence of antibody positive subjects for only *P. gingivalis* Su63 in CHD patients and periodontitis patients was 41·2% and 9·8%, respectively, while that for *P. gingivalis* FDC381 was 0% and 7·3%, respectively. The distribution of single-positive subjects for *P. gingivalis* Su63 was significantly different between the CHD patients and periodontitis patients (CHD versus periodontitis: $\chi^2 = 13·3$, $P = 0·0006$). This difference in distribution was not seen
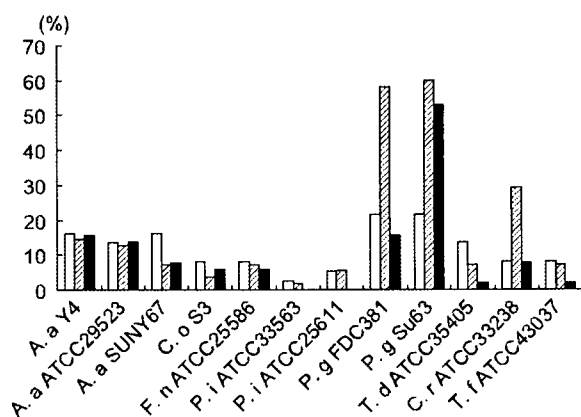
(%)

Fig. 1. Prevalence of antibody-positive subjects in each group. Serum antibody levels were evaluated against listed periodontopathic bacteria by enzyme-linked immunosorbent assay (ELISA). Values ≥ 1 represent more than 2 s.d. of the mean in controls and is considered to be antibody positive. Absolute measures of serum antibody were categorized into positive or negative groups. Data are expressed as percentages of antibody-positive subjects within each group. Control: open bar, periodontitis: hatched bar, coronary heart disease: closed bar. *Actinobacillus actinomycetemcomitans*: A. a., *Capnocytophaga ochracea*: C. o., *Fusobacterium nucleatum*: F. n., *Prevotella intermedia*: P. i., *Porphyromonas gingivalis*: P. g., *Treponema denticola*: T. d., *Campylobacter rectus*: C. r., *Tannerella forsythia*: T. f.

between periodontitis patients and controls ($\chi^2 = 1·07$, $P = 0·50$).

In order to evaluate the association of the pattern of antibody positivity for *P. gingivalis* with an increased frequency of CHD while adjusting for possible confounding factors, we further performed a logistic regression analysis. As age is a strong confounding factor for CHD, the analyses were performed for 46 CHD patients (mean age, 60·7 ± 10·1 years; range, 36–73 years) and 22 periodontitis patients (mean age, 59·4 ± 5·4 years; range, 52–70 years) to minimize age difference between two groups. Smoking status could not be adjusted because of the very low frequency of ever smokers in periodontitis patients. As can be seen in Table 3, the logistic regression analysis indicated that only the antibodies positive for *P. gingivalis* Su63, but not for both *P. gingivalis* Su63 and *P. gingivalis* FDC381 or negative for either as well as age, smoking and HDL-c, were significant factors of an increased frequency of CHD. Interestingly, antibody positivity was found to be a highly significant factor in the model ($P = 0·022$; OR 18·26, 95% CI = 1·53–218·48) and was even higher than smoking ($P = 0·016$; OR 8·56, 95% CI = 1·49–49·17). On the other hand, mBL and gender were not statistically significant.

Table 3. Logistic regression analysis for coronary heart disease (CHD) ($n = 46$) with periodontitis ($n = 22$).

Variable	OR	95% CI	P-value
Age	1·08	0·988–1·17	n.s.
Gender	0·34	0·042–1·61	n.s.
Smoking	8·56	1·49–49·17	0·016
HDL-c	0·93	0·87–0·99	0·023
mBL	0·99	0·95–1·04	n.s.
Antibody	18·26	1·53–218·48	0·022

Logistic regression with disease status (0: periodontitis without CHD, 1: periodontitis with CHD) as dependent variable, independent variables: ages as continuous, gender (0: male, 1: female), smoking (0: never smoker, 1: ever smoker), HDL-c (mg/dl) as continuous, mBL (%) as continuous and antibody positivity (0: either positive or negative for both *Porphyromonas gingivalis* Su63 and *P. gingivalis* FDC381, or negative for *P. gingivalis* Su63 and positive for *P. gingivalis* FDC381, 1: positive for *P. gingivalis* Su63 only); n.s.: not significant.

Table 4. Level of the serum inflammatory markers in each group.

