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Immunoglobulin A (IgA), IgA1, and IgA2 Antibodies to *Candida albicans* in Whole and Parotid Saliva in Human Immunodeficiency Virus Infection and AIDS

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Human immunodeficiency virus (HIV)-infected individuals are predisposed to recurrent oral candidiasis, and, although it has been assumed that this is because of deficient mucosal immune responses, this has not been properly established. The present study aimed to compare the concentrations and secretion rates of immunoglobulin A (IgA) and IgA subclass antibodies to *Candida albicans* in whole and parotid saliva samples from HIV-infected patients, AIDS patients, and control subjects. Levels of IgA antibody to *Candida* species in whole saliva were higher in the HIV group than in the controls and were highest in the AIDS group ($P < 0.05$). In parotid saliva, the mean antibody levels were significantly greater in HIV-positive patients than in controls ($P < 0.05$) but fell to lower levels in the AIDS group. The secretion rates of *Candida* antibodies in parotid saliva were reduced in AIDS patients compared with HIV patients. The specific activities of the IgA antibodies and both subclasses were significantly higher in the HIV and AIDS patients than in the controls in both whole and parotid saliva ($P < 0.05$). Antibody levels were significantly correlated with the numbers of *Candida* organisms isolated from saliva ($P < 0.05$). These results suggest clear differences in salivary antibody profiles among HIV-infected, AIDS, and control subjects and are indicative of a response to antigenic challenge by infecting *Candida* species. No obvious defect in the mucosal immune response in the HIV or AIDS groups that might account for the increased prevalence of candidiasis was apparent.

The main sequelae of human immunodeficiency virus (HIV) infection are frequent and persistent opportunistic secondary infections at mucosal surfaces. Oral candidal infections are the most common mucosal manifestation of HIV infection and may occur in up to 50% of HIV-infected subjects (13) and 90% of AIDS patients (13, 15, 19). This suggests that the oral mucosal defense mechanisms of these patients are compromised. Immunological protection of mucosal surfaces is mediated primarily by the secretory immune system, particularly immunoglobulin A (IgA) in secretions, which affords protection by inhibiting adherence and penetration of microorganisms and foreign proteins to mucosal tissues (6, 22, 25, 26). Secretory IgA may play a key role in protection against oral candidiasis, since IgA molecules have been identified on the surfaces of the *Candida albicans* cells (8), and it has been shown that secretory IgA antibodies can inhibit the adherence of *C. albicans* to epithelial cells (5, 24). Decreased production of IgA might therefore favor oral colonization and the development of candidiasis.

HIV infects cells via interactions with CD4 receptor sites on a number of human cell types, including the helper/inducer subset of T-lymphocytes (7) which play a pivotal role in most immunological processes, including the induction of secretory IgA responses (17). Abnormalities of salivary immunoglobulin levels in patients infected with HIV have been reported. Müller et al. (18) found that patients with AIDS had significantly lower levels of IgA, IgA1, and IgA2 in parotid saliva than control subjects. Jackson (10) also reported that IgA2 was significantly reduced in whole saliva from AIDS patients compared with controls. These observations support the suggestion that the level of secretory IgA may contribute to the frequent mucosa-related opportunistic infections seen in these patients.

There are few reports of specific antibodies in relation to mucosal immunity in HIV infection. A study of 10 HIV-infected subjects found that levels of IgA antibody to *C. albicans* in whole saliva were raised but found no correlation between candidal carriage and antibody titers (23). Another preliminary study reported similar increases in *C. albicans* IgA antibody levels in whole saliva from HIV-infected patients but noted decreased levels in patients with candidiasis (27). These somewhat contradictory studies suggest that alterations in IgA responses may occur in association with HIV infection; however, the nature of this association and the role of specific antibody in protection of mucosal surfaces remain to be fully elucidated. Therefore, the aims of the present study were to analyze the salivary concentrations and secretion rates of IgA and the subclasses IgA1 and IgA2 to *C. albicans* in whole and parotid saliva from HIV-infected, AIDS, and control subjects.

