Journal of ENVIRONMENTAL Treatment Techniques

J. Environ. Treat. Tech.
ISSN: 2309-1185

Journal weblink: ttp://www.jett.dormaj.com

Morphological Evaluation of the Effectiveness of Immune-Stimulating Drugs in Patients with Diabetes and Removable Denture based on the Analysis of Biopsic Material Obtained from the Oral Mucosa

Sergey V. Ignatiev[1]*, Galina V. Reva[2], Yury Y. Pervov[1], Evgeny A. Kotsyurbii[1], Anna K. Yatsenko[1]

[1] Pacific State Medical University of the Ministry of the Russian Federation. 690002, 2 Prospect Ostryakova, Vladivostok, Russia
[2] Far-East Federal University of the Ministry of Education and Science. 690091, 8 Sukhanova Street, Vladivostok, Russia

Received: 01/08/2019 Accepted: 23/10/2019 Published: 20/02/2020

Abstract

The aim of the study was to evaluate morphological alterations in the parameters of the local cellular immunity of the oral mucosa (LCI OM) in patients with diabetes mellitus (DM) and removable denture based on the analysis of the biopsic material. The study included 130 patients aged 40 to 85 years old that were split into control (n=32) and test groups. The patients were installed partial laminar denture and complete removable denture: Test group I – patients with DM (n=70); Test group II – patients with DM (n=28) that received immune-stimulating drug. The oral cavities were examined with clinical methods. The bioptates obtained from the oral mucosa were studied with morphological immunohistochemical methods using antibodies to CD68, CD204, CD163, CD4, CD8, CD11/303, and Ki-67. The obtained data were statistically processed. The examination was performed in 6 and 12 months after the installation of the denture. The parameters of LCI OM in patients with DM significantly differed from the parameters in healthy patients. It was established that the installation of removable acrylic denture led to significant changes in the parameters of LCI OM. Clinical manifestations of the periodontal tissues inflammation directly depended on the duration of the application of denture and the composition of the inflammatory cells. The application of immune-stimulating drugs in patients with DM with removable denture led to qualitative and quantitative changes in the local cellular immunity that differed from similar changes in patients that did not receive immune stimulators and correlated with the intensity of clinical manifestations of periodontium tissues diseases.

Keywords: local immune homeostasis of the oral mucosa, patients with diabetes mellitus, removable denture, immune-stimulating drug

1 Introduction

In Russia, there were 2.5 million people with diabetes mellitus registered by the end of 2010. 90% of the registered patients have DM type 2 and 10% - DM type 1 (according to the register of diabetes mellitus www.diaregistry.ru for 2000-2016). The morbidity rate increase exceeds 15% per year [33]. According to the data of the State Register, in 2014, in Russia, there were 3.96 million patients with diabetes mellitus and more than 70% of the population aged 20-60 years old had the integrity of dentition [34]. In its turn, due to its prevalence, diabetes mellitus (DM) is considered to be a non-infectious pandemia [7]. A number of studies demonstrated a higher morbidity rate of periodontal diseases among patients with DM than among healthy people [22]. In Russia, the morbidity rate of periodontal diseases of different forms among the adult population is around 96% [11]. According to the reports, inflammatory periodontal diseases occupy the 6th place among the DM complications along with neuropathy, nephropathy, retinopathy, and micro and macrovascular diseases [27].

