THE PATTERN OF IMMUNOPATHOBIOLOGICAL RESPONSE IN ORAL MUCOSA TO DISCLOSE THE IMMUNOPATHOBIOGENESIS OF *Candida albicans* INFECTION IN PATIENTS WITH DIABETES MELLITUS

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ABSTRACT

Candida albicans *infection is often found in oral cavity of DM patients. However, the mechanism of immune response change resulted from the infection remains unclear. Information on factors and immune response change occurring in* C. albicans *infection remains rare, because in such condition the clinical manifestation has not been induced.* C. albicans *infection may develop to become candidiasis, a manifest infectious disease, and further it becomes pre-malignant candidal leukoplakia and malignant squamous cell carcinoma.* C. albicans *infection usually occurs locally, but it may disperse to visceral organs, leading to a fatality.* C. albicans *is a normal flora, while it is also an opportunistic pathogen because it may become a pathogen in immunocompromised condition. This may occur in DM patients since high blood glucose level will react non-enzymatically to protein, changing protein structure and function to become immunogen. This study was done to disclose the immunopathobiogenesis of oral* C. albicans *infection in patients with DM. Systemic and local immune response were compared between DM groups with high HbA1c level with and without* C. albicans *and non-DM with and without* C. albicans*. We found no difference between patients with high HbA1c level with* C. albicans *and those with high HbA1c level without* C. albicans*, and between patients with high HbA1c level with* C. albicans *and non-DM patients with* C. albicans*. Difference was found between patients with high HbA1c level without* C. albicans *and non-DM patients without* C. albicans *infection, and between non-DM patients with and without* C. albicans *infection. Local immune response also showed no difference in all groups. Three predominant discriminant variables were found in those groups, and these were described in an immunopathobiological pattern. Based on this pattern, it can be summarized that the role of Th1 produces IFN-γ, increases IgM switching to IgG, which is important to prevent the occurrence of* C. albicans *infection. Conclusively, immunopathobiological pattern can be used to disclose the immunopathobiogenesis of oral* C. albicans *infection in patients with DM.*

Keywords: immunopathobiogenesis, oral immune mucosa, C. albicans *infection, Diabetes Mellitus*

INTRODUCTION

C. albicans infection often occur at oral mucosa of patients with Diabetes Mellitus (DM). However, the reduction mechanism of immunological defense in the body, which underlies the infection, remains unclearly understood (Kaposzta, 1998). *C. albicans* infection in oral mucosa of DM patients has a chronic characteristic. If it is not immediately overcome, it may develop to become a manifest infectious disease. Manifest *C. albicans* infection may also spread to various visceral organs, such as lung, kidney, liver, heart, and brain. In addition, antifungal treatment, either topical or systemic, has only temporary effectiveness in eradicating the infection and cannot prevent recurrence (Darwazeh, 1997). This can be indicated from the mortality rate of infected patients who received antifungal chemotherapy, which was reaching 70% (Matthews, 1992).

C. albicans is a normal flora and becomes pathogenic if a change in immune response occurs. In patients with Diabetes Mellitus, the change of immune response is possible since high blood glucose may non-enzymatically react with protein, leading to the increase of glycosilation, which is characterized by the increase of HbA1c level. This may affect protein structure and function, rendering it to be immunogenic (Kennedy, 1994) as it may result in the change of immune response.

To date, it is recognized that chronic mucocutaneus *C. albicans* infection results from the disturbance of cellular immunity function or Cell Mediated Immunity (CMI) (Levitz, 1996). A number of reports indicated that the result of high glycolisating process, Advanced Glycosylated End Products (AGE), is immunogenic and it may incite the production of cytokines of IFN-γ, TNF-α, TNF-β, IL-1, IL-2, IL-4, IL-6, IL-8, and IL-10 (Marohoshi, 1995).