MATERIALS AND METHODS

Subjects and collection of saliva. The study population consisted of 124 males: 45 asymptomatic HIV antibody-positive subjects without AIDS-defining criteria with a mean age of 36 years (standard deviation [SD], 11.1; range 20 to 69), 27 AIDS patients with a mean age of 40 years (SD, 10.5; range 24 to 64), and 52 male control subjects with a mean age of 30 years (SD, 11.9; range 19 to 73). Asymptomatic HIV-infected subjects who had not received antibiotic or antimycotic therapy for at least 3 months were selected, and none of the AIDS subjects

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were on antibiotic or antimycotic therapy at the time of sampling. Whole unstimulated saliva samples were collected from all subjects by expectoration into sterile plastic universals for 10 min and were clarified by centrifugation at 11,500 × *g* for 10 min. Parotid saliva samples were collected from 21 HIV-infected, 11 AIDS, and 24 control subjects by using Lashley cups (16) placed directly over one parotid duct and with salivary flow stimulated by the application of 100 μl of 5% citric acid to the tongue at 2-min intervals for 10 min.

Saliva samples were cultured for the presence of yeasts by plating 100 μl onto Sabouraud's dextrose agar plates and incubating at 37°C for 72 h. The CFU of yeasts per ml of saliva were counted, and isolates were identified to species level by using the API 20 AUX system (BioMerieux, Marcy l'Etoile, France).

Detection of antibodies. Levels of IgA, IgA1, and IgA2 antibodies to *C. albicans* NCPF 3153 (serotype A) in saliva were determined by a solid-phase enzyme-linked immunosorbent assay (ELISA) (2). Strain NCPF 3153 was considered antigenically representative of *C. albicans*, since 20 samples of saliva assayed against 100 other strains of *C. albicans* isolated from HIV-infected and control subjects gave mean antibody levels that were not significantly different from those found against NCPF 3153. *Candida* cells were grown on Sabouraud's dextrose agar and were suspended overnight in buffered formal saline. The cells were washed three times in phosphate-buffered saline (PBS) containing 0.0005% sodium azide (PBS-azide) and then suspended in PBS containing 0.3% methyl glyoxal to an optical density of 1.7 at 540 nm. Immulon 2 microtiter plates (Dynatech Laboratories, Inc., Chantilly, Va.) were coated with *Candida* cells by incubation with 100 μl of yeast suspension in each well at 37°C for 2 h. The plates were washed three times with PBS-azide, and subsequent nonspecific binding was blocked by incubation at 37°C for 2 h with 200 μl of PBS containing 0.5% bovine serum albumin (BSA) and 0.05% Tween 20 (T20). Saliva samples were diluted 1:5 in PBS-BSA-T20, dispensed into the top row of each microtiter plate, and diluted further to 1:640 in eight doubling serial dilutions, leaving 100 μl in each well. Salivary IgA bound during overnight incubation at 4°C was then detected by incubation for 2 h at 37°C with 100 μl of mouse monoclonal IgG anti-human IgA (diluted 1:1,000), IgA1 (1:500), or IgA2 (1:500; Becton Dickinson, San Jose, Calif.) and then by incubation for 1 h at 37°C with 100 μl of rabbit anti-mouse IgG alkaline phosphatase conjugate (1:300; Sigma Chemical Co., Poole, England). Phosphatase activity was assessed at room temperature with a 100-μl *p*-nitrophenol phosphate substrate (1 mg/ml; Sigma) dissolved in diethanolamine buffer (pH 9.8). The reactions were allowed to proceed until sufficient yellow had developed (20 to 60 min) and were then stopped by the addition of 50 μl of 3 M NaOH prior to reading of the plates in a Dynatech automatic ELISA reader at 405 nm. All antibody solutions were prepared in PBS-BSA-T20. The microtiter plates were washed three times with PBS between all stages.

