Original Article

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Diagnosis of oral manifestations in HIV/AIDS patients who used HAART and developed diabetes mellitus

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Abstract

Aim: To assess the prevalence of oral manifestations in HIV/AIDS patients and a possible correlation of the development of diabetes mellitus due to highly active antiretroviral therapy (HAART). **Methods:** 56 patients were examined, divided into two groups, Group 1, the HIV group, with 28 patients known to be HIV+, who developed diabetes mellitus due to HAART, and Group 2, the control group, with 28 patients with HIV- diagnosed with diabetes mellitus. **Results:** In Group 1, normal salivary flow rate and buffering capacity were observed in 18 (64.3%) patients, but the bleeding index high (46.53%) and higher incidence of periodontal disease was found in this group. In Group 2, 11 (39.2%) and 15 (53.5%) patients had low and normal salivary flow rate, respectively. High T-CD4 indices with mean value of 22.46 for each patient, showing xerostomia in 9 (32.1%) patients and dental caries in 11 (39.3%). **Conclusions:** Regarding the oral and general manifestations, the HIV group showed higher rates of pathologies when compared with the control group. The HIV group and the control group were diagnosed with diabetes, but this condition in the HIV group presented earlier than in the control group, suggesting a possible association with HAART.

Keywords: AIDS, HIV, diabetes m*ellitus*.

Introduction

Acquired immunodeficiency syndrome (AIDS) was first described in 1981 in the United States, and its causative agent is the human immunodeficiency virus (HIV). Since 1996, with the advent and introduction of highly active antiretroviral therapy (HAART), a profound impact on the natural history of HIV infection was observed, with a remarkable increase in the survival of HIV-infected individuals, transforming the panorama of the disease. Today, the morbidity and mortality ratios become significantly smaller in those adhering to the treatment. However, although the substantial benefits of HAART far outweigh its potential risks, it is known that prolonged treatment may result in a variety of disorders related to compliance and toxicity. Long-term HAART is accompanied by undesirable adverse side effects such as cardiovascular and metabolic alterations that are risk factors for cardiovascular disease and diabetes mellitus (DM). Metabolic alterations include dyslipidemia, diabetes mellitus type 2 (DM2), insulin resistance, hyperlactatemia, hyperlipidemia. A morphological, anatomical, metabolic change in body fat and bone metabolism is the set of changes known as lipodystrophy syndrome[1-8].

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The anatomical changes include lipoatrophy in the region of the face (facial fat loss), loss of limb fat (upper and lower), especially of the superficial veins, loss of fat from the buttocks associated or not with the accumulation of fat in the abdomen mainly due to fat deposition, visceral fat accumulation in the posterior cervical region (GIBA), accumulation of fat in the breasts that can occur in both women and men. Metabolic changes include the increase of serum lipids and peripheral insulin resistance resulting in DM[9-12].

Insulin resistance (IR) is common in HIV-seropositive patients, particularly among those receiving protease inhibitor (PI) and is more prevalent among those with lipoatrophy or fat accumulation in the visceral region. The prevalence of hyperglycemia and diabetes is significantly higher in those receiving HAART, compared to the general population. The occurrence of diabetes is four times greater in HIV-seropositive patients than in HIV-seronegative patients matched by age and body mass[10,13-16].

According to the American Diabetes Association[17], DM is a disease in which the body does not produce insulin or does not produce it correctly. Diabetes is latent when a blood glucose level of 100-126 mg/dl is detected on fasting.

Diabetes is relatively similar in HIV-positive and negative individuals. However, the association with HAART has shown an increased risk for developing DM, cardiovascular disease and metabolic syndrome. There is a relationship between diabetes and re-exposure to HAART, especially among individuals under therapy with stavudine, zidovudine, didanosine, and indinavir, while the risk is reduced in case of exposure to ritonavir and nevirapine. There is a clear cumulative effect of exposure to different classes of drugs on the incidence of diabetes, exposure to NRTI (Nucleoside reverse transcriptase inhibitors), a combination of NRTI with PI, or combination with NRTI, PI, NNRTI increasing the risk of developing DM [6,18-21].

The most common oral manifestations associated with HIV are candidiasis, GUN (necrotizing ulcerative gingivitis), PUN (necrotizing ulcerative periodontitis), hairy leukoplakia, herpes simplex, HPV (human papillomavirus) and Kaposi's sarcoma[22-25], but HAART is a associated with a significant reduction in the occurrence of oral manifestations. Currently, the oral manifestations of candidiasis, severe and rapid progression periodontal disease, hairy leukoplakia are important indicators, highlighting the increase of immunosuppression and/or the failure of HAART. However, these manifestations are more evident and exuberant with the development of DM as a result of the adverse effects of HAART[26-29].

