ORAL CANDIDIASIS IN HAEMODIALYSIS PATIENTS WITH DIABETES MELLITUS (DM): A PILOT STUDY THROUGH A CLINICAL CASE SERIES

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ABSTRACT

Objective: The purpose of the study was to investigate the relationship between oral candidiasis and diabetes mellitus (DM) in patients undergoing haemodialysis treatment.

Materials and methods: The study included ten patients (5 men and 5 women) with DM with a clinical picture of oral candidiasis who underwent haemodialysis treatment. The dental examination included extraoral and intraoral examination.

Measurements included: number of teeth in the upper and lower jaw, (maximum) probing depth (PD), bleeding papilla index (PBI), proximal plaque index (API), gingival recession (GR), degree of vertical and horizontal tooth mobility, number of carious teeth, the presence of soft and hard deposits and the presence or absence of bad breath. Fungal swabs were taken from the patients and sent for microbiological analysis.

Results: Clinical findings of the oral cavity and periodontal status showed that none of the subjects had satisfactory oral hygiene, considering that 66.67% of them had periodontitis stage IV, while the rest were completely toothless. The results of the statistical analysis showed that there are no statistically significant differences between the sexes in relation to (partial) toothlessness, dryness of the oral cavity, values of blood and biochemical parameters, and oral swab results.

Conclusion: A multidisciplinary approach that includes dentists, nephrologists and diabetologists can significantly contribute to reducing the prevalence of local and systemic manifestations and complications of oral health in patients with diabetes.

Keywords: candidiasis; diabetes mellitus; haemodialysis

Introduction

Diabetes mellitus (DM), also known as diabetes, is an endocrine disease caused by insulin insufficiency (type 1) or reduced tissue sensitivity to insulin (type 2), which results in a disturbance of carbohydrate, protein and lipid metabolism.

The key characteristic of DM is hyperglycaemia, i.e. elevated blood glucose level [1-3]. This disease is accompanied by three main symptoms: polyuria, polydipsia and polyphagia. Glycosuria occurs when the concentration of glucose in the blood exceeds the renal threshold [4, 5]. The most common type of disease is DM type 2, which occurs in approximately 90% of patients, and the main causes include obesity, tumours, drugs and surgical procedures that lead to the destruction of the endocrine part of the pancreas - the islets of Langerhans [3-5, 25]. In a significant number of cases (20-40%), patients with diabetes develop kidney diseases and complications that can lead to terminal kidney failure [6, 7]. This disease affects all tissues in the body, so its consequences are also visible in the oral cavity. Oral manifestations vary depending on the level and glycaemic control [1, 5, 11].

Symptoms of uncontrolled diabetes in the oral cavity include halitosis (acetone breath), xerostomia, candidiasis, delayed wound healing, periodontal inflammation, alveolar bone destruction, and an increased index of carious lesions [1, 12-14]. Among them, one of the most common is oral candidiasis, a fungal infection of the oral cavity usually caused by Candida albicans [12, 15]. Candida albicans is a normal inhabitant of the oral flora and does not cause infection in healthy people thanks to the protective mechanisms of saliva and the secretion of antimicrobial peptides and proinflammatory cytokines from the epithelium of the oral cavity, which act on fungal cells and prevent their reproduction [16, 17]. A decline in the immune response and disruption of immune function can lead to overgrowth of candida and the development of a fungal infection [16].

The aim of this pilot study, which includes a series of clinical cases, was to investigate the relationship between oral candidiasis and DM in patients undergoing haemodialysis treatment.

Materials and methods

The research was conducted in the Dialysis Centre of Županja after the approval of the Ethics Committee of the Health Centre of Županja (CLASS: 034-04/24-01/13, ID number: 2196-98-24-1/2) in the period from February to June 2024. The study included ten patients (5 men and 5 women) with diabetes with a clinical picture of oral candidiasis who underwent haemodialysis treatment.

Exclusion criteria included established malignant disease, chemotherapy and radiotherapy, HIV and hepatitis B and C. The participants were informed about the aims and methods of the research and voluntarily agreed to participate by signing the informed consent.

Procedures included a detailed history, filling out forms (FDI health questionnaire (23), Consent for research, quality of life and oral health survey (23)), review of medical records confirming the diagnosis of DM, clinical examination and reading of orthopantomographic images. The dental examination included extraoral and intraoral examination.