Salivary antibody concentrations were calculated by reference to a pooled standard saliva obtained from 10 healthy males with high levels of anti-*Candida* antibody activity. The standard saliva was assigned an arbitrary value of 1,000 U and was assayed in duplicate for every microtiter plate. Antibody concentrations were determined from the mean of all values falling within the range of the standard curve. The eight dilutions were also used to compare parallelism between the standard and sample curves. Coefficients of variation for each sample were calculated by dividing the standard deviations of the antibody concentrations of the dilutions used, determined by reference to the standard curve, by the mean antibody levels. Samples with coefficients of variation in excess of 15% were retested. Secretion rates were calculated by multiplying salivary concentrations by salivary flow rates, and specific activities were calculated by dividing salivary concentrations by total IgA or IgA subclass concentrations. The data were analyzed by an unpaired Student's *t*-test, the Mann-Whitney U test, or the chi-square test as appropriate.

Total IgA, IgA1, and IgA2 concentrations were measured by a sandwich ELISA technique. Microtiter plates were coated with 100 μl of a 1:1,000 dilution of rabbit anti-human IgA (Dakopatts A/S, Glostrup, Denmark) in PBS-azide by incubation at 37°C for 2 h. Doubling dilutions of saliva were made from 1:500 to 1:64,000 for IgA and from 1:100 to 1:12,800 for IgA1 and IgA2. Bound IgA was detected as in the *Candida* ELISA, and salivary IgA concentrations were calculated by reference to a standard preparation of purified human colostral IgA (Sigma). IgA in both colostrum and saliva has been shown to consist predominantly of secretory IgA, and the calculated concentrations of IgA1 and IgA2 were adjusted according to the IgA1/IgA2 ratio in colostrum, estimated to be 53:47 (4, 9, 14). Standard curves with colostrum IgA were constructed from six serial dilutions, in duplicate, beginning at 160 ng/ml.

Antibody specificity. Antibody specificity was determined by adsorption of six saliva samples with formalin-fixed *C. albicans* NCPF 3153 whole cells. A washed suspension of fixed *C. albicans* cells in PBS was adjusted to an optical density of approximately 1.5 at 600 nm, and the cells were centrifuged to form a pellet. The supernatant was replaced by saliva diluted 1:4 with PBS, and adsorption was performed at 37°C for 1 h and then overnight at 4°C. The cells were removed by centrifugation, and the supernatant was assayed for *C. albicans* antibodies by ELISA as described.

RESULTS

Antibodies to *C. albicans*. Concentrations of IgA, IgA1, and IgA2 antibodies specific to *C. albicans* in whole saliva were greater in both the HIV-infected and the AIDS groups than in the control subjects (Fig. 1a). These differences were statistically significant for AIDS patients compared with control subjects for IgA and IgA1, and also for IgA and IgA2 in the HIV-infected subjects ($P < 0.05$; Fig. 1a). In parotid saliva, statistically significant increases in IgA, IgA1, and IgA2 antibody levels were found in HIV-infected and AIDS subjects compared with control subjects ($P < 0.05$; Fig. 1b). There was no obvious change in the IgA1/IgA2 ratio in HIV-infected or AIDS patients compared with control subjects.

Adsorption of saliva samples with formalin-fixed *C. albicans* cells reduced the antibody titer by greater than 95%.

Specific activity. *Candida* antibody-specific activities (in units per microgram of IgA) were calculated by dividing the *Candida* IgA antibody levels (units per milliliter) by the total IgA concentrations (micrograms per milliliter) in saliva. The specific activities in whole saliva were markedly increased in both the HIV-infected and AIDS groups compared with the controls for both of the two subclasses ($P < 0.05$; Fig. 2a). A similar pattern was found with parotid saliva (Fig. 2b), although the specific activity in the AIDS group, which was greater than that in the controls, was less than that in the HIV-infected group.

Secretion rates. Secretion rates are a function of both antibody concentrations and whole or parotid saliva flow rates, expressed as the numbers of antibody units of IgA, IgA1, or IgA2 secreted per minute. The mean unstimulated whole saliva flow rates for the HIV-infected, AIDS, and control