The aim of this study was to determine the prevalence of oral manifestations in HIV/AIDS patients and a possible correlation of the development of DM due to HAART.

Material and methods

The research protocol was approved by the institutional Ethics Committee (Process# 015/09 CEP / ICS / UNIP) and all patients that agreed to participate in the study signed an informed consent form.

Individuals of both genders aged 27 to 75 years were tested for HIV/AIDS and distributed into two groups: Group I – HIV-positive patients referred to the CEAPE (Center of Study and Care of Patients with Special Needs) who were under HAART and had developed DM as an adverse effect of the antiretroviral therapy and/or their own immunosuppression; Group II (Control) - HIV-negative patients with DM referred to the CEAPE. The tests to confirm DM control of glycosylated hemoglobin or glucose were performed by the physician who referred the patient and not by CEAPE, so some patients could not inform how long they had the disease.

For both groups, relevant information on age, race, education, general and oral manifestations, and habits was collected. For Group I, information was collected on the probable means of contamination by HIV, the T lymphocyte-CD4 count, viral load, and HAART in use. For both groups, the following tests and examinations were performed: salivary flow rate, bacterial plaque index, gingival bleeding, periodontal pockets and DMFT (decayed missing and filled tooth) index.

Stimulated saliva of all patients was collected for 5 min and a saliva test method (DentoBuff Kit®; Inodon, Porto Alegre, Brazil) was used to assess salivary flow, daily secretion of saliva, buffering capacity, salivary pH. Normal salivary flow: 1.6 to 2.3 mL/ min, intermediate: between 1.0 and 1.5 mL/min and low: less than 1.0 mL/min. Normal buffering capacity, pH greater than 5.5, intermediate: between 4.5 and 5.5 and low: less than 4.5. A plaque disclosing agent (erythrosine tablet) was used to obtain bacterial plaque index. The result was evaluated using the Ainamo and Bay test (1975)[30] to determine the presence or absence of plaque in a standard binomial (dichotomous score).

The visible plaque received a visible marking "1" while the non-visible plaque received marking "0" for the analysis of the DMFT index. After pumice prophylaxis, clinical examination was performed using a dental mirror under relative isolation and artificial lighting to evaluate the presence of caries, missing and filled teeth, and the bleeding index, recorded by visible bleeding points within 15 s after probing, and periodontal pocket using Williams 1-10 mm periodontal probe. The probe was placed on the buccal and proximal gingival margin, around each tooth to measure sulcus/pocket depth.

For quantitative variables, the analysis was made through observation of minimum and maximum values, and calculation of means, standard deviations and medians. For qualitative variables, absolute and relative frequencies were calculated and the Student's t-test was used for comparison of the groups. When normality assumption was rejected, the nonparametric Mann-Whitney test was used. To test the homogeneity between the ratios, we used the chi-square test or Fisher's exact test (when we had frequencies below 5). Significance level used for the tests was 5%. The groups showed no significant differences regarding gender ($p = 0.109$) and race ($p = 1.000$), but they differed significantly

in age ($p < 0.05$). The HIV group presented age ($p < 0.001$) significantly lower than that of the control group. Regarding habit, the percentage of patients who did not state habits was practically the same in both groups.

Results

Fifty-six patients between 27 and 75 years of age (mean age of 53.96 years with standard deviation of 11.22 years and median of 54 years) were evaluated. Of the 28 patients examined in the HIV group, 17 (60.7%) were male and 11 (39.3%) female, 21 (75.0%) were Caucasian, 6 (21.4%) African descendants and 1 (3.6%) Oriental descendants and the mean age was 47 years.

Regarding the count of CD4 T lymphocytes, 1 (3.5%) presented T-CD4 inferior to 199 cells/mm ^{3}, while 14 (50.0%) had T-CD4 between 200 to 499 cells/mm ^{3} and 13 (46.5%) T-CD4 e" 500 cells/mm ^{3}. About the viral load (VL), 8 (28.5%) had less than 4999 virus, 2 (7.2%) between 5000 to 9999 virus, 3 (10.8%) e" 10 000 virus and 8 (28.5%) undetectable. All patients used HAART; of these, 20 (71.4%) used Biovir, 15 (53.6%) Efavirenz, 7 (25.0%) lamivudine, 7 (25.0 %) stavudine, 5 (17.9%) Zidovudine, 2 (7.1%) Tenofovir, 2 (7.1%) Kaletra, 2 (7.1%) abacavir, 1 (3.6%) Atazanavir, a (3.6%) Zalcitabine, 1 (3.6%) and a didanosine (3.6%) Ritonavir. For the variable means of contamination of the HIV group, 17 (60.7%) were infected through heterosexual contact, 9 (32.3%) MSM (Homosexual), 1 (3.5%) bisexual and 1 (3.5%) by transfusion.

