Oral mucosa symptoms, signs and lesions, in end stage renal disease and non-end stage renal disease diabetic patients

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Received: 7-01-2006
Accepted: 3-06-2006

Indexed in:
-Index Medicus / MEDLINE / PubMed
-EMBASE, Excerpta Medica
-Indice Médico Español
-IBECS

de la Rosa-García E, Mondragón-Padilla A, Aranda-Romo S, Bustamante-Ramírez MA. Oral mucosa symptoms, signs and lesions, in end stage renal disease and non-end stage renal disease diabetic patients. Med Oral Patol Oral Cir Bucal 2006;11:E467-73.

ABSTRACT

Aim: To assess oral signs, symptoms and oral lesions (OL) type and prevalence, in diabetic patients with end stage renal disease (ESRD DM), and compare them with analogous findings in a non-ESRD DM group; analyze the possible association between oral manifestations, as well as with relevant laboratory findings.

Research design. Two adult groups were studied: Group A: ESRD DM on dialysis, and group B: non-ESRD DM (serum creatinine <2.0 mg/dl). Known DM evolution time, dialysis treatment type and duration, and laboratory results were recorded. An oral exam was performed, searching for signs, symptoms and ESRD-associated OL. Associations were analyzed using Chi square, Fisher's exact test, and odds ratios (OR) with 95% confidence intervals. Ages, time on dialysis, and laboratory results were compared with Student's t test.

Results: 229 individuals were examined, group A 99, and group B 130 pts. Signs and symptoms prevalence was higher in group A: 77.8% vs. 57.6%, (P<0.001), uremic breath (48.5%), unpleasant taste (45.5%) and xerostomia (44.4%) being the most frequent ones. OL were also more prevalent in group A; 65.6% vs. 36.9% (P<0.001). The most frequent OL were dry, fissured lips (28.3%), saburral tongue (18.2%) and candidiasis (17.2%). No difference was found in candidiasis prevalence between groups. Candidiasis was found associated to xerostomia (P<0.05) and smooth tongue (P<0.05) only in group A.

Conclusions. ESRD DM patients had a significantly higher prevalence of signs, symptoms and OLs, as compared to non-ESRD DM pts. The high prevalence of uremic fetor, xerostomia, saburral tongue and candidiasis in group A, could be tried as warning signs on the possibility of non diagnosed advanced renal disease in other diabetic patients.

Key words: *End stage renal disease, diabetes, uremic fetor, xerostomia, saburral tongue.*

RESUMEN

Objetivos. Conocer el tipo y frecuencia de signos, síntomas y lesiones bucales (LB) en pacientes diabéticos (DM) con insuficiencia renal crónica (IRCT), y compararlos con un grupo de DM sin IRCT. Investigar la posible asociación de las manifestaciones bucales entre sí, y con resultados de laboratorio relevantes.

Diseño del estudio. Fueron dos grupos de adultos: grupo A: DM con IRCT y diálisis, y grupo B: DM sin IRCT (con creatinina sérica <2.0 mg/dl). Se registró tiempo de evolución conocida de la DM, tipo y duración del tratamiento dialítico y resultados de laboratorio. Se realizó un examen bucal registrando signos, síntomas y LB asociadas a IRCT. Las asociaciones se investigaron con $\chi 2$, prueba exacta de Fisher y razón de momios (RM) con límites confianza de 95%. Las edades, el tiempo en diálisis y los resultados de laboratorio se compararon con prueba de T de Student.
Resultados. Fueron 229 sujetos; grupo A 99 y grupo B 130. La frecuencia de signos, síntomas fue mayor en el grupo A: 77.8 % vs. 57.6%, (P <0.001); los más frecuentes fueron aliento urémico 48.5%, sabor desagradable 45.5% y xerostomía 44.4%. Las LB también fueron más frecuentes en el grupo A; 65.6% vs. 36.9%, (P<0.001). Las más frecuentes fueron labios secos y fisurados 28.3%, lengua saburral 18.2% y candidosis 17.2%. No se encontró diferencia en la prevalencia de candidosis entre los dos grupos. La candidosis se asoció con xerostomía (P<0.05) y con dorso de lengua liso (P<0.05) solo en el grupo A.
Conclusiones. Los diabéticos con IRCT presentaron un número significativamente mayor de signos, síntomas y LB que los diabéticos sin IRCT. La elevada frecuencia de aliento urémico, xerostomía, lengua saburral y candidosis en el grupo A, podrían probarse como señales de alerta sobre la posibilidad de enfermedad renal avanzada en otros pacientes diabéticos.