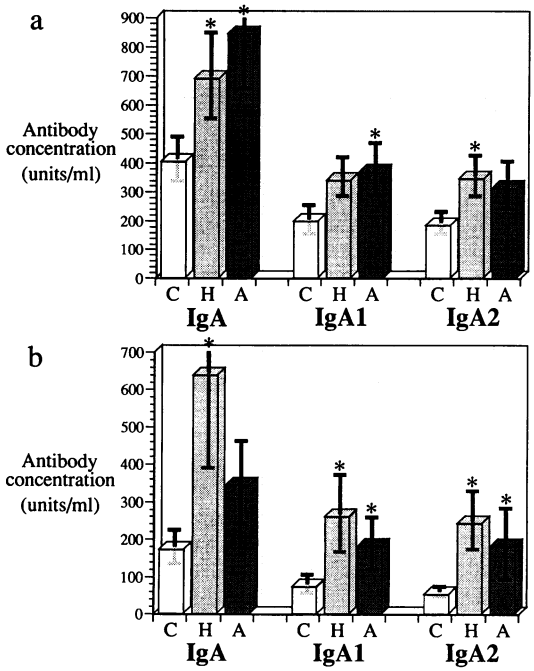

FIG. 1. Concentrations of IgA, IgA1, and IgA2 antibodies to *C. albicans* in whole (a) and parotid (b) saliva from control subjects (C) and HIV-infected (H) and AIDS (A) patients. Error bars refer to the SEMs.

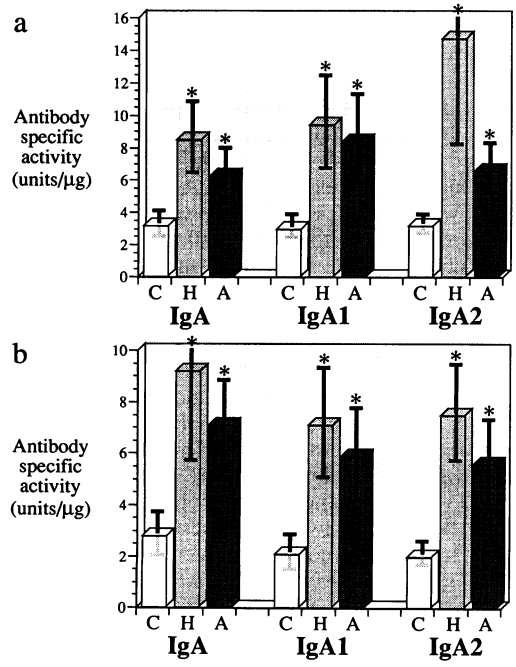

FIG. 2. Specific activities of anti-*Candida* IgA, IgA1, and IgA2 antibodies in whole (a) and parotid (b) saliva from control subjects (C), HIV-positive subjects. (H), and AIDS patients (A). Error bars refer to the SEMs.

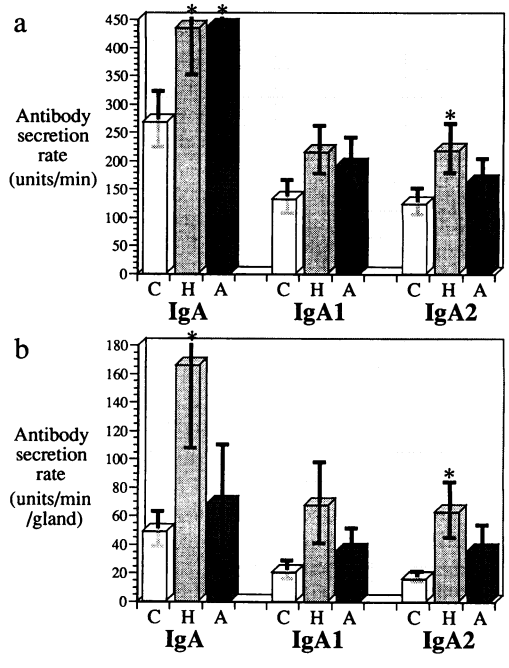

FIG. 3. Anti-*Candida* IgA, IgA1, and IgA2 antibody secretion rates in whole (a) and parotid (b) saliva from control subjects (C), HIV-positive subjects (H), and AIDS patients (A). Error bars refer to the SEMs.

