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Improving The Effectiveness of Treating Oral Changes Caused by Psychotropic Drugs

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ABSTRACT

Objective: *This study aimed to evaluate the effects of systemic hormone replacement therapy (HRT) on clinical and laboratory parameters of the oral cavity and salivary glands in women with surgically induced menopause.* ***Methods:*** *Seventy women aged 45 to 53 years with surgically induced menopause were examined. Thirty-four of these women received treatment to maintain dental health according to the traditional scheme, while thirty-six were additionally prescribed systemic HRT with transdermal gel "Estrogen" containing estradiol. A comparison group consisted of 34 premenopausal women. Hormonal status, dental condition indicators, and the properties and composition of mixed saliva were assessed. Cytological and microbiological studies of smears from the oral mucosa were conducted. Dynamic monitoring was performed preoperatively and at 3, 6, and 12 months post-surgery.* ***Results:*** *Women with surgically induced menopause, treated according to the traditional regimen, showed worsening clinical and laboratory indicators, including saliva quantity and quality, with signs of xerostomia, changes in the microbial landscape, and oral mucosal epithelium alterations. In contrast, women receiving HRT in addition to traditional treatment exhibited significantly less deterioration in these parameters.* ***Novelty:*** *This study reveals the positive effect of systemic hormone replacement therapy with transdermal estradiol on oral cavity health in women with surgically induced menopause, highlighting its role in mitigating adverse changes in the salivary glands and oral mucosa during early menopause.*

INTRODUCTION

has a significant impact on the hard tissues of the teeth, the oral mucosa, periodontal tissues, and the oral microflora. A number of studies have shown that the salivary glands change their structure and function with various fluctuations in sex steroids, which leads to qualitative changes in the composition of their secretion [1], [2]. In addition to the good vascularization of the oral tissues, i.e., the abundant supply of hormones through the bloodstream, the oral tissues have an additional source of free estrogens, the main female sex hormones contained in saliva [3], [4]. The direct effect of estrogens on salivary gland function has been demonstrated by studies showing increases in salivary flow rate, pH, and buffering capacity, decreased oral discomfort, and decreased lactobacilli burden in women undergoing natural menopause using hormone replacement therapy [2], [5].

Estrogen deficiency during menopause has a significant effect on the tissues of the oral cavity, as well as on other organs and systems of the female body, since the basal layer of the gingival epithelium contains specific nuclear receptors for estrogens, periodontal fibroblasts, the periodontal ligament, endothelial cells of the periodontal

vessels and the oral mucosa, cells of the alveolar and jaw bones, salivary glands and ducts, and tissues of the temporomandibular joints [6], [7], [8].