Palabras clave: *Insuficiencia renal crónica, diabetes, aliento urémico, xerostomía, lengua saburral.*

INTRODUCTION

End stage renal disease (ESRD) is the final syndrome for several primary renal diseases, and systemic diseases with renal involvement, causing kidney function loss. ESRD manifestations involve virtually every system, in a clinical condition known as uremic syndrome, characterized by a profound alteration of water, electrolyte, and acid-base homeostasis, as well as retention of uremic toxins normally eliminated through urine, especially protein catabolism nitrogen waste products (1). The condition is incompatible with life, unless the patient starts chronic dialysis treatment or kidney transplantation.

ESRD incidence and prevalence are increasing, as shown in consecutive United States Renal Data System (USRDS) annual data reports. All age groups are affected, but ESRD is predominantly an adult disease. ESRD cause was diabetes in 44.8% of incident USA cases in 2003 (2). In that same report, chronic dialysis patients prevalence was 1,496 per million, and median age at dialysis start increased from 52.8 years in 1980, to 62.7 years in 2003, reflecting improved kidney disease medical care (2).

An ESRD prevalence study on Instituto Mexicano del Seguro Social (IMSS)-affiliated adults (>18 yr), estimated 1.142 persons with creatinine clearance levels <15 ml/min per million adult affiliates (3). That level of renal function damage does already, or will soon, need dialysis treatment (4). Another study on IMSS affiliates found diabetes mellitus as the cause of ESRD in 41.1% of incident cases (5). ESRD mortality is increasing in Mexico; being now 9th cause for women and 10th for men (6).

Diabetes mellitus is an important risk factor for ESRD. In Mexico, Amato et al. (3) reported a 10.9% DM prevalence in 18 yr and older individuals, and found 48.6% of affected subjects unaware. Diabetic patients are at risk for acute and chronic complications, including those on the oral cavity (7) such as xerostomia, glossodynia, bacterial, viral, and fungal infections, and periodontal disease (7-9). A 36.6% to 67% association frequency has been reported between diabetes and oral candidiasis (10).

An up to 90% prevalence has been reported in renal disease patients, either on dialysis or with a kidney transplant, for at least one of more than 30 different signs, symptoms, or oral lesions associated in medical literature to uremic syndrome and kidney transplant, including xerostomia, uremic fetor, pale mucosa, uremic stomatitis and candidiasis (11,13).

The aim of this study was to assess signs, symptoms, and oral lesions (OLs) type and prevalence, in a group of ESRD DM patients on dialysis treatment, and compare them with a group of non-ESRD diabetic patients, exploring possible associations among oral lesions, and between OLs and relevant clinical laboratory results.

MATERIAL AND METHODS

Observational, comparative, transversal study, performed in two groups of patients: Group A, ESRD DM, formed by consecutive diabetic patients 18 yr and older, both sexes, with diabetic nephropathy – induced ESRD, attending the outpatient nephrology clinic or the peritoneal or hemodialysis units for dialysis treatment follow-up, and Group B, non-ESRD DM, formed by consecutive diabetic patients 18 yr and older, both sexes, attending outpatient family medicine clinic for diabetes mellitus follow-up. Patients with a serum creatinine ≥ 2.0 mg/dl were excluded. The study was carried out at an IMSS general hospital at San Luis Potosi. Demographical data, time from DM diagnosis, dialysis treatment type and duration, clinical laboratory results for blood hemoglobin, fasting glycemia, urea, creatinine and albumin were collected. Hb A1C results were not available. An informed consent was obtained from each patient to participate in the survey.

An examination was performed of all oral mucosa areas, recording ESRD-associated signs, symptoms, and OL absence or presence. Signs and symptoms identification was objectively searched for, and/or reported by patients. A diagnosis of xerostomia was made when a dry or sticky mucosa was found, and when the patient reported a dry mouth; saliva flow was not measured. Uremic fetor was identified when the patient had a urine-odor breath.