Measurements included: number of teeth in the upper and lower jaw, (maximum) probing depth (PD), bleeding papilla index (PBI), proximal plaque index (API), gingival recession (GR), degree of vertical and horizontal tooth mobility, number of carious teeth, the presence of soft and hard deposits and the presence or absence of bad breath.

All measurements were performed by the same doctor using a dental mirror (ASA DENTAL, Italy) and a calibrated periodontal probe (Deppeler HH12DMS-N, Switzerland). Measurements for each tooth were performed in four areas: mesial, distal, oral and buccal [21, 23, 24].

Fungal swabs were taken from the patients and sent for microbiological analysis. The fungi were proven by the standard method of cultivation on liquid and solid non-selective and selective-differential media (CAN2 bioMerieux, France).

Then, the subjects were educated, which included a demonstration of proper tooth brushing technique, the use of interdental brushes and dental floss, and the maintenance of dental prostheses. Patients were

also recommended to regularly come for dental check-ups twice a year, hydrate properly, repair carious lesions, carry out periodontal treatment if necessary and regularly monitor their health in cooperation with a specialist in oral diseases. In agreement with the general practitioner, it was suggested to check blood counts, levels of iron, zinc, selenium, magnesium, folic acid, and vitamins A and B6.

Respondent data were organized in spreadsheet files (Microsoft Excel®, Microsoft Inc., USA) and appropriately coded for statistical analysis performed using SPSS® 11.0 software (IBM Inc., USA). Variables were analysed using descriptive statistics and presented as proportions (percentages). Kruskal-Wallis test for independent samples was used to determine differences between continuous variables, while chi-square and Fisher's exact test were used to test differences between categorical variables. p-values below 0.05 ($p<0.05$) were considered statistically significant.

The results

Table 1 shows the data of the study respondents in detail. The average age of the respondents was 70 years for men, 62.4 years for women and 66.2 years for all respondents. No statistically significant difference in age was found between men and women included in this study, which enabled a relevant comparison of parameters between the sexes.

All female subjects included in this study reported a feeling of dryness in the oral cavity, unlike the male subjects who reported this complaint in 60% of cases. The smear test was positive in all patients who regulate their underlying disease with oral insulin preparation, while in less than half of the subjects (42.9%) this was the case for those who regulate it with parenteral insulin preparations. Diabetic retinopathy as one of the complications of DM was reported by 20% of patients.

Table 1. Descriptive statistics of the examined group (n=10).

Serial No. of the patient	Gender (age)	Anamnesis data	Medicines (taken orally)	Deviations in blood and biochemical parameters	Clinical findings of the oral cavity; periodontal status	Oral swab results
1.	F (71)	DM type II (+ DR), renal failure, HA, anaemia, hypothyroidism, psychiatric treatment	**gliquidone*,** lercanidipine, urapidil, bisoprolol, warfarin, atorvastatin, pantoprazole*, allopurinol, oxazepam*, tramadol*+paracetamol, levothyroxine, paricalcitrol	↑RDW, urea, creatinine, K, CRP, ferritin, PTH ↓e, Hb, Hct, Trc, ALT, Fe	Complete toothlessness, dryness of the oral cavity	Candida albicans and candida non-albicans
2.	F (67)	DM type II (+ DR), renal failure, HA, anaemia, hypothyroidism, angina pectoris	nebivolol, lercanidipine, moxonidine, furosemide*, perindopril,acetylsalicylic acid, atorvastatin, glyceryl trinitrate,pantoprazole*, allopurinol, levothyroxine, paricalcitol, calcium acetate and magnesium sub carbonate levothyroxine, paricalcitol, calcium acetate and magnesium sub carbonate	↑RDW, HbA1c, GUK, urea, creatinine, urate, PO4, ferritin, PTH ↓e, Hb, Hct, ALT, Fe	Complete toothlessness, dryness of the oral cavity	Yeasts are not isolated
3.	F (57)	DM type II, renal failure, HA, anaemia, hypothyroidism	lercanidipine, moxonidine, furosemide*, atorvastatin rabeprazole*, febuxostat, levothyroxine, paricalcitol	↑MCHC, HbA1c, GUK, urea, creatinine, Na, K, ferritin, PTH ↓e, Hb, Hct, albumin	API = 70% PBI = 2.6 PD moderate (4 mm) on 40% of teeth GR on all 10 teeth (up to 2 mm); dryness of the oral cavity	Yeasts are not isolated