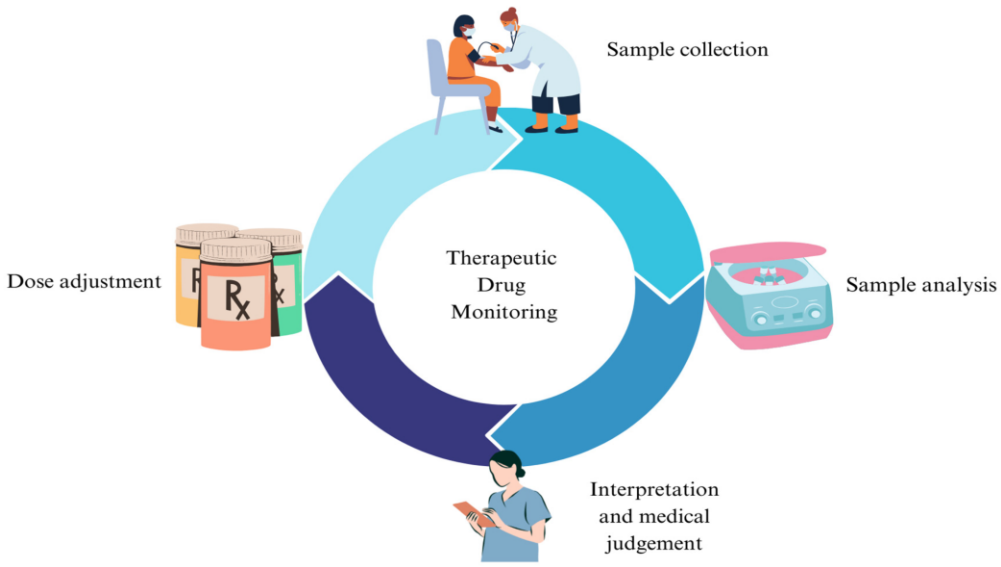

Figure 1. Therapeutic drug monitoring.

Changes in the state of the teeth that occur with estrogen deficiency in women with natural menopause are usually a smooth, genetically programmed process with specific adaptive mechanisms [9], [10]. Surgical menopause, which is a complete cessation of ovarian function once and for all, is the most severe biological stress for the body [3], [7]. The absolute and sudden lack of female sex hormones leads to maladaptation in the neuroendocrine system. The symptoms that appear in this case are more pronounced than in natural menopause [9], [11].

Changes in the state and function of the salivary glands during hypoestrogenism resulting from surgical menopause are still poorly understood, and there is practically no data describing the processes over time in the early postoperative stages. At the same time, the increase in the number of gynecological operations leading to complete cessation of ovarian function and the consistent development of medicine aimed at preventing the development of pathological processes determine the need to study this issue in order to predict and prevent complications from the dental system.

The aim of the study was to evaluate the effect of systemic hormone replacement therapy in the form of a transdermal gel "Estrogel" containing estradiol on clinical and laboratory parameters of the condition of the oral cavity and salivary glands in women with surgical menopause.

RESEARCH METHOD

The study included 104 patients, of whom the observation group included 70 women aged 45-53 years with surgical menopause. 34 of them (group 1) maintained their dental health according to the traditional regimen, and 36 (group 2) were additionally prescribed systemic hormone replacement therapy with transdermal gel "Estrogen"

containing estradiol. Patients were observed before surgical treatment (bilateral oophorectomy), and 3, 6 and 12 months after it. The comparison group consisted of 34 relatively healthy premenopausal women.

During the dental examination, special attention was paid to collecting complaints about dry mouth and its nature, clarifying the references. To obtain a detailed subjective description of the xerostomia syndrome and to determine its degree, the validated Russian version of the questionnaire for a comprehensive assessment of xerostomia "The Summed Xerostomia Inventory - XI" modified by Gileva OS was used. et al. (2014). To objectify the manifestations of dryness in the oral cavity, the clinical diagnostic scale of xerostomia "Challacombe Scale of Clinical Dry Mouth" (CSCOD) was used according to Challacombe SJ et al. (2008).

During a clinical examination of the oral cavity, the intensity of carious lesions was determined by the KPU and KPUp indices, the hygienic condition by the Green-Vermillion index (1964), the cariogenicity of dental plaque by Hardwick-Manlow. Edited by VB. Nedoseko (1991), the structural and functional resistance of enamel by the TER test by VR. Okushko in his modification (2011), the prevalence of gingivitis by the PMA index in the Parma modification (1960), bleeding gums by the Mulleman-Cowell index (1975).

When studying the physicochemical properties of mixed saliva, the secretion rate, viscosity were determined by the simplified method of Redinova-Pozdeeva (1994), pH by potentiometry, buffer capacity for acid and alkali by the method of VK Leontyev (1974), the quantitative content of K and Na ions on the ion-selective analyzer "EasyLyte Calcium" (Medica Corp, USA), the level of total Ca and inorganic P on the automatic biochemical analyzer "Sapphire-400" (TOKYO BOEKI. , Japan) using the reagents AS DiaS (with arsenazo III) and Phosphor-Vital calcium.