As the stabilization of immune response is determined by the balance between IFN-γ and IL-10 levels (Hamblin, 1993), and because cytokine has a role in regulating other cellular functions in immune response, including inflammation (Cotran, 1999), it can be concluded that oral infection of *C. albicans* in DM patients is possible due to the reduction of immune

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response as indicated by the reduction of serum IFN-γ and IL-10 level and reduced response of immunocompetent cells in oral mucosa. Therefore, the investigation in this study was focused on the change of immune response as reflected by the reduction of the levels of IFN-γ, IL-10 and the response of immunocompetent cells in oral mucosa of DM patients that underlie *C. albicans* infection. The purpose of this study is to prove that immunopathobiological pattern can be used to disclose the immunopathobiogenesis of oral *C. albicans* infection.

PATIENTS AND METHODS

This was an observational cross-sectional study, observing the patients admitted at Endocrinology Outpatient Clinic, Dr Soetomo Hospital, Surabaya, as case group. The control was patients who visited Dental Clinic, Airlangga University School of Dentistry, for dental examination. The criteria were as follows: male; aged 40 - 60 years; no cigarette smoking; no prosthetic use; good or moderate oral hygiene; no dental filling; no other diseases, such as AIDS, leukemia, or hypothyroid, not receiving steroid or antibiotic therapy. DM patients should have had HbA1c > 8%, and non-DM patients ≤ 6%. Total sample in each group was minimally 10.

The dependent variables in this study were the levels of IFN-γ (Th1), and IL-10 (Th2), and oral mucosa immunocompetent cells (lymphocyte, plasma cells, PMN, macrophage, monocyte, and eosinophil). The independent variables were Diabetes Mellitus, oral *C. albicans* infection as determined from culture on sabouraud agar media. The confounding variables were HbA1c level, which, using RIA method; poorly regulated DM patients with HbA1c level > 8%; and patients with good-moderate oral hygiene (OH).

Procedures

Patients visiting Endocrinology Outpatient Clinics, Dr Soetomo Hospital, Surabaya, were selected according to the criteria. Oral examination was carried out to define OH. Selected patients were those who had good (OHI = 0.1 - 1.2), and moderate OH (OHI = 1.3 - 2.0). Afterwards, they were asked to sign the informed consent. Venous blood was taken as much as 3 cc by medical analysts, and 1 cc was put into EDTA tube for HbA1c examination and 2 cc to heparin tube for lymphocyte (cytokine) examination. To examine the *C. albicans* growth, cotton swab was applied to the dorsal of the tongue, implanted into sabouraud dextrose agar, incubated 2 x 2 = 1 hour at 37°C, and the presence of colony was observed.

To observe the immunocompetent cells, a scrap was applied to buccal mucosa and the scrap was directly put into glass object and fixed with acetone for 10 minutes. The samples were stained with Papanicolau and observed using microscope (Olympus) to count the lymphocytes, plasma cells, PMN, macrophage, monocyte, and eosinophil per visual field in 400 times enlargement. Statistical analyses used in this study were normality tests, Anova, Manova, and Discriminant analysis.

RESULTS

Table 1. Mean and standard deviation of each variable in DM and control groups.

Variables	Groups							
	DM				Control			
	+ Inf. C. alb n = 10 A1		- Inf. C. alb n = 10 A2		+ Inf. C. alb n = 10 B1		- Inf. C. alb n = 10 B2	
	X	SD	X	SD	X	SD	X	SD
Systemic								
IFN-γ	.032	.016	.066	.044	.036	.027	.124	.079
IL-10	.153	.086	.169	.161	.171	.151	.135	.077
Local:								
Lymphocyte	.359	.582	.330	.551	.671	.613	.455	.607
Plasma cell	.079	.248	.157	.331	.079	.248	.111	.350
PMN	1.322	.470	.1.240	.467	1.482	.061	1.049	.725
MØ	.469	.630	.609	.560	.736	.658	.679	.724
Monocyte	.942	.524	1.096	.463	1.168	.430	.909	.640
Eos	.615	.675	.512	.668	.660	.669	.479	.621

Table 2. Discriminant test of IFN-γ and IL-10 levels in four sample groups, each comprising 10 respondents