OL diagnosis used acknowledged clinical diagnosis criteria for ESRD-associated oral manifestations (11-13), and oral candidiasis was diagnosed by Holmstrup criteria (14).

Uremic stomatitis: irregular-shaped mucosal erythema, covered by grayish pseudomembranes on the lateral borders or inferior aspect of the tongue, occasionally symptomatic (11, 12).

Saburral tongue (ST): Yellowish-white plaque on tongue dorsum, which could not be scraped-off by a blunt instrument. Slightly elongated filiform papillae and bacterial accumulation were found (15). A periodic acid-Schiff (PAS)-stained cytological smear ruled out candidiasis.

Erythematous candidiasis: Dorsal tongue or vestibular mucosal rounded or ovoid-shaped, depapillated, red area.

Sub plaque candidiasis: Red area on hard palate, comprising the total or partial prosthesis area, sometimes with a punctated or small papule-filled appearance. Candidiasis was confirmed by gemmating hyphae, found in a PAS-stained cytological smear (14).

Statistical analysis

Descriptive statistics were calculated: frequencies, percentages, means and standard deviations. Inter- and intra-group variable associations were analyzed with Chi square and Fisher's exact tests, where applicable, and by odds ratio (OR) with 95% confidence limits (95% CL). Age, diabetes, and dialysis duration were compared with Student's t test for unpaired samples with homogenous variances. A $P<0.05$ value was considered statistically significant.

RESULTS

A total of 229 individuals were studied. Group A, 37 men and 62 women, ages 57.9 ± 11.6 (17 to 83) years, and group B, 43 men and 87 women, ages 58.8 ± 11.6 (18 to 77) years (P = NS). Median known DM evolution time: group A, 240 (24 to 408), and group B, 84 (2 to 180) months (P <0.001). Median dialysis treatment time: group A, 8 (1 to 88) months. Table 1 shows clinical laboratory results, revealing, as expected, significant differences in urea, creatinine, and Hb values, corresponding to ESRD and Non-ESRD diagnosis for both groups.

Oral symptoms and signs: Table 2 compares their prevalence in groups A and B, showing odds ratios with 95% CL; Group A had a 77.8% and group B a 57.6% prevalence for at least one symptom or sign (P <0.001).

Oral lesions: 97 lesions were found in 65 group A patients; 41 cases had one lesion, 17 cases two, 6 cases three, and 1 patient had four simultaneous lesions; 67 lesions were identified in 48 group B patients; 33 individuals had one lesion, 12 had two, 2 had three lesions, and 1 patient had four simultaneous lesions. Total OL prevalence was greater in group A, 65.6% vs. 36.9% (P<0.001). Table 3 compares OL prevalence in both groups showing odds ratios and 95% CL. There was no difference in candidiasis prevalence. Table 4 shows identified intra-group associations between symptoms, signs, oral lesions and lab results, and odds ratios.

Table 1. Clinical laboratory studies, ESRD and Non-ESRD diabetic patients.

Laboratory results	ESRD DM, Group A	Non-ESRD DM, Group B	*P*
n	99	130	
Hemoglobin (g/dl)	9.4 ± 1.8	12.7 ± 2.4	<0.001
Fasting glycemia (mg/dl)	175 ± 110	176 ± 91	NS
Urea (mg/dl)	122 ± 54	38 ± 48	<0.001
Creatinine (mg/dl)	8.1 ± 3.2	1.0 ± 0.4	<0.001
Albumin (g/dl)	3.2 ± 0.8	3.9 ± 1.3	NS

Table 2. Oral symptoms and signs in ESRD and Non-ESRD diabetic patients.