4.	F (61)	DM type II, renal failure, HA, anaemia, thrombophilia, psychiatric treatment	**metformin***, nebivolol, ramipril, warfarin, rosuvastatin, esomeprazole*, allopurinol, alprazolam*, tianeptine*, paricalcitrol, calcium acetate and magnesium sub-carbonate	↑MCV, RDW HbA1c, GUK, urea, creatinine, GGT, ferritin, Mg, PTH	Toothlessness of the upper jaw; API = 100% PBI = 4.0 PD moderate (5 mm) on 33.33% of teeth, severe (+ 6mm) on 33.33% of teeth GR (up to 3 mm) and caries on all three teeth; dryness of the oral cavity	Candida albicans
5.	F (56)	DM type II, renal failure, HA, anaemia, hypothyroidism, epilepsy	**glikvidon***, urapidil, moxonidin, nifedipine, trandolapril, acetylsalicylic acid, atorvastatin, allopurinol, escitalopram*, oxcarbazepine*, diazepam, paricalcitol	↑MCV, RDW, HbA1c, GUK, urea, creatinine, urate, GGT, K, CRP, ferritin, Mg, PTH ↓e, Hb, Hct, ALP, albumins	API = 93.8% PBI = 2.94 PD – without pathological probing depths, GR on all 16 teeth (up to 2 mm); dryness of the oral cavity	Candida non-albicans
6.	M (82)	DM type II, renal failure, HA, cardiac pacemaker, anaemia	nebivolol, perindopril, nifedipine, urapidil, moxonidin, warfarin, atorvastatin, esomeprazole*, allopurinol, diazepam, promazine, paricalcitol, potassium supplement	↑ RDW, HbA1c, GUK,urea, creatinine, urate, PO4, ferritin, PTH ↓e, Hb, Hct, Trc, Na, Fe, total proteins, albumins	Complete toothless-ness	Yeasts are not isolated
7.	M (75)	DM type II, renal failure, HA, anaemia, hypothyroidism	metoprolol, amlodipine, ramipril, torasemide*, xipamide*, allopurinol,doxazosin thyroxine, sevelamer, vitamin D3 supplement, calcium acetate and magnesium sub-carbonate	↑ MCHC, GUK, urea, creatinine, ferritin, Mg, vitamin B12, folic acid, PTH ↓e, Hb, Hct, Trc, ALT, AST, GGT, ALP	of the lower jaw; API = 100% PBI = 4.17 PD moderate (4-5 mm) on 3 (50%) teeth, GR on 4 (66.67%) teeth (up to 2 mm); dryness of the oral cavity	Yeasts are not isolated
8.	M (75)	DM type II, renal failure, HA, anaemia,	bisoprolol, furosemide*, warfarin, atorvastatin, pantoprazole*, allopurinol, paricalcitrol	↑MCV, RDW, HbA1c, GUK, urea, creatinine, GGT, ALP, ferritin, PTH ↓e, Hb, Hct, Na, Fe, albumin	API = 100% PBI = 2.85 PD – without pathological probing depths, GR on all 7 teeth (up to 2 mm); dryness of the oral cavity	Candida albicans
9.	M (70)	DM type II, renal failure, HA, anaemia,	bisprolol, lercanidipine,perindopril, moxonidine, methyldigoxin, warfarin, atorvastatin, pantoprazole* allopurinol, metoclopramide, paricalcitrol, calcium acetate and magnesium sub carbonate	↑MCV, RDW, HbA1c, GUK, urea, creatinine, CRP, ferritin, Mg, PTH ↓ e, Trc, Na, Fe, albumin	API = 100% PBI = 2.76 PD – without pathological probing depths, GR (up to 2 mm) and caries on all 17 teeth	Candida albicans and candida non-albicans

10.	M (66)	DM type II (+ DR), renal failure, HA, anaemia, hypothyroidism, gastrointestinal ulcer, psychiatric treatment	lercanidipine, urapidil, nebivolol, moxonidin, furosemide*, atorvastatin, pantoprazole*, allopurinol, glyceryl trinitrate, oxazepam*, tramadol*+paracetamol, zolpiden*, levothyroxine, paricalcitol, calcium acetate and magnesium bicarbonate	↑ RDW, Leu, HbA1c, GUK, urea, creatinine, urate, Ca, ferritin, PTH ↓e, Hb, Hct, ALT, ALP, Na, Fe	API = 89.6% PBI = 2.88 PD – without pathological probing depths, GR on all 24 teeth (up to 2 mm); dryness of the oral cavity	Yeasts are not isolated