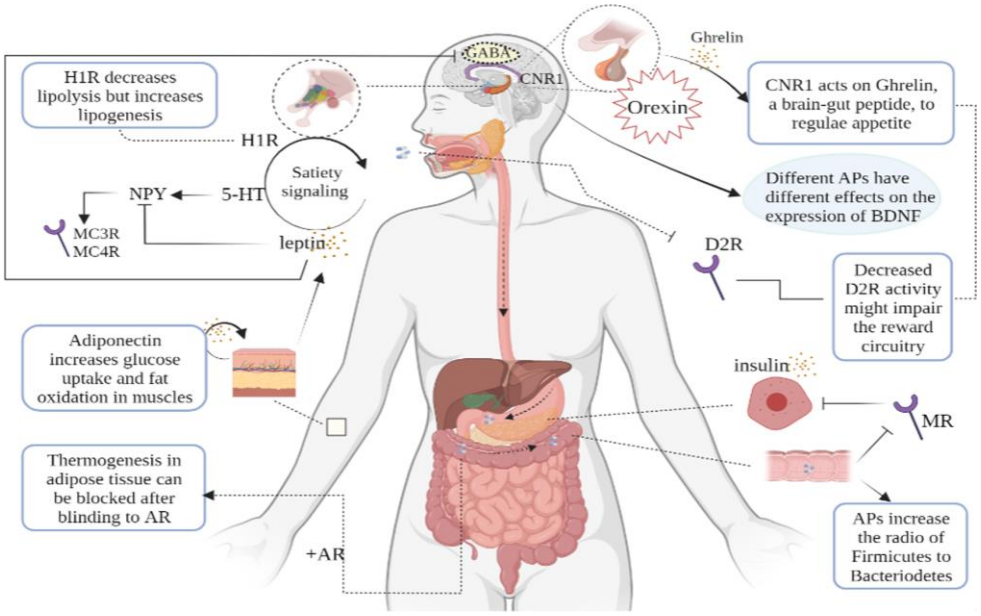

Figure 2. Measurement of physicochemical properties of mixed saliva using various methods and devices.

As a material for cytological research, smears of the oral mucosa were used, which were taken from the anterior third of the hard palate (the anterior two pairs of transverse palatine folds), the alveolar tubercles of the upper jaw and the lower retromolar region. jaw. Cytological examination was carried out by calculating the differentiation indices (IDI) and keratinization (IC) of epithelial cells. The stages of differentiation of epithelial cells were determined according to the method of Bykova IA. et al. (1987). The keratinization index (KI) was determined by calculating the percentage of anucleate cells in the cytological preparation according to NF. Danilevsky (1997). The nonspecific resistance of the oral mucosa was assessed by the adsorption reaction (RAM) of microorganisms by epithelial cells of the oral mucosa proposed by TA. Belenchuk (1985).

Microbiological studies were performed using traditional and instrumental methods on an automatic bacteriological analyzer WalkAway 40 SI (Siemens Healthcare Diagnostics Inc., USA). Material for the study was collected by taking smears from the mucous membranes of the cheeks along the line of closure of the teeth, alveolar tubercles and mandibular tubercles.

In the study of hormonal status, the state of the hypothalamic-pituitary-ovarian system was assessed by the level of follicle-stimulating hormone (FSH), luteinizing hormone (LH), as well as estradiol (E2) and progesterone (P) in the blood plasma. The study was conducted using a solid-phase enzyme-linked immunosorbent assay method using a vertical Multiscan photometer from Labsystem (Finland) and a special set of reagents from DRG Diagnostics (Germany).

The concentration of the free fraction of estradiol in mixed saliva was determined using a DYNEX MRX microplate spectrophotometer (Dynex Technologies, USA) and a special 17beta-Estradiol Saliva ELISA kit (IBL International GMBH).

Statistical processing of the material was carried out using the Statistica 8.0 program (StatSoft Inc., USA). The significance of differences between quantitative data in independent groups was determined by calculating the Mann-Whitney test, for the corresponding groups (within the group by type before and after) - by determining the Wilcoxon test, the differences were considered significant at p values ≤0.05.