	ESRD DM, Group A		Non-ESRD DM, Group B			
	Cases	**%**	**Cases**	**%**	***P***	**OR (95% CL)**
Uremic fetor	48	48.5	0	0.0	NA	NA
Unpleasant taste	45	45.5	35	26.9	<0.01	2.3 (1.3 to 3.9)
Xerostomia	44	44.4	47	36.2	NS	1.4 (0.8 to 2.4)
Pale mucosa	40	40.4	16	12.3	<0.001	4.8 (2.5 to 9.3)
Yellowish mucosa	14	14.1	6	4.6	<0.01	3.4 (1.3 to 9.2)
Burning tongue	13	13.1	13	10.0	NS	1.4 (0.6 to 3.1)
Total symptoms or signs	77	77.8	75	57.6	<0.001	2.6 (1.4 to 4.6)

OR= Odds ratio, 95% CL= 95% confidence limits, NA = not applicable

Table 3. Oral lesions in ESRD and Non-ESRD diabetic patients.

	ESRD DM, Group A		Non-ESRD DM, Group B			
Oral lesions	**Cases**	**%**	**Cases**	**%**	***P***	**OR (CL 95 %)**
Dry, fissured lips	28	28.3	20	15.4	<0.05	2.2 (1.1 to 4.1)
Saburral tongue	18	18.2	4	3.0	<0.001	7.0 (2.3 to 21.4)
Candidiasis	17*	17.2	29**	22.3	NS	0.7 (0.4 to 1.4)
Erythematous	11	11.1	20	15.4	NS	0.7 (0.3 to 1.5)
Subplaque	8	8.0	14	10.8	NS	0.7 (0.3 to 1.8)
Petechiae or ecchymoses	15	15.1	1	0.8	<0.001	23.0 (3.0 to 178)
Smooth tongue	13	13.1	5	3.8	<0.01	3.8 (1.3 to 11.0)
Ulcerative stomatitis	2	2.0	0	0	NA	NA
Herpes simples	2	2.0	2	1.5	NS	1.3 (0.2 to 9.5)
Angular cheilitis	2	2.0	6	4.6	NS	0.4 (0.1 to 2.2)
Total oral lesions	65	65.6	48	36.9	<0.001	3.3 (1.9 to 5.6)

OR=Odds ratio, 95% CL= 95% confidence limits, NA= not applicable, NS = not significant
* Two patients presented simultaneous erythematous and sub-plaque candidiasis
** Five patients presented simultaneous erythematous and sub-plaque candidiasis

No association was found between smooth tongue and serum albumin or hemoglobin, or between the presence of up to eight signs, symptoms, or OL, and a serum albumin below 3.0 g/dl. No association was found between xerostomia and fasting glycemia or saburral tongue. Microscopic examination of saburral tongue smears revealed abundant bacteria. No cultures were made allowing identification.

DISCUSSION

Symptoms, signs and OL prevalence were significantly higher in ESRD DM patients as compared to Non-ESRD DM. Almost 78% of group A patients had at least one symptom or sign, the most prevalent ones being uremic fetor and unpleasant taste, which were found associated. Uremic fetor was also associated to a yellowish discolora-

Table 4. Intra-group associations found between, symptoms, signs, oral lesions and clinical laboratory data in ESRD and Non-ESRD diabetic patients.

Group A	Symptom, sign or lesion 1	Symptom, sign or lesion 2	Test	*P*	OR (CL 95 %)
	Uremic fetor	Xerostomia	χ^2	<0.05	2.6 (1.1 to 5.8)
	Uremic fetor	Unpleasant taste	χ^2	<0.001	14.0 (5.3 a 37.0)
	Uremic fetor	Yellowish mucosa	χ^2	<0.01	8.2 (1.7 to 38.8)
	Xerostomia	Unpleasant taste	χ^2	<0.05	2.3 (1.0 to 5.2)
	Xerostomia	Erythematous candidiasis	χ^2	<0.05	3.8 (1.0 to 15.5)
	Pale or yellowish mucosa	Erythematous candidiasis	Fisher's e.t.	<0.01	10.0 (1.2 to 81.5)
	Smooth tongue	Erythematous candidiasis	Fisher's e.t.	<0.05	5.0 (1.2 to 20.5)
	Fasting glycemia ≥ 200 mg/dl	Erythematous candidiasis	χ^2	<0.05	3.4 (1.1 to 10.7)
	Albumin < 3.0 g/dl.	Erythematous candidiasis	Fisher's e.t.	0.07	4.7 (0.8 to 26.8)
Group B	Xerostomia	Unpleasant taste	χ^2	<0.001	8.3 (3.5 to 19.9)