	CHD (n = 51)		Periodontitis (n = 55)		Control (n = 37)	
CRP (ng/ml)	3958·9 ± 1855·4 (918·0)[a]		765·0 ± 148·1[b] (349·0)		426·9 ± 121·5 (217·0)	
IL-6 (pg/ml)	4·00 ± 1·41[c] (1·56)		0·64 ± 0·08 (0·57)		0·82 ± 0·32 (0·44)	
TNF-α (pg/ml)	0·86 ± 0·18 (0·57)		1·36 ± 0·08[d] (1·32)		1·96 ± 0·22[d] (1·42)	

Data are expressed as mean ± s.e. and median values are indicated in the parentheses. [a]P < 0·0001 versus periodontitis and controls; [b]P = 0·014 versus controls; [c]P < 0·0001 versus periodontitis and controls; [d]P < 0·0001 versus coronary heart disease. CHD: coronary heart disease; CRP: C-reactive protein; IL: interleukin; TNF: tumour necrosis factor.

For IgG antibody to C. pneumonia, 42·9% of the CHD patients were antibody-positive. However, there were no correlations between antibody levels to either P. gingivalis FDC381 and C. pneumoniae (r = − 0·142, P = 0·33) or P. gingivalis Su63 and C. pneumoniae (r = − 0·175, P = 0·24), suggesting that there is no cross-reactivity between these two bacteria.

Systemic inflammatory markers

Serum levels of hs-CRP, IL-6 and TNF-α are shown in Table 4. The values of hs-CRP and IL-6 in the CHD patients were significantly higher compared with those of the periodontitis patients and control subjects (P < 0·0001). The value of hs-CRP of the periodontitis patients was also significantly higher than that of controls (P = 0·014). In contrast to hs-CRP and IL-6, the CHD patient TNF-α level was significantly lower than that of periodontitis patients and control subjects (P < 0·0001). The TNF-α level of periodontitis patients tended to be lower compared with that of control subjects, but did not reach statistical significance.

Discussion

In spite of epidemiological evidence for an association between CHD and infection, and the effect of periodontal infection on the systemic inflammation, the contribution of periodontal disease to such an infectious burden is largely unknown. Here, we first report a relationship between the systemic immune response to a particular strain of periodontopathic bacteria (e.g. P. gingivalis Su63) and clinical manifestation of CHD. Although the association of infectious agents such as C. pneumoniae with CHD has been explored previously by serological testing, only a few studies have been performed specifically for the association with periodontal infection. In the present study, it was demonstrated that there was no correlation of antibody levels between both strains of P. gingivalis and C. pneumoniae.

Pussinen et al. reported that antibodies to selected periodontal pathogens were associated with CHD. They used a mixture of three serotypes of P. gingivalis as antigens in their multi-serotype ELISA [18]. In a prospective follow-up study by the same group, it was demonstrated that high-serum IgA antibody to P. gingivalis and Actinobacillus actinomycetemcomitans were associated with future incidence of CHD [24]. Beck et al. also demonstrated an association of elevated IgG antibodies to oral microorganisms and atherosclerosis [25]. In addition, Dye et al. showed that an elevated IgG titre to P. gingivalis was associated independently with high serum CRP [26]. However, these studies did not take into account the difference in the strains of each bacterium. In addition, none of these studies showed the antibody levels to periodontopathic bacteria in CHD patients without periodontal disease as a control. Our study was also unable to set such control groups. Age is a crucial risk factor for both CHD and periodontal disease, and a number of epidemiological studies have demonstrated that periodontal disease could be a risk for cardiovascular diseases [27]. According to the fact-finding survey of dental diseases conducted by the Ministry of Health, Labour and Welfare of Japan in 1999, more than 88% of the population whose ages are similar to those of patients analysed in this study had periodontal disease. Therefore, although the control data are important, it was difficult to include such patients in this study.

Because peripheral blood T cells from CHD patients with gingivitis and those with periodontitis showed a distinct proliferative response to bacterial HSP65 but not to human HSP60, the immune response may be different between CHD patients with periodontitis and those without periodontitis [28]. None the less, the antibody response in CHD patients without periodontitis remains to be determined.

It is reported that the different strains of P. gingivalis vary in their ability to invade human coronary artery endothelial cells [15]. These results therefore suggest that several species of periodontopathic bacteria are of particular importance in the association with CHD. In the present study, 12 putative periodontal pathogens were used as antigens. Of these, antibody positivity to two strains of P. gingivalis was much higher compared with the other bacteria. Several studies have demonstrated a clonal heterogeneity in virulence among various P. gingivalis strains [29]. P. gingivalis can be classified into six genotypes based on the genomic diversity of the fimA gene [30] in addition to serological classification. The fimA genotypes of P. gingivalis FDC381 and Su63 are type I and type IV (Amano A, personal communication), respectively. The abscess formation caused by fimA type II and type IV organisms in mice leads to higher levels of systemic inflammation compared to the other fimA

genotypes [31]. Although the virulence of *P. gingivalis* Su63 has not been characterized fully, it is assumed to have equivalent pathogenic activity to other strains with fimA type IV, such as *P. gingivalis* W50 and W83. The pathogenicity of these strains is mediated at least in part by the cysteine proteinases called gingipains. It is shown that the biological effects of gingipains are related directly to the pathogenesis of atheroma formation and atherosclerotic plaque rupture [32–35]. *P. gingivalis* can be found in approximately 64% of the periodontal pocket of Japanese patients with periodontitis [36]. However, the prevalence of each strain of *P. gingivalis* in the periodontal pockets is not known. In this context, Amano *et al.* investigated the relationship between the prevalence of fimA genotypes of *P. gingivalis* and periodontal status and demonstrated that occurrence of fimA types I and IV within *P. gingivalis*-positive patients was 2·5% and 16·5%, respectively [37].