groups were 0.63 (± 0.07), 0.52 (± 0.10), and 0.67 (± 0.04) ml/min (± standard error of the mean [SEM]), respectively. The mean secretion rate of antibodies in the AIDS group was significantly greater than that for the control group ($P < 0.05$; Fig. 3a), even though the salivary flow rates were lower. The mean stimulated parotid saliva flow rates for the HIV-infected, AIDS, and control groups were 0.26 (± 0.06), 0.20 (± 0.04), and 0.29 (± 0.03) ml/min per gland (± SEM), respectively. The mean parotid flow rate of the AIDS group was significantly lower than that of the control group ($P < 0.05$) and resulted in mean antibody secretion rates that were not significantly different from those of the controls (Fig. 3b). However, the significant increases in IgA and IgA2 antibody levels in the parotid saliva of the HIV-infected group (Fig. 1b) were maintained in the secretion rates ($P < 0.05$; Fig. 3b).

***Candida* species in saliva.** Thirteen of the 52 control subjects carried *C. albicans* in their saliva, but only 2 carried more than 1,500 CFU/ml of saliva. In contrast, 18 of the 44 HIV-infected patients ($P < 0.001$) and 11 of the 27 AIDS patients ($P < 0.001$) had more than 1,500 yeast CFU/ml of whole saliva (Table 1). All of the yeasts isolated from the control group were identified to species level as *C. albicans*, and although

TABLE 1. Carriage rates of yeasts in whole saliva of control, HIV-infected, and AIDS subjects

Subject	No. (%) of subjects with		
	<10 CFU/ml	10–1,500 CFU/ml	>1,500 CFU/ml
Control ($n = 52$)	39 (75)	11 (21)	2 (4)
HIV infected ($n = 45$)	13 (29)	14 (31)	18 (40)[a]
AIDS ($n = 27$)	10 (37)	6 (22)	11 (41)[a]

[a] Significant difference ($P < 0.001$) compared with control subjects.

TABLE 2. Whole-saliva IgA antibodies to *Candida* species in relation to candidal carriage in HIV-infected and AIDS subjects

Salivary *Candida* count (CFU/ml)	Anti-*C. albicans* IgA (U/ml of saliva ± SEM)
<10 (n = 23)	490 ± 157
>10 (n = 49)	860 ± 158[a]
>5,000 (n = 16)	1,077 ± 376[a]

[a] Significant difference ($P < 0.05$) compared with <10 CFU/ml.

most (32 isolates) of the 47 isolates obtained from the HIV-infected- and AIDS groups were *C. albicans*, other species were also found, including *C. paratropicalis* (6), *C. tropicalis* (2), *C. glabrata* (1), *Trichosporon capitatum* (1), *Kloeckera apiculata* (1), and four *Candida* strains that could not be reliably identified to species level.

An analysis of antibody concentrations in whole saliva according to salivary *Candida* load (Table 2) indicated that IgA antibody levels increased significantly with the number of *Candida* CFU in saliva ($P < 0.05$). In HIV-infected and AIDS subjects with recoverable *Candida* CFU in their saliva, the mean level of IgA antibody was significantly higher than that in subjects from whom no *Candida* CFU were isolated ($P < 0.05$) and was highest in subjects with greater than 5,000 CFU/ml.

DISCUSSION

Yeasts are found as oral commensals in about 40% of the population, but usually in low numbers (1), while counts of greater than 10^4 CFU/ml are commonly found in patients with various forms of candidiasis (3). The ubiquitous nature of *Candida* species and relative rarity of clinical manifestations in the absence of underlying systemic disorders emphasize the role of host factors in the etiology of candidiasis. Host defense mechanisms against diseases such as oral candidiasis may involve both the secretory and systemic immune systems, although in most forms of candidiasis, the infecting organisms appear to be limited to the epithelial surface. This suggests that humoral immunity and especially secretory IgA may play a role in disease modulation (3).