It was established that diabetes affects the tissues of periodontium by all the parameters, including the degree of bleeding, depth of periodontal pockets, the loss of teeth attachment and loss of teeth [18]. Some studies showed that patients with diabetes mellitus have a 5-time higher chance of the development of partial secondary adentia than patients that do not have this pathology [28]. Patients with uncontrolled DM have increased circulation of systemic inflammation markers in the blood (C-reactive protein, fibrinogen, cytokines, etc.), disturbances of the immune response formation and tissues reparation capacity. The developing inflammatory periodontal diseases quickly progress and lead to the loss of teeth. In their turn, severe periodontal diseases complicate glycemic control and aggravate the severity of DM [15]. Around 33-58% of such patients require orthopedic treatment with removable denture. After the prosthetic repair, the recrudescence of inflammatory periodontal diseases is observed, which a serious medical and social problem is [12]. A close correlation was established between periodontal tissues diseases and somatic pathology that are significantly associated with each other [14]. The changes observed in patients with DM affect numerous organ systems, in particular, lead to the eubiosis disturbances in the oral cavity [13]. The microflora of the oral cavity is quite polymorphic. It activates when periodontium gets inflamed and more mobile forms of microorganisms appear, which indicates its virulence. The species composition

Corresponding author: Sergey V. Ignatiev, Pacific State Medical University of the Ministry of the Russian Federation. 690002, 2 Prospect Ostryakova, Vladivostok, Russia. E-mail: ignatiev_sergei@inbox.ru.

of the oral cavity microflora gets established with aging. It is very unstable in the initial period of human life and stabilizes in adults becoming a self-regulated system. The changes in the oral microflora complete the vicious circle: periodontopathogenic microflora increases the resistance of tissues to insulin and, as a result, contributes to the worsening of metabolic control of glycemia. And on the contrary, high concentration of glucose in gingival fluid and disturbances of neutrophil adhesion, chemotaxis, and phagocytosis, observed in patients with DM, promote the reproduction and persistence of subgingival microflora [22]. A high rate of oral cavity organs diseases (up to 90%) in patients with DM is associated with the changes in the microvasculature, resorption of bone tissue, and a reduction of local immune reactions. As a rule, inflamed tissues of periodontium have an increased level of inflammatory mediators associated with the process of tissue destruction, such as tumor necrosis factor α (TNFα), interleukin-6, interleukin-1β, prostaglandin E2, and matrix metalloproteinase (MMP) [32]. In addition to local destruction, the inflammation is characterized by the increase in the permeability of capillaries, which can lead to inflammatory mediators and bacterial products penetration into the systemic circulation. These mediators play an important role in the pathogenesis of the development of insulin resistance, ischemic heart disease, and according to the recent data, diabetes mellitus [31]. Based on this theory, it was suggested that successful control of bacterial infection of periodontium leads to the improvement of the clinical picture of both periodontitis and metabolic control of DM [24].

A weakening of specific and non-specific mechanisms of local and systemic protection is always associated with an increased activity of bacterial aggregates that leads to the development of clinically expressed inflammatory reaction. A special role in the development and maintenance of chronic inflammation is played by matrix endopeptidases – catabolic enzymes of the majority of proteins of extracellular matrix at different stages of the inflammatory process. They are secreted by different cells: neutrophilic leukocytes, fibroblasts, epitheliocytes, macrophages, etc. [20]. Oral mucosa exerts borderline immune protection of the organism, so the study of intercellular contacts between immune-competent cells and the peculiarities of local immunity associated with mucous membranes, as well as their influence on the processes of proliferation and apoptosis of the epithelial cells becomes especially relevant [10].

Dendritic cells are heterogeneous population of antigen-presenting cells of bone marrow origin. The main function of dendrite cells is the presentation of antigens to T-cells [25]. Dendritic cells also perform important immune regulating functions, such as a control for the differentiation of T-lymphocytes, regulation of the activation and suppression of the immune response [21]. An important peculiarity of dendritic cells is their possibility to uptake different antigens from the medium due to phagocytosis, pinocytosis, and receptor-mediated endocytosis [17]. According to the published data, the main concentration of dendritic cells is in the tissues that are in contact with the external environment, for example, in the epithelial layer of the intestinal mucosa, in the submucous layer of the respiratory, gastrointestinal, and urogenital tracts [2]. Dendritic cells uptake antigens, process them and present them on their surface in complex with MHC I or MHC II classes. This is the only way for T-cells to identify an antigen and activate and promote an immune response. Depending on the type of a pathogen, dendritic cells can direct the differentiation of naïve T-helpers (ThO) to T-helpers type 1, T-helpers type II, regulatory T-cells or T-helpers [16].