It is interesting that the antibody positivity to *P. gingivalis* Su63 was similar among the CHD and periodontitis patients, whereas that to *P. gingivalis* FDC381 was much lower in the CHD patients compared to the periodontitis patients. The logistic regression model showed clearly a strong correlation between the antibody positive for *P. gingivalis* Su63, not for *P. gingivalis* FDC381, and an increased frequency of CHD ($P = 0·022$; OR 18·26). This suggests that in spite of the similar infectious capability of these *P. gingivalis* strains, in the periodontitis lesion only *P. gingivalis* Su63-susceptible patients are at risk for CHD. Alternatively, it is possible that antibodies against *P. gingivalis* FDC381 cross-react with *P. gingivalis* Su63, whereas antibody to *P. gingivalis* Su63 does not cross-react with *P. gingivalis* FDC381. If this is the case, *P. gingivalis* Su63 is considered to be more probably involved in CHD than *P. gingivalis* FDC381. In the present study, we used sonic extracts of the bacteria as antigens instead of purified antigen(s). Although we have not determined the specificity of the antigens, as with other studies in which similar bacterial preparations are used [38,39], variable patterns of antibody response to different bacteria or to different species of the same bacteria in each patient suggest that the antibody response to each bacterium can be considered as specific, even though the reactivity may be reflected by some cross-reactive response. In addition, the number of false negatives undoubtedly increases when only one antigen has been chosen as a source of antigen [38]. Nevertheless, the differential antibody response to different strains of *P. gingivalis* needs to be clarified further.

Treponema denticola, Tannerella forsythia and *Campylobacter rectus* as well as *P. gingivalis* FDC381 are considered periodontal pathogens as the bacteria possess several virulence factors such as fimbriae, proteases, haemagglutinins and lipopolysaccharide [40]. However, antibody response to these bacteria was low in CHD patients. Although the precise reason is not known, prevalence of these bacteria in the plaque may be low compared with *P. gingivalis* Su63 in CHD patients, or the immune response to *P. gingivalis* FDC381 in

CHD patients may be different from that in periodontitis patients.

In the present study, intergroup variation of the serum lipid profile was found and the variation in HDL cholesterol was of particular interest. HDL cholesterol is considered to be an anti-atherogenic lipoprotein [41,42], and a low HDL cholesterol concentration is one of the established independent CHD risk factors [43].

HDL cholesterol concentration was the lowest in CHD patients, the highest in controls and with periodontitis patients between these two. It has been reported that although the concentration of total cholesterol and triglyceride was higher than that of controls, no difference in HDL cholesterol was observed [44,45]. In support of our results, Pussinen *et al.* demonstrated that high combined serum antibody levels against *A. actinomycetemcomitans* and *P. gingivalis* were associated significantly with low HDL cholesterol concentrations [18]. Furthermore, the same group demonstrated that periodontitis decreases the serum HDL cholesterol by comparing the levels before and after treatment [46]. Although it is well established that infection and inflammation are associated with a reduction in serum HDL cholesterol, the exact mechanism has not yet been established. Nevertheless, our study suggests that periodontal infection exerts effects on both systemic inflammation and the serum lipid profile towards pro-atherogenesity.

In spite of huge diversity of microflora in periodontal pockets, only a small number of species are involved in the pathogenesis of periodontal disease. Each individual species of bacteria has a different genotype with a different virulence. We show here for the first time that a particular genotype of *P. gingivalis* is probably involved in the mechanisms linking periodontitis and CHD. Further study will enable us to identify the particularly important virulence factors in both the development and progression of atherosclerosis.

Acknowledgements

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投稿
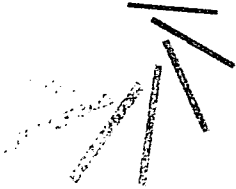
歯科臨床実習生における感染制御専門資格および組織に関する認知度調査

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I 目 的

歯科医療は，唾液などの体液曝露や観血を伴う外科処置が多く，そこには病原微生物，感染症，消毒・滅菌，抗菌薬などをはじめとする幅広い領域の感染制御（感染対策）に関する知識と，それを実践する能力が必須となる．そのため，将来歯科医療スタッフとなる歯学科学生や歯科衛生士学校生には，感染制御に関する基礎知識や実践技能の修得が必要である．この点を怠れば感染事故を引き起こすことになるが，現に，歯科医療従事者からの患者への感染，およびその逆の感染の事例も報告されている[1,2]．