	A1	A2	B1	B2
A1	-	F = 0.086 p > 0.05	F = 0.752 P > 0.05	-
A2	F = 0.086 p > 0.05	-	-	F = 0.044 p < 0.05
B1	F = 0.752 p > 0.05	-	-	F = 0.005 p < 0.05
B2	-	F = 0.044 p < 0.05	F = 0.005 p < 0.05	-

Table 3. Discriminant test of immunocompetent cells count in oral mucosa in four sample groups, each comprising 10 respondents

	A1	A2	B1	B2
A1	-	F = 0.750 p > 0.05	F = 0.699 P > 0.05	-
A2	F = 0.750 p > 0.05	-	-	F = 0.905 p < 0.05
B1	F = 0.699 p > 0.05	-	-	F = 0.947 p < 0.05
B2	-	F = 0.905 p < 0.05	F = 0.947 p < 0.05	-

Immunopathobiological Response Pattern

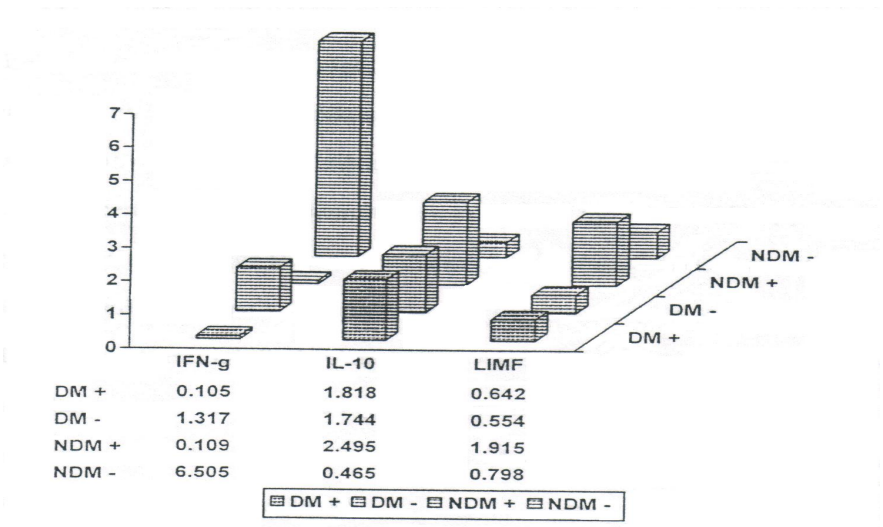

Figure 1. Immunopathobiological pattern in DM and control groups. X axis represents the discriminant variables, and y axis is reflecting the effectiveness of each discriminant variables.

DISCUSSION

Diabetes mellitus is a metabolic abnormality characterized by hyperglicemia and closely related to the occurrence of infection. Infection occurs when host immune response is decreasing. In DM patients, the decrease of immune response is possible since hyperglicemia may increase non-enzymatic glycosilation, as marked by the increase of HbA1c level. This is because glucose covalent binding may change the structure and function of protein, including immunoglobulin that provides contribution to various DM complications, one of which is infection (Sasaki, 1993). Nawroth (1999) stated that AGE is a novel approach in biochemistry and molecular biology in disclosing the pathophysiology of various chronic diseases due to DM complications. Although at early stages the glycosilation process that produces Schiff base or Amadori products remains reversible, the process tends to form an irreversible molecular complex (Chappey, 1997), resulting in the production of advanced glycation end product (AGE). AGE provides pathogenic effects by interacting with more specific cellular receptors (Lalla, 1998). This is because AGE may stimulate the induction of cross-reaction that leads to the change of protein biophysical characteristics by rising the fibrous protein rigidity and resistance against protease (Sterberg, 1995; Nawroth, 1999).