Abbreviations and symbols:

DM – diabetes mellitus, DR – diabetic retinopathy, HA – arterial hypertension, e – erythrocyte count, Hb – haemoglobin concentration; Hct - haematocrit; MCV - mean volume of erythrocytes; MCHC - mean concentration of haemoglobin in erythrocytes; RDW - erythrocyte distribution width, Leu - leukocyte count, Trc - platelet count, GUK - blood glucose, HbA1c - glycated haemoglobin, AST - aspartate aminotransferase, ALT - alanine aminotransferase, GGT - gamma glutamyl transferase, ALP - alkaline phosphatase, CRP - c -reactive protein, Fe - iron, Ca - calcium, K - potassium, Na - sodium, Mg - magnesium, PO4 - inorganic phosphorus, PTH - parathyroid hormone; API – proximal plaque index, PBI – bleeding papilla index, PD – probing depth, GR – gingival recession; ↑ - increased value; ↓- reduced value.
Oral medications for diabetes are marked in bold in the table (the rest of the subjects took insulin preparations parenterally), and * medications for which the side effect of dry mouth is described in the literature.

The clinical findings of the oral cavity and the periodontal status showed that none of the subjects had satisfactory oral hygiene, considering that 66.67% of them had stage IV periodontitis, while the rest were completely toothless (Figures 1-3).

The results of the statistical analysis showed that there are no statistically significant differences between the sexes in relation to (partial) toothlessness, dryness of the oral cavity, values of blood and biochemical parameters, and oral swab results. Also, no statistically significant difference was found between patients with a positive oral swab result in relation to the presence or absence of teeth, dryness of the oral cavity, values of blood and biochemical parameters, nor the used insulin preparation (oral vs. parenteral).

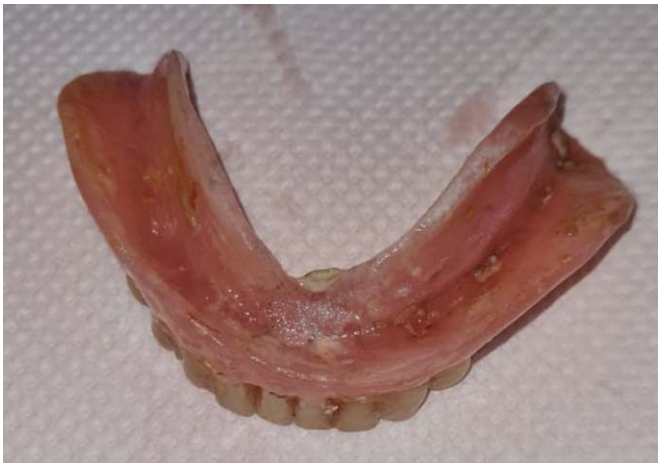

Figure 1. Outdated and inadequate prosthetic replacement of a patient with diabetes.

Discussion

With the increase in obesity, hypertension and low-quality nutrition, there is also an increase in the number of patients with DM. Due to the slow development of symptoms, most patients already have systemic complications at the time of diagnosis. Complications include diabetic retinopathy and nephropathy (gradual increase in proteinuria, which is paralleled by an increase in kidney dysfunction), atherosclerotic changes with the risk of stroke and heart attack, and gangrene. The risk of kidney failure is even twenty times higher in patients with DM compared to the rest of the population [6, 7, 25-30]. Control of glycemia, dyslipidaemia, and blood pressure, along with quality nutrition, smoking cessation, and reduction of obesity, are the main factors affecting the reduction of progression of diabetic nephropathy and chronic kidney disease, the consequences of which include dialysis treatment and kidney transplantation [8-10].

Due to the numerous symptoms and manifestations of DM in the oral cavity, dentists are often the first to suspect the diagnosis of diabetes in

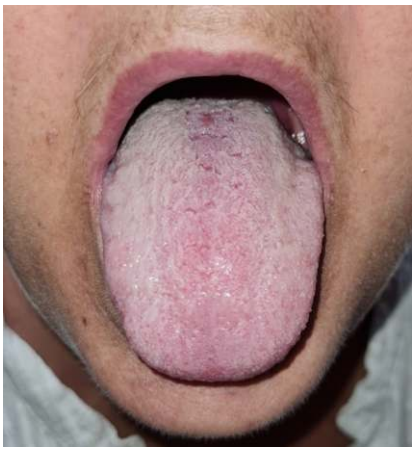

Figure 2. Coating of the tongue as a result of toothlessness, difficult consumption of solid food and dryness of the oral cavity.