また，歯科での感染制御は，医科と同様に，歯科医師や歯科衛生士などに加えて，さまざまな医療系資格者および感染制御専門資格者とともに，最新の情報や知識を共用し協力して，歯科医療を行うことが重要となる．

今回，我々は，将来歯科医療スタッフとなる歯学科学生および歯科衛生士学校生に対して，感染制御専門資格および組織の認知度調査を行った．本調査において，歯科臨床実習生の感染制御専門資格や組織の認知度を把握することにより，ほかの感染制御専門資格との連携体制をどのように確立すればよいか，また，日々新たに講じられている感染制御法などにおいて，歯科医療スタッフとしてどのように行動すればよいのかなど，感染制御教育の観点から考察することを目的とした．

II 方 法

◆対象者

対象者は，歯科臨床実習を受ける歯学部歯学科学生（5・6年生）および歯科衛生士専門学校に所属する歯科衛生士学校生（2年生）である．

留置法により，実施前に個人情報保護の説明および個人評価を行わない点などを説明し，無記名方式にて実施した（調査期間：2005年7月～2006年7月）．

◆質問内容

質問は，下記の感染制御専門資格および組織名を知っているかどうかである．

①インフェクションコントロールドクター
（Infection Control Doctor：ICD）

②感染管理認定看護師
（Infection Control Nurse：ICN）

③感染制御専門薬剤師
（Infection Control Pharmacist：ICPh）

歯科臨床実習生における感染制御専門資格
および組織に関する認知度調査

表1　各学生群の回答結果

質問項目	質問回答	歯学科学生 (N≒109)	歯科衛生士学校生 (N≒161)	合計 (N=270)
質問①「あなたは，病院感染対策などを専門とするインフェクシ ョンコントロールドクター（Infection Control Doctor：ICD） という専門資格があることを知っていますか？」	はい	35 32.1	11 6.8	46 17.0
	いいえ	74 67.9	150 93.2	224 83.0
質問②「あなたは，看護における感染制御を専門とする感染管理 認定看護師（Infection Control Nurse：ICN）という看護師の専 門資格があることを知っていますか？」	はい	10 9.2	15 9.3	25 9.3
	いいえ	99 90.8	146 90.7	245 90.7
質問③「あなたは，薬剤における感染制御を専門とする感染制御 専門薬剤師（Infection Control Pharmacist：ICPh）という薬 剤師の専門資格があることを知っていますか？」	はい	8 7.3	5 3.1	13 4.8
	いいえ	101 92.7	156 96.9	257 95.2
質問④「あなたは，臨床検査における感染制御を専門とする感染制 御認定臨床微生物検査技師（Infection Control Microbiological Technologist：ICMT）という検査技師の専門資格があることを 知っていますか？」	はい	8 7.3	5 3.1	13 4.8
	いいえ	101 92.7	156 96.9	257 95.2
質問⑤「あなたは，医師の専門医制度として，感染症治療を専門 とする感染症専門医という専門医資格があることを知っています か？」	はい	10 9.2	8 5.0	18 6.7
	いいえ	99 90.8	153 95.0	252 93.3
質問⑥「あなたは，医療環境におけるインフラの構築・管理を専 門とする医療環境管理士という専門資格があることを知っていま すか？」	はい	7 6.4	5 3.1	12 4.4
	いいえ	102 93.6	156 96.9	258 95.6
質問⑦「あなたは，医療器材などの滅菌処理を専門とする滅菌技 士（師）という専門資格があることを知っていますか？」	はい	7 6.4	5 3.1	12 4.4
	いいえ	102 93.6	156 96.9	258 95.6
質問⑧「あなたは，医療施設において，感染制御を専門とする感 染制御チーム（Infection Control Team：ICT）という医療チー ムがあることを知っていますか？」	はい	8 7.3	5 3.1	13 4.8
	いいえ	101 92.7	156 96.9	257 95.2

（上段は人数，下段は％）（小数第二位四捨五入）

④感染制御認定臨床微生物検査技師（Infection Control Microbiological Technologist：ICMT）

⑤感染症専門医

⑥医療感染環境管理士

⑦滅菌技士（師）

⑧感染制御チーム（Infection Control Team：ICT）

結　果

◆回答者データ

対象者283名のうち，有効回答総数は，270名（回収率95.4%，平均年齢22.0歳）であった．

なお，各学生群の詳細は，歯学科学生109名（回収率95.4%，平均年齢24.5歳），歯科衛生士学校生161名（回収率95.3%，平均年齢20.3歳）であった．

◆質問回答

表1に示す結果が得られた．

質問①の「インフェクションコントロールドクターの認知度」が歯学科学生35名（32.1%）と最も高かったが，それ以外の感染制御専門資格と組織の認知度は，すべて1割以下の回答であった．