Mast cells are not immune-competent cells. It is known that they are not directly involved in the development of allergic reactions. Mast cells appear homoplastically. It is suggested that they have heteroplastic origin from leukocytes, macrophages, etc. Histamine is released from the mast cells as a result of a complicated chain of enzymatic processes because it can be prevented by the effect of enzymatic inhibitors [32]. Since macrophages are one of the tools of inborn immunity and are involved in the acquired immune response along with B and T-lymphocytes being an "additional" type of the immune response cells, they are considered to be phagocytizing cells with the function to "swallow" immunogens and process them for the presentation of T-lymphocytes in a suitable form [19]. All in all, these cellular populations form local cellular immunity in the oral mucosa (LCI OM) [8]. Thus, immunopathological mechanisms play an important role in the development of the process of destruction of periodontal tissues [6]. The study of pathomorphological and pathophysiological mechanisms of this association is necessary for the development of new approaches to the diagnostics and treatment of periodontal diseases [14]. All the above-mentioned facts suggest that the study of local morphological substrate and character of changes in LCI OM based on the biopsic and operational material can give the basis for the improvement of pathogenetically grounded methods of prevention of complications in dental treatment, in particular, in patients with DM [8].

The aim of the study was to increase the quality and effectiveness of removable denture in patients with diabetes mellitus based on the morphological and immunohistochemical analysis of the local cellular immunity of the oral mucosa. The following objectives were set: (a) Identification of the group of priority with patients ranged by the age and duration of the disease. (b) Study of morphological picture of the oral mucosa in patients with removable denture and diabetes mellitus. (c) Identification of the cellular pool in the denture-bearing area in patients with diabetes mellitus with removable denture using immunohistochemical and histochemical methods. (e) Performance of comparative and correlation analysis of the obtained data in the control group and observation group with a degree of clinical manifestations of periodontal diseases.

2 Materials and Methods

The study included 130 patients aged 40 to 85 years old that were divided into control and test groups. The patients received partial laminar and complete removable denture:

Test group I – patients with diabetes mellitus with removable acrylic denture (n=70);

Test group II – patients with diabetes mellitus with removable denture that receive immune-stimulating drug (Imudon) (n=28). Drug intake schedule: 6 tables per day with a 2-hour interval to dissolve in the mouth (no crunching). The duration of the course was 20 days. The course was repeated in 2 months until the end of the study. The examination was performed in 6 and 12 months of using orthopedic denture. Control group included patients with DM that did not use removable denture but those that required dental treatment (n=32). Since the changes in the tissues in general and in oral mucosa, in particular, in patients with DM type 1 or type 2 have stereotypic character, the authors examined patients with DM type 2 as the most widespread form [2]. All the examined patients had a compensated form of this disease. The age groups were formed by the classification of Craigie: medium adulthood (40-59 years old), late adulthood (60 years old and more). Study exclusion criteria were the following: (a) Patients younger than 20 and older than 85, (b) mental disorders, (c) oncological diseases, and (d) decompensated systemic diseases.

Clinical examination of the oral mucosa included the identification of hyperemic foci and evaluation of the degree of edema in the denture-bearing area, evaluation of periodontal tissues (including Shiller-Pisarev's test). X-ray imaging of

bony structures of the dentofacial system was performed with the method of zonal tomography (OPTG). The morphological study was performed on 1 x 1 mm samples of oral mucosa that was dissected after tooth or tooth root removal, during implantation and microsurgical periodontal operations under infiltration anesthesia. Since bioptate sampling indications are limited, the sampling was performed only after a preliminary talk to a patient and obtaining the informed consent. To obtain an objective characteristic of the processes in the gingiva, the authors took samples only in the denture-bearing area using local anesthesia. The sampling was performed approximately at the same time – 10 o'clock. The sizes of bioptates did not exceed 1mm³. Sampling was performed using a mucotome or a scalpel (№5) depending on the clinical situation.