From the 28 patients of the control group, 11 (39.3%) were male and 17 (60.7%) female, 21 (75.0%) were Caucasian, 5 (17.8%) African descendants and 2 (7 2%) Oriental descendants, and the mean age was 60.11 years.

Initially all variables were analyzed descriptively. The most prevalent habits in both groups were smoking and alcohol, being present in 64.3% of patients in the control group and 67.9% of patients in the HIV group.

Table 1 shows the frequency distributions between distribution of frequencies of the variable salivary flow and buffering capacity. Table 2 presents the means, standard deviations, medians and p values for the variable DMFT index, plaque index and bleeding index. Table 3 presents the joint frequency distribution for the variable oral manifestations. These tables also present the descriptive p value of Fisher's exact test. It was observed that for these variables there was no significant difference.

The groups did not differ significantly regarding plaque index. The most prevalent oral manifestations in the HIV group were oral candidiasis, herpes simplex and periodontal disease, and the control group caries, bleeding on probing and xerostomia.

The percentage of patients who had no oral manifestation in the HIV group is 32.1% higher than in the control group that is 21.4%. The groups differ in relation to caries ($p = 0.004$), xerostomia ($P = 0.005$), oral candidiasis ($p = 0.001$) and herpes simplex ($p = 0.010$). The HIV group had a higher percentage of cases with oral candidiasis (35.7%) and herpes simplex (25.0%) and lower percentage of cases with caries (7.1%) and xerostomia (3.6%) compared to control group. The groups did not show significant difference compared with other oral manifestations.

Discussion

Regarding the oral manifestations present in the HIV group, the most common manifestation was oral candidiasis, affecting 35.7% patients, which is in accordance with the literature[22-25,28-29]. Besides oral candidiasis, other oral manifestations were found, such as herpes simplex (25%), periodontal disease (21.4%), oral ulcer (14.3%), hairy leukoplakia (10.7%), caries and Kaposi's sarcoma (7.1%), xerostomia, nicotinic stomatitis and lichen planus (3.6%). This is consistent with the findings of Coogan et al. (2005)[23] and Giovani et al. (2007)[24], who reported that the most frequent

Table 1- Distribution of frequencies of Salivary Flow Rate and Buffering Capacity

	Salivary Flow				Buffering Capacity			
Group	Low	Intermediate	Normal	Total	Low	Intermediate	Normal	Total
Control	11(39.2)	2(7.14)	15(53.5)	28(100.0)	0(0.0)	11(39.3)	17(60.7)	28(100.0)
HIV	6(21.4)	4(14.3)	18(64.3)	28(100.0)	2(7.2)	8(28.5)	18(64.3)	28(100.0)
Total	17(30.3)	6(10.8)	33(58.9)	56(100.0)	2(3.6)	20(35.7)	34(60.7)	56(100.0)
	*p**=0.332				*p**=0.413			

(*) descriptive level of probability of Fisher's exact test.

Table 2 - Mean, standard deviation, median and descriptive p level for dmft index, plaque index and bleeding index

	DMFT Index			Plaque Index			Bleeding Index		
Group	Mean	Standard deviation	Median (Min-Max)	Mean	Standard Deviation	Median (min-max)	Mean	Standard Deviation	Median (min-max)
Control	22.46	5.12	23.5(11-32)	49.19	29.12	52.0(0-100)	32.14	26.76	24.0(0-98)
HIV	17.54	8.11	16.0(2-32)	54.80	24.98	52.0(17-100)	46.53	25.21	45.0(0-100)
	*p**=0.019			*p**=0.533			*p**=0.017		

(*)descriptive level of probability of Mann-Whitney's non-parametric test.