考　察

今回の調査では，歯科臨床実習生である歯学科学生および歯科衛生士学校生の感染制御専門資格と組織に関する認知度は，きわめて低い結果を得た．質問①「インフェクションコントロールドクターの認知度」が歯学科学生35名（32.1%）と，ほかの専門資格と比較して認知度が高かったのは，指導教官である口腔外科専門医や歯周病専門医などのなかにICD有資格者がおり，講義や実習指導中にその資格の存在を知ったためではないかと推測される．

今回の調査対象者は，歯科臨床実習生として，すでに臨床現場に出ている者ばかりである．歯学科学生は，実際に患歯の切削や抜歯などの歯科治療を行っており，患者からすれば，歯科臨床実習生は歯科医療従事者の一員と認識されていると思われる．そのため，臨床現場における実践的な感染制御の知識と技能が必要となる．つまり，歯科臨床実習生は臨床実習中に感染制御教育を受けて修得すればよいというものではなく，臨床実習の始まる前の学年（3・4年生）において，基礎系および臨床系における連携した感染制御教育，ならびにほかの感染制御専門有資格者やICTによる臨床実習で役立つ実習や教育などを行う必要があると考える．

また，感染制御を実践するICTにはさまざまな役割が存在し，日々活動している（図1）．これらの活動のなかに歯科臨床実習生を参加させ，感染制御の担う役割や連携協力体制を学ばせることは，有効な教育の一つであると考える．

また，歯科医師にはICDなどの専門資格を取得する道があるが，現在，大半の養成機関を専門学校に頼っている歯科衛生士には，ICDを取得するのは非常に困難であると考える．現在，社団法人日本歯科衛生士会では，歯科衛生士に対して「感染症予防歯科衛生士講習会」を開催し，感染制御教育を行っているが，これをさらに感染管理歯科衛生士（Infection Control Dental Hygienist：ICDH）（仮称）のような専門認定制度に発展させ，歯科衛生士養成期間中から感染制御に関する関心を持つ教育を実践する方法も有効であると考える[3]．

他方，歯学科学生では，ICDに対する関心があるが実際に取得しようと考える学生は少ないとの

ICC（感染対策委員会）
経営者
施設管理者（院長）
施設部門の管理職（部長・課長など）
診療部門の管理職（部長・科長・師長など）
ICTの代表者（ICDなど）
オブザーバー（法律・経営専門家など）

感染制御関連の国内
外学会・研究会での
学術発表
各種教育機関での講
習会・講義
市民講座や患者への
講習会
出版
広報
　　　　　　　　　など

医師，歯科医師，薬
剤師，保健師，看護
師，歯科衛生士，歯
科技工士，臨床検査
技師，診療放射線技
師，臨床工学技士，
滅菌技士，介護福祉
士，歯科助手，ボラ
ンティア，臨床実習
生
　　　　　　　　　など

感染制御の報告
および提言

評価・
権限付与

学術および
社会活動

臨床部門への
提言・実践

ICT（感染制御チーム）

ICD
感染制御の専門家

感染症専門医

感染症治療の
専門家

ICTへの
要望

ICPh

薬剤の専門家

ICMT

臨床検査の
専門家

ICTへの
要望

ICN

看護の専門家

滅菌技士（師）

医療器材の
専門家

医療環境管理士

インフラの
専門家

ICTへの
要望

ICTへの
要望

ICS

施設の
感染症担当者

協力専門家

法学，政策学，
経済学などの
専門家

医師，歯科医師，薬
剤師，保健師，看護
師，歯科衛生士，歯
科技工士，臨床検査
技師，診療放射線技
師，臨床工学技士，
滅菌技士，介護福祉
士，歯科助手，ボラ
ンティア，施設管理
者，施設職員，施設
関連組織職員，搬入
業者，行政官，学
生，臨床実習生，教
員
　　　　　　　　　など