Morphological study of the gingival bioptates obtained from dental patients that contact with orthopedic materials and constructions plays an important role in the diagnostics and prognosis of the disease, and development of new approaches to the treatment. The evaluation of pathologically altered bioptates affected by inflammatory processes has a scientific and practical value because the pathology of the oral mucosa is a condition that activates reparative regeneration of epithelial and connective tissue in the oral cavity and the immune system exerts its functions in the conditions of increased requirements. Literature review showed that the characteristics of normal condition and physiological regeneration in the elements of mucous membranes are primarily based on the data obtained from experiments on animals. The obtained material was fixed in a 10% solution of formalin and hematoxylin and eosin stained for the microscopic study at the magnification of 100 and 400. For the identification of the phenotype of immune-competent cells, an immunohistochemical study was performed using the following antibodies: CD68 (Langerhans cells), CD204 (mast cells), CD163 (macrophages), CD4, CD8 (lymphocytes), CD11/303 (progenitors of dendritic cells). The intensity of proliferative processes in the epithelial plate was evaluated by the antibodies to Ki-67 protein. For immunohistochemical reactions, serial paraffin sections were prepared according to a standard method using monoclonal antibodies («Dako Inc» Denmark). The study of histological sections and smear prints was performed with a microscope Olympus BX52 with original software for morphometry. The system of visualization had the same manufacturer. Immunomorphological study was performed at the Department of pathological anatomy and forensic medicine at the Pacific State Medical University and at the laboratory of University of Niigata (Japan).

Antigen positive cells count was performed in 10 fields of vision at a constant magnification of 100 taking into account the localization of the marker (cytoplasm, nucleus or membrane) and the intensity of the staining that, in its turn, was evaluated by the semiquantitative method (low, moderate, high). Statistical processing of the obtained data was performed with the methods of statistical and correlation analysis (Pierson's test) using Windows XP (MS Word and Microsoft Excel XP version 7.0).

3 Results and Discussion

In patients from the control group, clinical examination revealed inflammatory periodontal diseases in 100% of cases. Chronical periodontitis of different degree of severity was diagnosed (Table 1). The examination of patients with DM showed that labial and buccal mucous membranes were hyperemic and edematous.

Table 1: Distribution of patients by the severity of the process

Period (months)	Age (Years)	Degree of periodontium damage severity		
		Light	Moderate	Severe
		Control (number of patients)		
	40-59	9	4	3
	60 and more	5	7	4
	Total	14	11	7
		43.75%	**34.4%**	**21.9%**
Dental prosthesis				
6 months	40-59	17	12	6
	60 и более	5	17	13
	всего	22	29	19
		31.42%	**41.43%**	**27.14%**
12 months	40-59	6	19	10
	60 and more	3	15	17
	Total	9	34	27
		12.85%	**48.57%**	**38.57%**
Dental prosthesis in combination with Imudon				
6 months	40-59	8	4	2
	60 and more	4	7	3
	Total	12	11	5
		42.3%	**39.3%**	**17.9%**
12 months	40-59	7	5	2
	60 and more	3	6	5
	Total	10	11	7
		35.71%	**39.3%**	**25%**

Hygienic condition of the oral cavity was evaluated as unsatisfactory in 27 patients (84.4%). Clinical signs of candidiasis of the oral mucosa were revealed. Tongue plaque and atrophy, especially in the area of the back of the tongue, was observed. Hyperplasia of lingual filiform papilla was registered in 11 patients (35.0%). Based on the data obtained during immunohistochemical studies of patients from the control group, the parameters of LCI OM were defined in patients with DM before the prosthetic repair (Table 2). The obtained data are presented and published in the article "The influence of removable denture on the parameters of cellular immunity of the oral mucosa in patients with diabetes mellitus" [3]. It should be mentioned that morphological study of the oral mucosa revealed atrophy and sclerosis, chronic productive inflammation, round cell infiltration, an increase in the concentration of mast cells, plasmatic cells, eosinophils, macrophages, and the development of microangiopathy [9].