RESULTS AND DISCUSSION

When analyzing the state of hormonal levels in women after surgery without hormonal correction (group 1), a significant decrease in estrogen levels was detected in the blood plasma (twice) and in mixed saliva (five times) at the three-month follow-up stage) compared with the initial state. In response to the cessation of endocrine activity of the ovaries in the pituitary gland, the release of gonadotropins FSH and LH increased. Progesterone concentrations remained stable throughout the study period. In patients in group 2, who received hormone replacement therapy (HRT) with a transdermal gel containing estradiol, no significant changes in the concentrations of the studied hormones were observed, which can be explained by the beneficial effect of the drug against the

background of acute reduction in estrogen production due to removal of the ovaries - the main sources of estrogen.

Figure 3. Change in pH of mixed saliva in patients from group 1 who did not receive hormonal correction after 12 months of observation.

Thus, in patients in group 1, a significant decrease in the rate of saliva secretion was noted against the background of an increase in its viscosity. In women in both compared groups, the pH change in mixed saliva at stages up to six months was insignificant and within normal limits, but in patients without hormonal correction at the twelfth month of observation, the acidity of the oral cavity increased liquid from 7.06 ± 0.07 to 6.6 ± 0.08.

Analysis of the dynamics of the composition of inorganic components of mixed saliva in women without hormone replacement therapy revealed a gradual decrease in the concentration of Na and total Ca, an increase in the concentration of K, while the concentration of P decreased significantly only after twelve months. surgical treatment. In patients with HRT, the concentration of the studied components remained at the initial level at all stages of the study.

The changes in buffer capacity values for acid and alkali in the patients under study did not differ significantly throughout the entire observation period.

A decrease in the rate of salivary flow, an increase in its viscosity and a change in its composition contributed to the appearance of dry mouth complaints in the examined patients with surgical menopause without hormonal correction. After three months, an increase in the sum of the scores on the questionnaire for a comprehensive assessment of xerostomia "Summated Xerostomia Inventory - XI" was noted, followed by a transition from mild to moderate xerostomia over the year of observation (Fig. 1).

The properties of mixed saliva and changes in the volume of its secretion were also reflected in other indicators of the dental condition of women with surgical menopause without hormonal correction. Thus, with a constant intensity of carious lesions of the hard tissues of the teeth (KPU = 12.3 ± 0.4, KPUp = 15.3 ± 0.52), a gradual deterioration of the hygienic condition of the mouth, assessed by the Green-Vermillion index, was observed. , a year after the operation, the result was from 0.93 ± 0.09 to 1.43 ± 0.1 points. An increase in dental plaque cariogenicity was noted from 1.68 ± 0.15 in the first stage of the study to 2.44 ± 0.14 points in the last, and from 5.79 ± 0.46 to 7.65 ± 0.43 points in the enamel resistance test (ER-test), respectively. . In addition, the above indicators in women changed significantly one year after surgery. In women in group 2, there were no significant negative changes in oral hygiene, dental plaque cariogenicity, and enamel resistance to acids.