OR = Odds ratio, 95 % CL= 95% confidence limits, Fisher's e.t = Fisher's exact test.

tion in the mucosa, and to xerostomia. Uremic fetor occurs as a result of a high urea concentration in saliva, and its ensuing conversion to ammonia (16). additional possible causes are increased phosphate and protein concentrations, and changes in saliva pH, which might explain a metallic or unpleasant taste (1, 12, 17). The 48.5% uremic fetor and 45.5% unpleasant taste found in group A is similar to that reported by Kao et al. (50.0%) (17) and Kho et al. (34.1%) (18) in ESRD hemodialysis patients. Chuang et al. (19) informed a higher prevalence of severe symptoms in diabetics, as compared to non-diabetics in a study of ESRD patients. The higher prevalence of oral manifestations in ESRD DM could be either a worsening of preexisting alterations, caused by longer evolution of DM in group A, or be caused by uremia.

Dry mouth in ESRD patients is a multifactorial phenomenon (17): water restriction, low saliva flow (17, 18, 20, 21), minor salivary glands parenchymal fibrosis and atrophy (21), mouth breathing and medication use (12) being identified factors. The 44.4% found xerostomia prevalence in group A agrees with 32.9% to 68% figures reported in other studies of dialysis patients (17, 18, 21). Xerostomia is also a frequent symptom in the non-ESRD DM patient (7,8), and its prevalence in group B was 36.2%. Minor salivary glands involvement by microvascular disease and neuropathy play an important role in this symptom (7,8,10). Xerostomia in the ESRD DM patient is a risk factor for candidiasis, dental caries, periodontal disease, and bacterial infections, because of the lost protective action of saliva (17,20). Xerostomia is also associated to taste loss (21). A higher prevalence of oral manifestations (19) and gingival calculi (16, 18) has been described in ESRD patients with xerostomia. Chuang

et al. (19) reported a possible association between dry mouth and poor glycemic control in hemodialysis patients. Glycemic control was poor for both of our study groups, which probably was a factor in the high prevalence of the symptom.

Mucosa pallor is explained mainly by anemia, a multifactorial complication in the ESRD patient caused by erythropoietin and folic acid deficiencies, inhibited erythropoiesis, shortened erythrocyte life span, hemolysis and hemodialysis complications, among other (1,11,12). Pale mucosa prevalence was significantly higher in group A. The χ^2 test could not, however, find an association to blood Hb, perhaps because normal Hb values were missing in group A patients. Pale mucosa has also been associated to malnutrition (11), a reportedly frequent finding (82%) in Mexican dialysis patients, especially diabetic women (22). We were not able to find an association between pale or yellowish mucosa and a serum albumin <3.0 g/dl. The yellowish mucosa discoloration is caused by urocromo pigments (1,11, 12).

Our findings are in agreement to previous reports of ESRD predisposing to oral lesions. The most frequent OL were dry- fissured lips, saburral tongue, and candidiasis. Saburral tongue is an asymptomatic entity. Its prevalence in group A was 18.2%, no association being found to other oral manifestations. Reported prevalences are 12.2% to 47.1% (17-19). Chuang et al. (19) found 47.1% in non-diabetic and 39.5% in diabetic Chinese hemodialysis patients. Saburral tongue is caused by retention of desquamated epithelial cells and dead leucocytes on filiform papillae (15), and by volatile sulfurous compounds produced by anaerobic bacteria on the tongue surface, almost always the same as those found in the subgingival plaque (23). Saburral tongue has also been described as filiform papillae enlargement, with bacteria accumulation due to factors such as a water-restricted diet, low saliva flow, poor oral hygiene, and even the emotional condition of the dialysis patient (15, 24). It has also been reported in transplanted patients: 22.2% in kidney- and 28.3% in liver- transplant patients (25, 26).