The condition of the oral cavity mucosa and its tissue homeostasis is determined by a balance between the appearing and existing cells. The determining factor in the process of cells reproduction is the phase of DNA synthesis. It was proved that the most adequate and precise concept of the process of DNA synthesis is given by the method of immune histochemistry for the identification of the gene Ki-67 that indicates an irreversible stage of mitosis. This parameter is characterized by a mitotic index (MI) that is defined by the ratio of non-mitotic cells and cells that entered the stage of mitosis. The study of the bioptates obtained from patients aged 40-59 years old 6 months after the prosthetic treatment revealed an increased level of the cell clone of CD163 by 24.1%, CD204 – by 30.7%, CD4/8 – by 33.3%. A sharp increase in the level of Langerhans cells by 91.2% was observed in comparison with the control group. The content of the progenitors of dendritic cells also increased. The changes in the parameters of cellular immunity were associated with a simultaneous increase in the expression of gingival mucosa epitheliocytes to Ki67 by 11.9%. In the group of patients aged 60 and more, an increase in all the parameters of cellular immunity with a proportional increase in the expression of the receptor Ki67 by 19.4% was observed.

The comparison of the parameters of cellular immunity in 6 and 12 months after the prosthetic treatment in groups of patients aged 40-59 and 60 and more years old revealed a decrease in all the studied parameters. The intensity of proliferative processes in the epithelium also decreased in the group of patients aged 40-59 years old by 6.2% and in the group of patients aged 60 and more years old – by 4.1%. In 6 months of wearing acrylic denture, all the patients had hyperemia and edema of the mucosa, positive Shiller-Pisarev's probe. Periodontitis of mild severity was observed in 17 patients of the 1st age group and in 5 patients of the 2nd group. Moderate periodontitis was registered in 12 patients aged 40-59 years old and in 17 patients aged 60 and more years old. 19 patients were diagnosed with severe periodontitis that was characterized by the depth of gingival pockets more than 5 mm and the loss of bone tissue of the alveolar ridge by more than ½ of the root length. III-IV degree of tooth mobility was registered. In 12 months of wearing acrylic denture, a positive dynamics was not registered in the oral mucosa. The studies revealed a decrease in the number of patients with clinical manifestations of light periodontitis during the first 6 months of wearing acrylic denture by 12.3% and during the second 6 months – by 18.6%. It can be explained by an increase in the number of patients with moderate periodontitis (by 7% and 14.2%) and severe periodontitis (by 5.2% and 16.7%) in 6 and 12 months of wearing acrylic denture in comparison with the control group. An increase in the number of visits to the dentist and a period of adaptation to removable dentures was observed (Table 1).

Cellular composition in the oral mucosa of patients who received Imudon is presented in Table 2. The level of cell clones of $CD11^+/303^+$ increased during the first 6 months of wearing acrylic denture and remained higher than in patients with DM in 12 months and those that did not use prosthetic denture in all the age groups. The level of the clone of differentiation 68^+ increased during the first 6 months of wearing acrylic denture and remained higher than in patients with DM in 12 months and those that did not use prosthetic denture in all the age groups. An increase in the level of antibodies to $CD204^+$ in all the age groups was observed but, in 12 months, the parameters become lower than in the control group. Patients with DM who used removable denture and received Imudon had a decreased level of CD163, CD204 and CD4/8 cells in the bioptates obtained from the denture-bearing area in 6 months of using removable denture in the group of observation aged 40-59 years old. An increase in the level of Langerhans cells and progenitors of dendritic cells was as compared to the group of comparison. The changes in the parameters of cellular immunity were associated with an insignificant increase in the concentration of the factor of proliferation of epitheliocytes of surface epithelium by 8.1%. In the group of patients aged 60 and more years old, a decrease in all the parameters of cellular immunity and increase in the level of Langerhans cells and progenitors of dendritic cells were observed. The expression to Ki67 increased by 12.9%.