This study showed that in both DM groups systemic immune response was decreasing, as reflected by the reduction of IFN-γ level. However, after multivariate statistical test was carried out, there was no significant difference between DM group with *C. albicans* infection and that without infection, with F Wilks = 0.086 ($p > 0.05$). This indicates that DM patients have reduced immune response due to glycosilation, so that the influence of *C. albicans* presence on the change of immune response was not high. The results of multivariate test showed no significant difference. However, when we observed the role of IFN-γ only, the result of univariate test had demonstrated significant difference between DM patients with and those without *C. albicans*, with $F = 0.033$ ($p < 0.05$).

AGE accumulation in tissue increases along with age. Blood glucose level in elderly will increase the AGE. Therefore, it can be concluded that elderly with DM have an increasing accumulation of AGE (Chappey, 1997; Nawroth, 1999). Such increasing accumulation may stimulate changes in tissue structure, and these changes may become permanent or irreversible, damaging various components of extracellular matrix and stimulate the production of cytokines and free radicals and change the structure of intracellular protein (Brownlee, 1995).

Results of this study showed that the immune response of control group with *C. albicans* infection decreased, and there was a highly significant difference from control group without *C. albicans*, with F Wilks = 0.005 ($p < 0.05$). This means that the presence of *C. albicans* also suppresses immune response. Zegarelli (1993) confirmed this fact by stating that oral *C. albicans* infection is also found either in locally or systemically immunocompromised host. He also stated that the infection of *C. albicans* itself could also suppress host immune system. In control group without *C. albicans* infection, the mean level of IFN-γ was 0.124 and that of IL-10 was 0.136. This indicated that the levels of IFN-γ and IL-10 were similar. This is also in line with theoretical basis that the stability of immune system is determined by the balance between IFN-γ and IL-10 (Hamblin, 1993). The results of this study also showed that immune response in DM patients without *C. albicans* infection decreased and there was significant difference from control without infection with F Wilks = 0.044 ($p < 0.05$). This is possible because a high HbA1c level may cause damaged function of macrophage as APC.

According to Grossi and Genco (1998), an infection is mediated by an uncontrolled cycle from cytokine synthesis and secretion due to chronic stimulation of immunogen, including the product of microorganisms. This also explains the importance of AGE in cytokine response in patients with DM. As to correlation between cytokine and *C. albicans* infection, such correlation results from inadequate response of host IFN-γ (Szaradkiewics, 1998), since IFN-γ is more superior than G-CSF or GM-CSF in increasing PMN microbicidal activity against opportunistic fungi (Gaviria, 1999). The results of studies on *C. albicans* infection in murine showed that the resistance against the disease is related to Th1 response, i.e., IFN-γ (Lavigne, 1998).

The results of this study showed that systemic immune response in DM patients with *C. albicans* infection and control with infection is reducing, as reflected by the decreasing level of IFN-γ, although significant difference was not found ($F = 0.752$, $p > 0.05$). This indicated that *C. albicans* also suppresses immune response. This is possible since the components of *C. albicans* cell wall also comprised of protein structure, i.e., mannoprotein, glucan, and chitin, all of which are virulence factors. Results of in vitro study showed that *C. albicans* adherence to the mucosa is affected by some factors, such as the mucosa of donor cells, time of mucosal removal, the original site of the mucosa, cell size, and mucosal viability (Olsen, 1990). Even though the certain mechanism, by which *C. albicans* infection

in DM patients becomes high, remains unknown, studies showed that this is due to the change of host immune response and virulence factor of *C. albicans* (Plotkin, 1996).