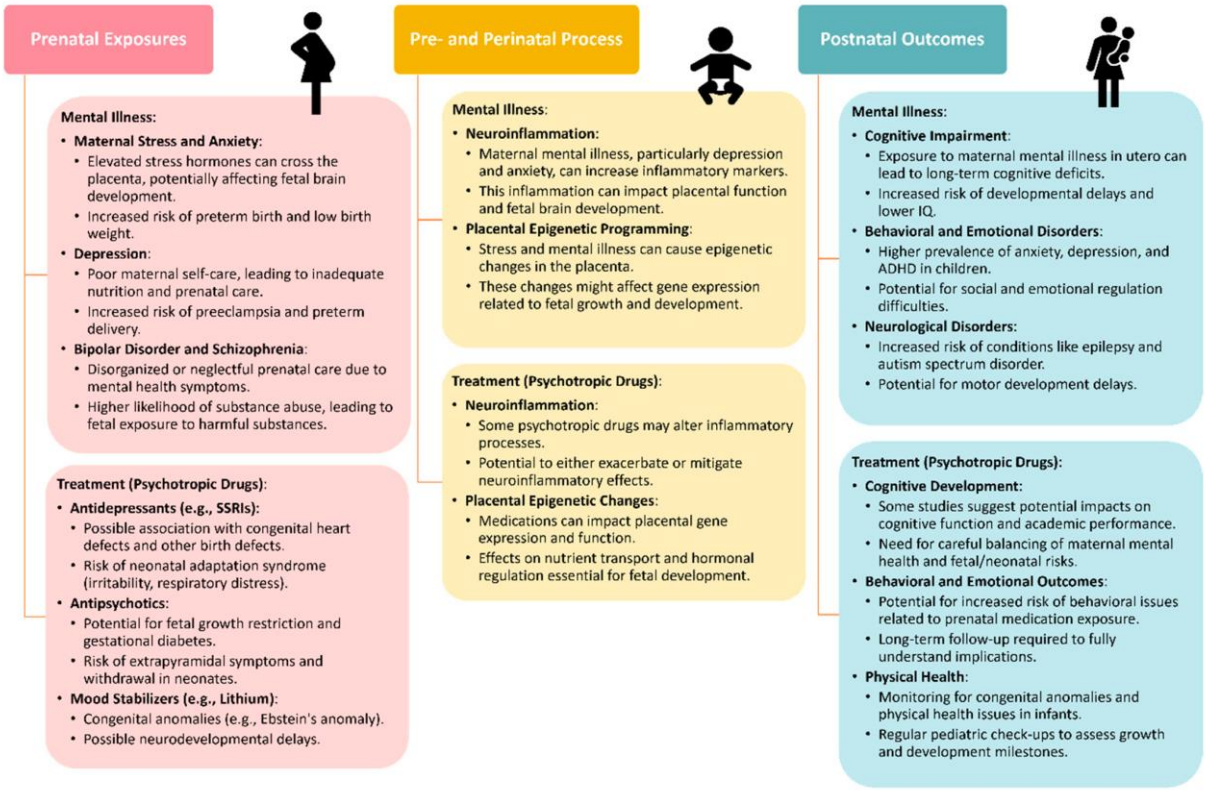

Figure 4. Changes in periodontal tissues in women.

In women of group 1, periodontal tissues underwent significant negative changes already in the third month of observation. Thus, in the study of the prevalence of gingivitis, a progressive increase in the values of the papillary-marginal-alveolar index was noted, which at the end was 16.22±1.52%, after 3 months - 19.49±1.63, after 6 months. - 22.3 ± 1.73, and a year after surgery - 25.12 ± 1.84.

In recent decades, a trend towards an increase in the number and expansion of the spectrum of lesions caused by opportunistic fungi has been clearly observed in all countries of the world, which poses the task of a targeted search for these pathogens,

effective identification in pathological material, as well as a correct assessment of their significance both in individual patients and in the pathology of modern man as a whole.

In the structure of mycotic pathology, opportunistic fungi occupy a leading place [3], [11], [12], they have a common feature - the ability to maintain long-term contact with human skin and mucous membranes, without causing pathological changes and causing them only on the skin. the presence of additional factors that suppress the body's local and systemic defense mechanisms. The increase in diseases caused by opportunistic fungi is associated with both an expansion of the range of risk factors and an increase in the number of people exposed to these factors [12], [1]. The oral mucosa can serve as a site of colonization and infection by potentially pathogenic microorganisms [3]. The main factor in the onset of the infectious candidiasis process is a violation of the body's nonspecific and specific resistance at the local and general levels [11]. The genus Candida includes 163 species, but the main role in human pathology is played by a limited number of species with a sharp predominance of C. albicans [3], [11]. Fungi of the genus Candida are classified as completely T-dependent antigens. The most active stimulators of cellular immunity are Candida proteins, and the most active stimulators of humoral immunity are mannan proteins of the fungal cell wall [12]. Specific IgG antibodies to cell wall proteins of Candida fungi are found in the majority of patients with candidiasis [1]. In modern therapy of mucosal candidiasis, antifungal azoles prevail. These drugs can be used locally or systemically. However, after therapy, some patients remain prone to relapses, the cause of which remains unknown. According to some authors Kent HL, Mardh PA , 1999, the cause of relapse lies in the failure of the body's immune system [9]. In particular, the main role is played by the deficiency of local immune mechanisms mediated by cells of the immune system. Changes in humoral immunity are associated with a decrease in the function of immunoregulatory suppressor T cells, which significantly affect the level of B-cell activity and, accordingly, the production of antibodies. In this regard, the use of immunocorrective therapy is justified. The search for new immunomodulatory drugs has allowed us to focus on the immunocorrector "Gepon", which is easily absorbed through the epithelium of the oral mucosa and effectively activates local immunity. Gepon has anti-inflammatory properties and improves regeneration [6], [13], [4], [15], [16].