The causes of the immunocompromised condition of the dialysis patient are uremia, malnutrition, dysfunctional celular immunity. Immunocompromise increases the risk for opportunistic Candida sp infections. (12). Other known risk factors for candidiasis are xerostomia, low saliva flow, total dental prosthesis, poor oral hygiene, age, diabetes (13, 27). In agreement to other reports (18, 19), candidiasis was found associated to xerostomia in group A, and an almost significant association was also found to a low serum albumin, odds ratio 4.7, 95% CL 0.8 to 27. The association of candidiasis to pale mucosa and smooth tongue could suggest malnutrition predisposing Candida infection. Erythematous candidiasis was the most common type, in most cases occurring on tongue dorsum. The similar prevalence of candidiasis found in groups A and B could mean a stronger association of candidiasis to diabetic, as compared to ESRD condition. Poor glycemic control in both groups could also be a risk factor for candidiasis. We found candidiasis associated to a fasting glycemia above 200 mg/dl in group A, but not in group B. On the other hand, dental prosthesis-associated candidiasis was more prevalent in group B, because edentulous non ESRD DM patients wore a total prosthesis more frequently than edentulous ESRD DM patients. Reported prevalences of oral Candida sp infection in dialysis patients are 5.7 to 37% (28,24), differences probably being caused by diagnostic criteria discrepancy. Klassen and Krasko (29), for instance, reported a 1% central rhomboid glossitis and 12% erythematous patches prevalences in dialysis patients, both probably equivalent to candidiasis. In that same study (29), angular cheilitis was reported in 4% patients. Angular cheilitis has been found associated to Candida sp. infections and anemia (14,27). Its prevalence in group A was 2%. The impact of oral candidosis diagnosis and treatment is to improve oral symptoms and lowering the risk for dissemination to other organs.

Platelet aggregation is altered in uremia (1, 30), which, added to heparin and other anticoagulants used in hemodialysis, predisposes to ecchymosis, petechiae and hemorrhages in the oral cavity (24,30). We found 15.2% cases with ecchymosis and/or petechiae in group A, vs. 0.8% in group B (P<0001). Kho et al. (18) found petechiae and/or ecchymosis in 12.2% of their dialysis patients, and figures as high as 23.3% have been reported in diabetic and non diabetic ESRD patients (17, 19). These lesions were found on oral examination, and had modest clinical relevance.

Oral mucosa ulcerations are yet another class of OLs in dialysis patients, with reported prevalences of 1.2 to 10% (17, 19, 28, 29). Uremic stomatitis, now an uncommon OL because of usually earlier dialysis therapy for ESRD patients, is a localized or generalized burning oral mucosa erythema, with erythematous areas covered by a grayish pseudomembranous exudate leaving, on removal, an intact (type I) or ulcerated (type II) mucosa (12, 13, 31). It has also been described as white plaques on vestibular mucosa and tongue dorsum or belly (31, 32), called hyperparakeratosic uremic stomatitis, often coexisting with Candidiasis. Its etiology is unknown. It has been considered the reaction to a tissular irritant (13, 32) possibly ammonia compounds derived from urea hydrolysis by salivary urease, whenever saliva urea concentration exceeds 180 mg/dl (32). We found two cases, just starting dialysis therapy, with OL matching uremic stomatitis description. Uremia control is the main therapy; 10% hydrogen peroxide gargles (1:1 in water) q.i.d. assist on lesion healing (32).

CONCLUSIONS

ESRD DM patients had a significantly higher prevalence of signs, symptoms and oral lesions, as compared to non-ESRD DM patients. This observation agrees with previous reports of ESRD predisposing to oral manifestations in the diabetic patient. Even if an association might be expected between oral manifestations type or number and nutritional status in the diabetic dialysis patient, we were not able to find an association between several oral manifestations and serum albumin, a sensible –but non specific- marker of nutritional status in the diabetic dialysis patient. Oral

manifestations were, moreover, barely symptomatic when present, or were probably less of a trouble for the patient as compared to other manifestations of ESRD. Those frequently found conditions of uremic fetor, unpleasant taste, xerostomia, pale or yellowish mucosa, burning tongue, dry-fissured lips, candidiasis, saburral- or smooth tongue in our study group, could be tried as warning signs for undiagnosed kidney disease in other diabetic patients. OL diagnosis and treatment will contribute to improve the quality of life of the difficult ESRD DM patient.

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