Although information describing inflammatory response and host defense mechanism in *C. albicans* infection is very limited (William, 1997; Leigh, 1998), this study showed that the predominant oral mucosal immunocompetent cell was PMN. This is also supported by another study revealing that the earliest response playing a role in *C. albicans* infection is exerted by PMN and macrophage (Plotkin, 1996). The results of this study revealed no significant difference in the change of immune response in oral mucosa between DM patients with *C. albicans* infection, DM patients without infection, control with infection, and control without infection. This was because the increase of both HbA1c and *C. albicans* played a role as immunogene, or, possibly, because the observed variables were at cellular level, instead of molecular level. Other possibility was that changes found locally in oral cavity had occurred at systemic level, as could be reflected in saliva. These possibilities were not investigated here, so they become the shortcomings of this study. As reported by Leigh (1998), in host defense against oral *C. albicans* infection, the role of local CMI as reflected from salivary cytokine level can be as the same as or even more important than cytokines in peripheral areas. This report is supported by Chalacombe (1997) who reported that oral cavity fluids could be used as marker for mucosal immune response. Darwazeh (1997) also reported that the activity of nystatin in the inhibition of *C. albicans* adherence to buccal epithelial mucosa is possibly hindered by certain component of the saliva.

Furthermore, to disclose the immunopathobiogenesis of *C. albicans* infection in DM patients, discriminant test should be undertaken to obtain the most predominant discriminant variable to create a pattern. For this purpose, the means of the discriminant variables were multiplied with a constant that reflects the magnitude of the role of each variable. The results of discriminant analysis showed that from 8 variables in this study, it was only 3 variables that were predominant to discriminate the four sample groups, i.e., IFN-γ, IL-10 and lymphocytes, so that the immunopathobiological pattern is only formed by the three variables (Figure 1). It is apparent that the most predominant variable is IFN-γ. This indicates that IFN-γ provides the highest effectiveness in the protection against *C. albicans* infection. This can be elaborated in four patterns as follows:

1. Pattern A1 is used to explain the decrease of immune response in DM patients that leads to the susceptibility to *C. albicans* infection. The decrease of immune response occurred due to the increase of glycosilation in DM that causes the formation of glucitol lysin, an important part of the epitope. Since macrophage function in DM patients is damaged, the triggering of T cells by macrophage-produced cytokines becomes ineffective, resulting in an excessive reduction of IFN-γ production. This condition enhances Th2 to compensate by producing IL-10, although it is not sufficient, as indicated by low total lymphocyte counts.
2. Pattern A2 is used to explain the decrease of immune response in DM patients. In this pattern, there is a reduction of IFN-γ. Although it is not excessive, it is still not compensating the increase of IL-10, so that total lymphocyte still decreases, even though it is effective enough to prevent *C. albicans* infection.
3. Pattern B1 is used to explain the decrease of immune response in non-DM patients that are susceptible to *C. albicans* infection. Apparently, there is a mechanism in which *C. albicans* itself is able to suppress Th1 function, resulting in the insufficient reduction of IFN-γ, which is not compensating the increase of IL-10. Thereby, the patients remain susceptible to infection.
4. Pattern B2 is used to explain a reliable immune surveillance in non-DM patients who do not experience *C. albicans* infection. This reliable immune surveillance is possible because in such condition the function of macrophage is excellent, so that the triggering of T cells, particularly Th1, may produce optimal IFN-γ that may trigger the switching from IgM to IgG, so that IgG can assist the function of macrophage to optimalize phagocytic function. The result shows that the individual is not infected with *C. albicans*.

The results of this study are in line with those reported by Kaposzetta (1998), that in his in vitro study the IFN-γ was found to have an important role in host defense against *C. albicans* infection. Hayashi (1995) also reported that Th1-produced cytokines, particularly IFN-γ, play an important role in inflammatory process and the destruction of β pancreatic cells in DM patients. Other study also reported that IFN-γ is a pleiotropic cytokine implicated in immunopathogenetic mechanism that results in inflammation or infectious diseases (Egwuagu, 1999). IFN-γ plays a role as immunomodulator because it activates inflammatory cells and it also plays a role in natural immunity (Cotran, 1999).

CONCLUSIONS AND RECOMMENDATIONS

It is concluded that the immunopathobiological pattern can be used to disclose the immunopathobiogenesis of

oral *C. albicans* infection in patients with DM. It is recommended to conduct further studies to examine cytokine in the saliva to detect local immune response in oral cavity and to investigate the change of oral mucosal immune response at molecular level in relations to the protection against *C. albicans* infection.

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