Patients with a preliminary diagnosis of oral candidiasis underwent microscopy of a smear taken from the oral mucosa, as well as cultural diagnostics to identify the pathogen and determine its sensitivity to antifungal drugs [17], [18], [19]. The material for the study was oral fluid from patients with oral candidiasis, as well as venous blood from patients [20], [21], [22]. Oral fluid and venous blood were collected in the morning, on an empty stomach [23], [24]. To assess the local immunological status of the patient, the content of immunoglobulins in oral fluid was determined. Also, to detect specific antibodies to yeast-like fungi, an enzyme-linked immunosorbent blood test was used using a diagnostic kit to determine the titer of immunoglobulin G to fungi of the genus Candida. Blood serum was used for the study [25], [26], [27]. A study of immunological

parameters of oral fluid was carried out before treatment, an immunogram of oral fluid was performed a month after complex therapy. We observed 15 patients with oral candidiasis, in whose complex therapy the immunomodulator Gepon was used. The results of direct and long-term observations were obtained. Here is an example of a clinical case.

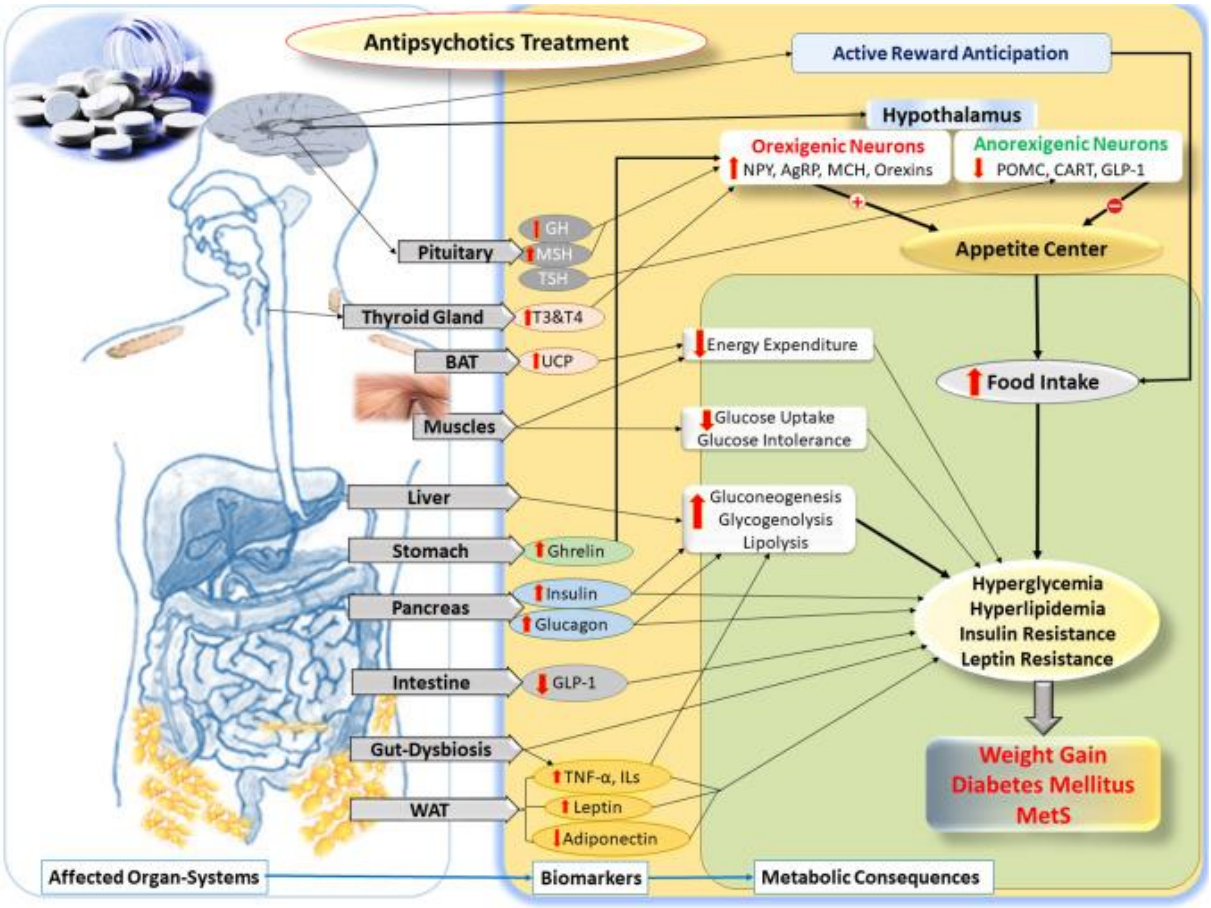

Figure 5. Clinical case.

When conducting an immunogram of oral fluid, the titer of immunoglobulins of the IgA, IgG, IgM classes was determined. According to the results, a decrease in secretory IgA to 0.03 g / l, compared to the norm of 0.069 ± 0.028 g / l, and IgG in oral fluid to 0.042 ± 0.017 g / l, compared to the norm of 0.026 g / l in the control group, as well as a decrease in the content of IgM to 0.04 g / l, compared to the norm of 0.055 ± 0.011 g / l.

Enzyme immunoassay of blood showed a deficiency of serum immunoglobulin G to Candida albicans fungi, its content in serum was 1.21 g / l, normal level is 1.5 ± 0.2 g / l. Based on the anamnesis, examination and diagnostic studies, a diagnosis of chronic pseudomembranous candidiasis was made.