A number of studies have investigated salivary antibodies to *Candida* species, but few have considered the effect of HIV infection on mucosal immune responses, despite the associated high prevalence of candidiasis. It has been shown for non-HIV-infected subjects that salivary IgA antibodies are raised in patients with candidiasis and that salivary IgA antibodies are able to inhibit the adherence of *C. albicans* to buccal epithelial cells (5). Salivary IgA subclass antibodies to a *Candida* antigen extract have also been reported for patients with oral candidiasis and were found to be significantly higher in such patients, compared with control subjects (11). Previous studies have reported that IgA antibodies to *C. albicans* are higher in whole saliva from HIV-infected patients (23, 27). The present investigation concurs with these results showing increases in IgA antibodies to *C. albicans* in HIV-infected and AIDS patients in parotid as well as in whole saliva (Fig. 1). These differences reflected larger increases in the specific activities of antibodies to *Candida* species (Fig. 2), presumably with a concurrent decrease in levels of antibodies directed against other microorganisms. The ability of both the HIV-infected and the AIDS patients to produce high levels of anti-*Candida* antibodies in whole and parotid saliva (Fig. 1), despite an overall decrease in secretory IgA production, suggests that an adequate mucosal immune response to infecting *Candida* species is maintained. This increase in antibody secretion may be related to antigen challenge, since almost half of the HIV-infected and AIDS patients carried more than 10^3 yeast CFU/ml of saliva, and salivary antibody production significantly correlated with salivary *Candida* load (Table 2). Increased salivary IgA *Candida* antibody concentrations may, therefore, be a consequence of infection, instead of having a protective role.

The correlation between oral infection and salivary response could also be due in part to ingestion of *Candida* cells. Antibodies can be induced in saliva either by local immunization or by stimulation of gut-associated lymphoid tissue by ingestion of antigen. This leads to the release of IgA plasma cell precursors from Peyer's patches that migrate via the vascular network to mucosal tissues such as the salivary glands. Local immunization leads to a proliferation of these cells and an enhanced local secretory IgA response (3). It may be possible to analyze a protective aspect of this increased response by undertaking longitudinal studies of HIV-infected subjects with high and low antibody titers. However, it would be necessary to monitor these patients sequentially and to look at other parameters including antibody-binding avidity.

Although candidal carriage appears to be related to salivary *Candida* antibody levels, the presence of large numbers of infecting yeast cells could conversely adsorb out specific antibodies in the oral cavity, leading to artificially lowered antibody concentrations, at least in whole saliva. Also, the production of candidal proteases able to degrade IgA or the secretion of specific IgA1 proteases by various oral bacteria (12, 20) may similarly affect antibody levels. The concentration of IgA antibodies measured in whole-saliva samples may also be influenced by supplementation with antibodies from crevicular fluid and mucosal serum transudate. These theoretical considerations illustrate the possible advantages of the direct collection of uncontaminated parotid secretions, although different salivary glands make different contributions to whole saliva. Parotid anti-*Candida* IgA, IgA1, and IgA2 antibody concentrations, specific activities, and antibody secretion rates were all lower in AIDS patients than in HIV-infected subjects (Fig. 1b, 2b, and 3b). This falling titer may therefore be a useful indicator of the development of the immunodeficiency that marks the progression toward AIDS.

HIV infection has been associated with a form of salivary gland disease that is pathologically similar to Sjögren's syndrome (21). Although none of the subjects in the present study were diagnosed with HIV-salivary gland disease, the mean parotid saliva flow rate of the AIDS group was significantly reduced compared with that of the control subjects. Decreased saliva flow will affect antibody secretion rates, which may be a better reflection of local immunity than actual concentrations of antibodies in saliva, since the total delivery of antibodies to the mucosa may be more relevant to secretory immune function. In parotid saliva, the marginally decreased flow rate in the HIV-infected subjects is more than compensated for by increased antibody concentrations, although the significant decrease in the parotid saliva flow rate in the AIDS subjects results in an IgA delivery rate to the oral cavity that is only slightly raised compared with that in the control subjects (Fig. 1b and 3b). This factor, combined with a progressively compromised immune system, may account for the notable increase in prevalence of oral candidiasis upon progression to AIDS. However, this study does not support the view that the opportunistic infections of mucosal surfaces associated with HIV disease are largely attributable to deficient mucosal immune responses. Although altered antibody concentrations were detected and a decreased humoral response was noted in the progression from HIV infection to AIDS, it is likely that

other factors contribute to the increased prevalence of candidiasis found in HIV-infected individuals.

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