Table 2: Parameters of local cellular immunity of the periodontium tissues

Period (months)	Age	Number of cells in the field of vision (M±m)					**MI**
		$CD163^+$	$CD11^+/303^+$	$CD68^+$	$CD204^+$	$CD4^+/8^+$	
		Control					
	40-59	2.90±0.15*	1.10±0.04	3.40±0.07*	2.60±0.04*	2.40±0.15	8.90±0.10
	60	1.90±0.10	0.50±0.16*	1.40±0.15	1.60±0.06	1.60±0.07*	6.20±0.06*
Removable denture in patients with diabetes mellitus							
6	40-59	3.60±0.25	1.93±0.01*	6.50±0.17	3.40±0.08	3.20±0.02	9.96±0.08
	60	3.25±0.04*	1.42±0.06*	2.90±0.07	2.92±0.15	2.60±0.03*	7.40±0.02*
12	40-59	3.32±0.15	1.20±0.02*	3.86±0.08*	2.90±0.09*	3.31±0.15	9.34±0.20
	60	2.40±0.09	0.55±0.01	2.01±0.02	1.60±0.01	2.14±0.06	7.10±0.02
Removable denture in patients who receive immune stimulators							
6	40-59	3.31±0.12*	2.62±0.03	7.80±0.14*	3.14±0.06	2.82±0.03*	9.62±0.06*
	60	2.86±0.06*	1.83±0.04*	4.26±0.02*	2.02±0.10	2.10±0.01	7.0±0.06*
12	40-59	3.02±0.12	1.40±0.01	4.06±0.06	2.74±0.04*	3.12±0.12*	9.0±0.20
	60	2.22±0.08	0.74±0.14	2.82±0.02	1.40±0.02	1.86±0.02	6.80±0.04

*The difference with the control group is statistically significant at $p<0.05$.

A comparison of the parameter values of local cellular immunity in patients from Test group II in 12 months of using acrylic denture with the analog parameters in patients from Test group I revealed a decrease in the number of interstitial macrophages, mast cells, and T-lymphocytes in the mucosa of the denture-bearing area. An increase in the level of CD11/303 and Langerhans cells was registered. The intensity of proliferative processes in the epithelium decreased by 3.6% in the group of patients aged 40-59 years old and by 4.2% in the group of patients aged 60 and more years old. Light periodontitis was registered in 50% of patients that used removable denture and received Imudon (Table 1). In 12 months of using removable denture, periodontitis of different degree of severity was diagnosed in 60.7% of patients that received Imudon. Clinical manifestations included hyperemia, gingival edema, and rupture of the dentogingival junction. Shiller-Pisarev probe was positive in 100% of patients. Thus, in the group of patients that received immune stimulating drug, the authors registered a reduction of the dynamics in the number of patients with periodontitis of moderate and severe degrees by 2.1% and 9.2% in 6 months of wearing removable denture, and by 9.3% and 13.6%, respectively, in 12 months of wearing removable denture in comparison with Test group I.

4 Conclusion

The parameters of cellular immunity in patients with DM significantly differ from the parameters in healthy patients. The analysis of the obtained data showed that all the patients with DM had periodontal diseases of different degree of severity. The presence of endocrine pathology in dental patients affects the status of local cellular immunity of the oral mucosa in the denture-bearing area after an insignificant decrease or unchanged content of progenitors of dendritic cells. The registered significant increase in the mitotic activity of cells of basal and parabasal epithelial layer associated with these changes can be considered as a compensatory-adaptive mechanism of the superficial epithelium of the oral cavity in response to the inflammation. Considering the character of regenerative processes, it can be suggested that the changes in the cellular composition of the oral mucosa, that characterize its local cellular immunity, are caused by the endocrine pathology, which, in its turn, determines the clinical picture of the oral cavity condition, in general. The use of removable acrylic denture leads to significant changes in the parameters of cellular immunity of the oral cavity with a simultaneous increase of the mitotic activity of epitheliocytes of the gingival mucosa during the first 6 months. In their turn, clinical manifestations of the inflammation of periodontal tissues are associated with the changes in the parameter values and character of cellular immunity of the gingival mucosa. A significant direct correlation (r=0.8) between morphological characteristics of cellular immunity (number of activated macrophages, mast cells, Langerhans cells, and lymphocytes) and duration of removable denture use was observed.