感染制御
教育

施設部門への
提言・実践

経営者
施設管理者
施設職員
施設関連組織職員
搬入業者
行政官（中央官庁・
地方自治体）
　　　　　　　　　など

ICD：インフェクションコントロールドクター
ICPh：感染制御専門薬剤師
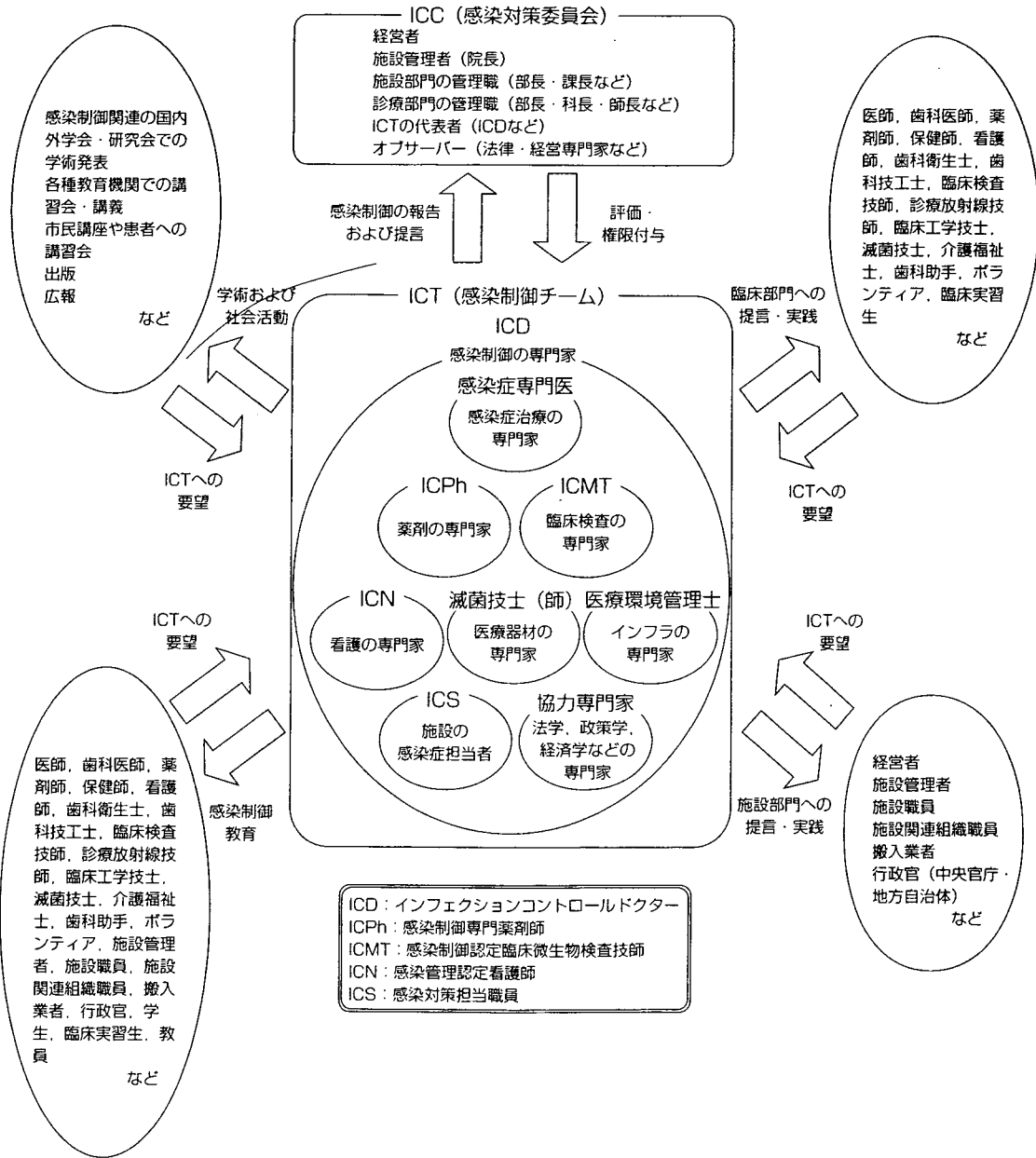ICMT：感染制御認定臨床微生物検査技師
ICN：感染管理認定看護師
ICS：感染対策担当職員

図1　ICT（感染制御チーム）の役割

報告もある[4]. これは，歯科医師の大半は開業医となるうえ，感染制御専門資格より歯科関係の専門医資格を取得した方が，メリットが大きい点にある. しかし，前述したように，現在，感染制御は医療において必要不可欠となっている. 感染制御の重要性と科学的根拠に基づいた対策方法を，学生のうちから教育することに加えて，ICDの資格や重要性を認識させることも重要であると考える.

今後，複雑高度化する医療において，歯科臨床実習生が確実に感染制御を行うためには，感染制御専門資格者の教育参加，さらに卒業後の専門認定制度の充実などを講じることが重要であり，これが結果的に医療を利用する国民の利益と公衆衛生の向上に寄与すると考える.

┃ 結 論
①歯科臨床実習生における，感染制御専門資格および組織に関する認知度はきわめて低い.
②歯科臨床実習生は，肩書きこそ実習生であるが，実際に医療行為や診療補助を行うため，医療従事者としての感染制御に関する実践的な知識と技能が必要である.

③ほかの感染制御専門資格者との連携を図るためにも，感染制御専門資格者や組織について教育する必要がある.
④感染制御教育には，歯科の教員だけでなく，ほかの感染制御専門資格者やICTが積極的に教育カリキュラムに参画する必要がある.

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教育ノート

独立行政法人 大学評価・学位授与機構における「学士（口腔保健学）」の新設について

Announcement for new establishment of bachelor's degree program of Oral Health Sciences in National Institution for Academic Degrees and University Evaluation.