Table 3 - Joint frequency distribution for oral manifestations

Oral Manifestations	Control	%	HIV	%	*p*
Oral Candidiasis	0	0.0	10	21.2	0.001(1)
No	6	21.4	9	19.1	0.365(1)
Herpes Simplex	0	0.0	7	14.9	0.010(2)
Periodontal Disease	10	35.7	6	12.8	0.237(1)
Oral Ulcer	0	0.0	4	8.6	0.111(2)
Hairy Leukoplakia	0	0.0	3	6.4	0.236(1)
Kaposi's Sarcoma	0	0.0	2	4.3	0.491(2)
Caries	11	39.3	2	4.3	0.004(1)
Xerostomia	9	32.1	1	2.1	0.005(1)
Nicotinic Stomatitis	0	0.0	1	2.1	1.000(2)
Sinus Oral Communication	0	0.0	1	2.1	1.000(2)
Lichen Planus	0	0.0	1	2.1	1.000(2)
Radicular Cyst	1	3.6	0	0.0	1.000(2)

(1) descriptive level of probability of the chi-square test.
(2) descriptive level of probability of Fisher's exact test.

oral manifestations in HIV were candidiasis, GUN (necrotizing ulcerative gingivitis), PUN (necrotizing ulcerative periodontitis), hairy leukoplakia, herpes simplex, HPV (human papillomavirus) and Kaposi's sarcoma. In the control group, the most frequent oral manifestation were caries (39.3%), followed by periodontal disease (35.7%), xerostomia (32.1%) and radicular cyst (3.6%); 21.4% did not show any kind of utterance. Thus, the Group HIV had more oral manifestations than the control group, demonstrating the susceptibility of patients to opportunistic infections because of the immunosuppression of HIV-positive individuals.

According to De Wit et al. (2008)[6], with the use of Stavudine, the risk of developing diabetes was higher, as well as the use of Zidovudine and Didanosine, disagreeing with this research, which revealed that the highest risk of developing diabetes comes with prolonged use of Combivir (71.4%) and Efavirenz (53.6%). It was also observed in this study that the use of Zalcitabine (3.6%) and Didanosine (3.6%) was associated with low risk for developing diabetes. Among the most common manifestations observed in patients with diabetes are xerostomia, caries and periodontal disease[29], in agreement with our research, which revealed that these diseases were most prevalent in the control group (39.3% for caries, 35.7% for periodontal disease and 32.1% for xerostomia).

For the analysis of DMFT index in our sample, it was found a statistically significant difference ($p = 0.019$) between groups. For the control group, the mean was 22 for each patient and for the HIV group, the mean was 17 for each patient. In addition to the high DMFT presented index, the groups also had high plaque index. The control group had a mean of 49% and 54% HIV group, which indicates that the control group is more prone to a higher prevalence of caries due to poor hygiene, the possible intake of foods rich in sucrose, presence of cariogenic bacteria and even the longest living with the disease diabetes than the patients who developed diabetes due to adverse effects of HAART. So, patients should be counseled about oral hygiene and should maintain regularity in the treatments and have a low-sucrose diet.

Thus, oral pathologies can be minimized by maintaining the oral health of patients. The buffering capacity was also evaluated and represented as follows: low ($pH < 4.5$), intermediate (pH between 4.5 and 5.5) and normal ($pH > 5.5$). In the control group, 60.7% patients had normal buffering capacity, 39.3% had intermediate buffering capacity and no patient had low buffering capacity. In the HIV group, 64.3% patients had normal buffering capacity, 28.5% intermediate buffering capacity and 7.2% low buffering capacity. These results show that the control group had better buffering capacity of saliva than the HIV group, which is the capacity of saliva to maintain the a constant pH in the oral cavity, thus maintaining the health of the oral mucosa and teeth, unlike the two patients of the HIV group who had low buffer capacity. If the buffering capacity is low, the pH is not constant and the action of saliva against acid attacks to the oral cavity becomes ineffective, making these patients more susceptible to oral pathologies. In the present study, the bleeding index score was determined by a dichotomous count, marking the presence or absence of bleeding. Significant differences ($p = 0.017$) were found between groups.

In the control group, the mean of bleeding tooth surfaces was 32% and 46% in the control and HIV group, respectively. The HIV group showed higher bleeding index than the control group, and also higher prevalence of periodontal diseases, with the formation of periodontal pockets with faster evolution, which may be caused by the body's own immunosuppression by HIV or even HAART.

The HIV group and the control group were diagnosed with diabetes, but this condition in the HIV group presented earlier than in the control group, suggesting a possible association with HAART.

There is an increased prevalence of oral manifestations in immunocompromised patients and general. The study showed a correlation between the administration of HAART with the development of diabetes mellitus, as well as a increased prevalence of oral manifestations, suggesting a more pronounced worsening immunosuppression in these patients.

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