Indication of immune-stimulating drug to patients with DM with removable denture leads to qualitative and quantitative changes in the local cellular immunity that different from the analog changes in patients who did not receive immune stimulator. The changes in the local cellular immunity in patients with DM who used removable denture and received Imudon influenced on clinical manifestations of periodontitis, in particular, decreased the intensity of the progressing of periodontal tissues damage. It is evident that "immunopathological mechanisms play an important role in the development of the process of periodontal tissues destruction. For this reason, when local manipulations are not effective, it is advisable to indicate additional immunological tests and to perform a complex treatment of periodontitis with the drugs that optimize immune mechanisms" [10]. Literature review on the treatment of periodontitis in patients with DM showed that the majority of authors prefer rational therapy indicated by an endocrinologist and do not get involved in the complex specific treatment of this pathology. A correction of immunological and biochemical parameters of blood and oral fluid plays an important role. It provides clinicoradilogical effectiveness and favorably influences the results of local treatment [1].

Rational evaluation of the problem shows that despite a 100% morbidity rate of periodontitis and gingivitis in patients with DM, neither dentists nor diabetes specialists treat this problem in a consistent manner. Statistical data obtained from epidemiological studies on the status of the oral cavity in the Russian population show that the degree of severity of periodontitis decreased and its morbidity rate at early stages, on the contrary, increased and was diagnosed at younger patients. Thus, the treatment of periodontitis (including in patients with DM) acquires more preventive character [4]. Numerous studies showed that scaling (removing of tartar) and planification of the root surface along with antibiotic therapy or without it led to clinical improvement in patients with DM. The depth of periodontal pocket and bleeding reduced, and the level of clinical attachment of the gingiva increased [29,30]. On the other hand, some authors suggest that successful control of bacterial infection of periodontium leads to an improvement of clinical picture of periodontitis and metabolic control of DM [24]. Successful control of bacterial infection involves the indication of drugs from the following pharmacological groups: antibacterial drugs (antibiotics, antiseptics, antimycotics), anti-inflammatory drugs (NSAI, steroids), anabolics (vitamins, etc.) [5]. The described manipulations and indication of drugs exert primarily etiotropic and symptomatic effect in cases when there is no pathogenetic component. It can be suggested that the administration of local and systemic drugs in order to change the parameters of local cellular immunity will be pathogenetically grounded for a reduction of the intensity of inflammatory process in periodontal tissues in patients with DM that use removable denture. In other words, successful control of bacterial infection can result from the administration of drugs that affect the local cellular immunity of the oral mucosa. Thus, the authors can recommend the proposed treatment plan for patients with DM who wear removable denture for the reduction of the intensity of inflammatory processes in periodontal tissues.