佐藤 法仁[2,3]　　渡辺 朱理[1,2]　　苔口 進[2]　　福井 一博[2]
Norito Sato　　　Akari Watanabe　　Susumu Kokeguchi　Kazuhiro Fukui

1）岡山県歯科衛生士会　　2）岡山大学大学院 医歯薬学総合研究科 口腔微生物学分野
3）社会健康観研究会

和 文 抄 録

2008年4月から独立行政法人 大学評価・学位授与機構（National Institution for Academic Degrees and University Evaluation：NIAD-UE）において，「学士（口腔保健学）」の学位の授与制度が新設される。これにより，一定の基準を満たせば，専門学校修了者や短期大学卒業者が自らの専門領域である口腔保健学の学士の学位を取得することができる。学士の学位を取得後は，国内外への大学院進学や学士編入学ができるようになり，自己の能力を高めることができると共に口腔保健学の学問的構築と充実に大きな影響を与え，引いては，国民の公衆衛生の向上に寄与することができる。

また，より多くの歯科衛生士学校生および歯科衛生士がこの制度を利用し，多様なキャリアアップができる環境を整備することが，大学，歯科衛生士養成機関および医療現場に求められており，柔軟かつ多様性のあるカリキュラムを構築することが重要な課題になると考えられる。

キーワード　学位，教育，人材育成，キャリアアップ，歯科衛生士

【はじめに】

現在，歯科衛生士の養成は多くの専門学校課程に設置されている。しかし，歯科衛生士の職務が高度化し，他の学際領域や業種との連携などが求められる中で，歯科衛生士教育の多様化と高度化が求められている。この様な状況下で，すでに大学学士課程に歯科衛生士養成課程が設置されたり，大学院修士課程および博士課程において学術研究に従事する歯科衛生士も存在する。だが，専門学校修了者や短期大学卒業者が再度，国内外の大学院で研究やその専門性を磨くためには，学士の学位が必要となる。

今回，学位授与事業を行っている独立行政法人

大学評価・学位授与機構（National Institution for Academic Degrees and University Evaluation：以下NIAD-UEと呼称する）において，2008年4月より，「学士（口腔保健学）」の学位が新設されることになった。これにより，大学学士課程を卒業していない専門学校修了者および短期大学卒業者が，NIAD-UEの学位授与事業に申請し合格すれば，自らの専門領域である口腔保健学の学士の学位を取得することができるようになる。さらに，学士の学位の取得により国内外への大学院進学や医学科，歯学科などへの学士編入学の道などが切り開かれることになる。

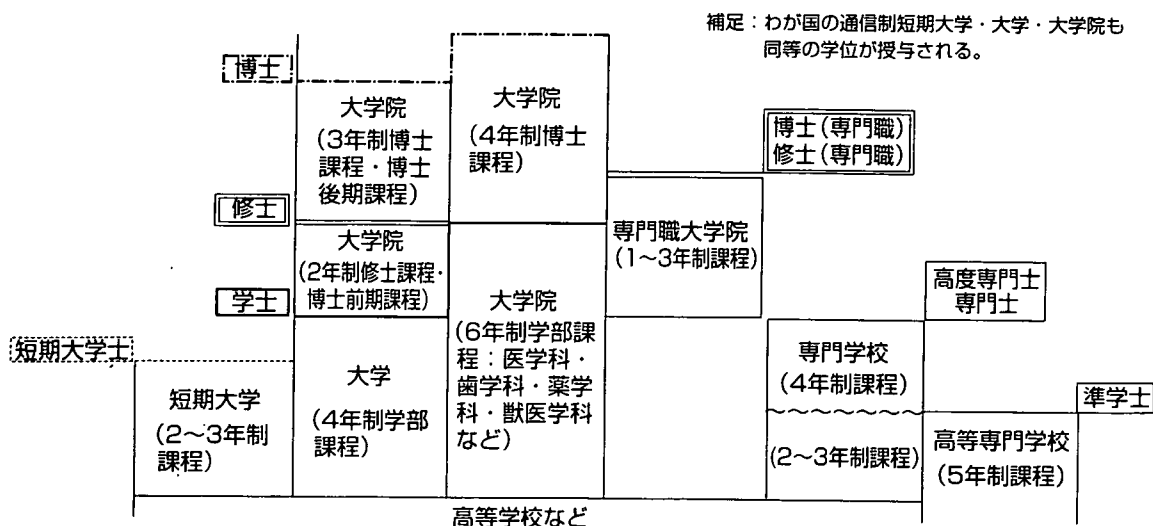今回，NIAD-UEで新設される「学士（口腔保健学）」の学位に関して，その概要を説明し，より多くの歯科衛生士学校生および歯科衛生士がキ

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補足：わが国の通信制短期大学・大学・大学院も
同等の学位が授与される。