Figure 3
2. Abundance of plaque and calculus on the front teeth of the lower jaw (periodontitis stage IV) in a patient with DM.

undiagnosed patients and refer them to their general practitioner. Thus, they help the patient to start therapy and treatment as soon as possible, which greatly contributes to reducing the complications of the disease and favours the overall health of the patient [1, 13]. The previously mentioned oral manifestations are collectively called diabetic stomatitis and include changes in the oral mucosa, blood vessels and salivary glands, which is associated with increased susceptibility to infections, weaker tissue healing and increased mucosal vulnerability [1, 5, 11]. In our research, as many as 80% of respondents reported the feeling of dry mouth.

According to the results of earlier research, among the most common symptoms in this group of patients, xerostomia and a tendency to fungal infections of the oral mucosa with the appearance of exfoliation on the lips predominate. Namely, the higher concentration of glucose in the saliva of patients with DM contributes to the acidity of the saliva, which, along with the lack of saliva secretion, creates favourable conditions for the development of microorganisms and the occurrence of caries and fungal diseases (22). In general, predisposing factors for the occurrence of fungal infection of the oral cavity include conditions and situations that lead to a decrease in the quantity and quality of saliva and changes in the microbiome of the oral cavity, among which are xerostomia and salivary gland dysfunction, age, wearing dental prostheses, smoking, malnutrition, use of antibiotics and immunosuppressants and xerogenic drugs, long-term use of mouth rinses and corticosteroid gels, a diet rich in carbohydrates and the consumption of dairy products with a high percentage of lactase that reduce the pH of the oral cavity, poor oral hygiene and systemic diseases and immunodeficiency conditions. Lack of iron, zinc, selenium, magnesium, folic acid, and vitamins A and B6 are also associated with candidiasis [16-20].

Dental therapy, as part of this research, also included education on the correct way to maintain oral hygiene. The treatment of oral candidiasis includes instructing the patient in the principles of proper oral hygiene, with a special emphasis on cleaning dentures with mandatory removal from the oral cavity before going to bed, and putting them in a glass of water with disinfectant for dentures. In addition to the above, it is necessary to carry out local or systemic antimycotic therapy and remove the previously mentioned risk factors (16). Although the results of this pilot study suggest that none of the investigated parameters has a significant influence on the interrelationship of oral candidiasis in haemodialysis patients with DM, they should be interpreted with caution. Namely, the limitations of this study include a small number of subjects who were not monitored longitudinally but cross-sectionally, and therefore it is not possible to clearly determine the influence of other anamnestic factors (e.g. subject to secondary anaemia, the effect of polytherapy) on the obtained values.

Also, the fact that patients are smokers, ex-smokers or non-smokers was not taken into account,

which, along with DM, is the main modifier of periodontitis class in the latest classification of periodontal diseases. Nevertheless, it is a pilot study that lays the foundation for monitoring this group of patients and for future research, but also highlights the fact that clinicians should rely solely on their clinical assessment and the possibility of recognizing the clinical picture of oral candidiasis without relying on the diagnostic examination of oral swabs, considering the fact that in 40% of cases yeasts are not isolated in patients with an evident clinical picture of fungal infection of the oral cavity (false negative results).

Conclusion

The results of this series of clinical cases showed that none of the patients had satisfactory oral hygiene, which emphasizes the importance of education and raising awareness about the importance of oral health and its impact on nephrological and general health of the organism at the national level. These findings indicate the need for additional research to precisely determine the mechanisms of mutual influence between DM and oral candidiasis. Further studies should focus on the development and implementation of preventive measures and the evaluation of their effect on improving the oral and general health of DM patients undergoing haemodialysis treatment. Patient education on proper oral hygiene techniques, regular dental check-ups and the adoption of healthy lifestyle habits, together with a multidisciplinary approach that includes dentists, nephrologists and diabetologists, can significantly contribute to reducing the prevalence of local and systemic manifestations and complications in this population. Ultimately, the results of this research can serve as a basis for creating guidelines and protocols to improve the oral health of patients with DM, thereby reducing the risks of DM-related complications and improving the quality of life of these patients.

Declaration of Interest: Authors declare NO conflict of interest

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