Treatment: after cultural diagnostics and determination of antifungal sensitivity, the drug Diflucan, a selective inhibitor of sterol synthesis in fungal cells, was prescribed (50 mg, orally, once a day for 14 days). As an immunocorrector, the immunomodulator

"Gepon" was prescribed in the form of application to the oral mucosa for 20 minutes every day, the course was 7 days.

7 days after the start of therapy, a follow-up examination was performed with four applications of Gepon; The patient's complaints of burning sensation decreased, dry mouth disappeared, plaque on the tongue was significantly reduced and remained only on the root of the tongue. On examination, the oral mucosa was pale pink and normally moist. Local application of Gepon had a pronounced anti-inflammatory effect and effectively eliminated dryness of the oral mucosa.

CONCLUSION

Fundamental Finding : The study highlights that treatment of oral candidiasis, particularly chronic forms, is challenging due to a high relapse tendency. Long-term results suggest that restoration of the local immune status is essential for managing Candida albicans infections effectively. **Implication :** These findings suggest that therapeutic strategies should focus on enhancing the local immune response to prevent relapse in patients with oral candidiasis. Future treatments should prioritize immune restoration alongside antifungal therapy. **Limitation :** A key limitation of this study is its limited scope regarding the diversity of patients and the potential variability of immune response in different populations. Further research on broader patient groups is needed to validate these findings. **Future Research :** Future studies should explore more in-depth mechanisms of immune restoration and its integration with antifungal treatments for oral candidiasis. Investigating potential therapies targeting immune modulation could offer new solutions to prevent relapse in chronic cases.

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