図1　わが国おける高等教育機関の学位と称号

ャリアアップにつながる多様な道を見出せること
を目的として本稿を記すものである。

【学位と称号】

Ⅰ．学位

現在，わが国の法令により授与される学位には，
下記のものが存在する（図1）。

1．博士の学位

大学院博士課程（通信制を含む）を修了した者
に授与される学位である（学校教育法第67条およ
び第68条の2，文部科学省令学位規則第4条）。
また，各省庁大学校博士課程相当修了者がNIAD-
UEの審査に合格した者にも同等の学位が授与さ
れる（学校教育法第68条の2第4項第2項）。標
記は，「博士（○○学）」とされる。

2．修士の学位

大学院修士課程（通信制を含む）を修了した者
に授与される学位である（学校教育法第68条の2
および第4項，文部科学省令学位規則第3条）。
また，各省庁大学校修士課程相当修了者がNIAD-
UEの審査に合格した者にも同等の学位が授与さ
れる（学校教育法第68条の2第4項第2項）。標
記は，「修士（○○学）」とされる。

3．専門職学位の学位

専門職大学院課程を修了した者に授与される学
位である（学校教育法第67条および第68条の2，
文部科学省令学位規則第5条の2）。標記は，「○
○博士（専門職）」，「△△修士（専門職）」とされ

る。

4．学士の学位

大学学士課程（通信制を含む）を卒業した者に
授与される学位である（学校教育法第68条の2第
1項，文部科学省令学位規則第2条）。また，各
省庁大学校学部相当課程修了者がNIAD-UEの審
査に合格した者にも同等の学位が授与される（学
校教育法第68条の2第4項第2項）。標記は，「学
士（○○学）」とされる。

5．短期大学士の学位

短期大学（通信制を含む）を卒業した者に授与
される学位である（学校教育法第68条の2第3項，
文部科学省令学位規則第5条の4）。標記は，「短
期大学士（○○学）」とされる。なお，2005年10
月以前は，短期大学卒業者には「準学士」の称号
が授与されていた。

Ⅱ．称号

学位以外に，わが国における学術関係の称号は，
下記のものが存在し，学位と区別されている。

1．準学士

高等専門学校卒業者に付与される称号である。

2．専門士

修業年限2年以上で，修了に必要な総授業時数
が1,700時間以上の専門学校を修了した者に付与さ
れる称号である。2005年12月現在，全国2,844校
6,892学科でその称号が付与されている[1]。

3．高度専門士

修業年限4年以上で，修了に必要な総授業時数

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が3,400時間以上の体系的な教育課程が編成されている専門学校を修了した者に付与される称号である。また，大学院入学資格も認められる。2005年12月現在，全国119校192学科でその称号が付与されている[2]。

【独立行政法人 大学評価・学位授与機構】

Ⅰ．独立行政法人 大学評価・学位授与機構 （NIAD-UE）とは

NIAD-UEとは，文部科学省所管の独立行政法人であり，大学などの評価事業，学位授与事業，これらに関連する出版事業などを行っている。その事業内容は，独立行政法人大学評価・学位授与機構法などによって規定されている。

Ⅱ．学位授与事業

学位を取得する方法には，高度多様化する高等教育の中で，大学に進学し，その課程を修めるだけではなくなっているのが現状である。特に学士の学位は，教員免許や学芸員などの資格取得に必要であり，国内外への大学院進学や学士編入学の際にも必要となってくる。NIAD-UEでは，一定の基準を満たす者に対して，学位授与事業を年2回（4月期および10月期）行っており，その学位は一般の大学および大学院が授与する学位と同等のものである。

2007年現在，NIAD-UEでは，26種類の専攻分野，56種類の専攻区分の学士の学位を授与している（表1）[3]。そして，2008年4月より「学士（ロ

表1　（独）大学評価・学位授与機構が授与する学士の学位（2007年度現在）

専攻の分野	専攻区分の名称
文学	国語国文学
	英語・英米文学
	独語・独文学
	仏語・仏文学
	中国語・中国文学
	ロシア語・ロシア文学
	歴史学
	哲学
	心理学
	宗教学
教育学	教育学
神学	神学
社会学	社会学
	社会福祉学
教養または学芸	比較文化
	地域研究
	国際関係
	科学技術研究
	社会科学
社会科学	法学
法学	政治学
政治学	経済学
経済学	商学
商学	経営学
経営学	数学・情報系
理学	物理・地学系
	化学系
	生物学系
	総合理学

専攻の分野	専攻区分の名称
薬学	薬学
看護学	看護学
保健衛生学	検査技術科学
	臨床工学
	放射線技術科学
	理学療法学
	作業療法学
	言語聴覚障害学
鍼灸学	鍼灸学
栄養学	栄養学
工学	機械工学
	電気電子工学
	情報工学
	応用化学
	生物工学
	材料工学
	土木工学
	建築学
	社会システム工学
芸術工学	芸術工学
商船学	商船学
農学	農学
水産学	水産学
家政学	家政学
芸術学	音楽
	美術
体育学	体育学

※「専攻の分野」が学士授与記に記載される。
（例：学士（保健衛生学））

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