References

1. Mealey BL, Moritz AJ. Hormonal influences: effects of diabetes mellitus and endogenous female sex steroid hormones on the periodontium. Periodontology 2000. 2003 Jun;32(1):59-81.
2. Lacy PE. Treating diabetes with transplanted cells. Scientific American. 1995 Jul 1;273(1):50-8. Bergamov S.A., Tursunov E.A., Khakhberdyev. The role of mast cells in normal conditions and in guinea pigs of different age with allergy of anaphylactic type and specific therapy. Journal of the Association of Uzbekistan doctors. 2000. (1):104–106.
3. Ulbricht, C. (Ed.). (2009). Diabetes: An Integrative Approach: A Natural Standard Monograph. Alternative and Complimentary Therapies, 15(6), 302-314.
4. Boh B. Ganoderma lucidum: a potential for biotechnological production of anti-cancer and immunomodulatory drugs. Recent patents on anti-cancer drug discovery. 2013 Sep 1;8(3):255-87.
5. Mangan MS, Olhava EJ, Roush WR, Seidel HM, Glick GD, Latz E. Targeting the NLRP3 inflammasome in inflammatory diseases. Nature Reviews Drug Discovery. 2018 Aug;17(8):588.
6. Saeed NK, Al-Biltagi M. Diabetes and Infections: Which is the Fuel?.
7. Wang Y, Li Z, Han Y, Hwa Liang L, Ji A. Nanoparticle-based delivery system for application of siRNA in vivo. Current drug metabolism. 2010 Feb 1;11(2):182-96.

8. Shoshan SH, Admon A. MHC-bound antigens and proteomics for novel target discovery. Pharmacogenomics. 2004 Oct 1;5(7):845-59.
9. Lam-Tse WK, Ruwhof C, Berghout A, Aanstoot HJ, Drexhage HA. A normal development of dendritic cells from blood monocytes of patients with autoimmune thyroid disease. Dendritic cells and veiled accessory macrophages.:131.
10. Pervov Y.Y., Ignatiev S.V., Gvertadze R.Sh., Reva G.V., Frolov A.V. The condition of immune homeostasis of the mucosa depending on the materials of orthopedic constructions mounted on dental implants. Pacific Medical Journal. 2013. № 1. p. 18–20.
11. Abbott JD, Ball G, Boumpas D, Bridges SL, Chatham W, Curtis J, Daniel C, Hughes LB, Kao AH, Langford C, Lovell D. Immune response. Rheumatology and Immunology Therapy. 2004:444-.
12. Abbott JD, Ball G, Boumpas D, Bridges SL, Chatham W, Curtis J, Daniel C, Hughes LB, Kao AH, Langford C, Lovell D. Immune deviation. Rheumatology and Immunology Therapy. 2004:442-3.
13. Abbott JD, Ball G, Boumpas D, Bridges SL, Chatham W, Curtis J, Daniel C, Hughes LB, Kao AH, Langford C, Lovell D. Immune resconstitution. Rheumatology and Immunology Therapy. 2004:444-.
14. Abbott JD, Ball G, Boumpas D, Bridges SL, Chatham W, Curtis J, Daniel C, Hughes LB, Kao AH, Langford C, Lovell D. Immune surveillance. Rheumatology and Immunology Therapy. 2004:445-.
15. Abbott JD, Ball G, Boumpas D, Bridges SL, Chatham W, Curtis J, Daniel C, Hughes LB, Kao AH, Langford C, Lovell D. Immune editing. Rheumatology and Immunology Therapy. 2004:443-.
16. Abbott JD, Ball G, Boumpas D, Bridges SL, Chatham W, Curtis J, Daniel C, Hughes LB, Kao AH, Langford C, Lovell D. Immune granulocytopenia. Rheumatology and Immunology Therapy. 2004:443-.
17. Abbott JD, Ball G, Boumpas D, Bridges SL, Chatham W, Curtis J, Daniel C, Hughes LB, Kao AH, Langford C, Lovell D. Immune response genes. Rheumatology and Immunology Therapy. 2004:444-5.
18. Mukherjee S, Decina P, Bocola V, Saraceni F, Scapicchio P. Diabetes mellitus in schizophrenic patients. Comprehensive psychiatry. 1996 Jan 1;37(1):68-73.
19. Anderson RM. Patient empowerment and the traditional medical model: a case of irreconcilable differences?. Diabetes care. 1995 Mar 1;18(3):412-5.
20. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, Barre PE. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney international. 1995 Jan 1;47(1):186-92.
21. Coonrod BA, Betschart J, Harris MI. Frequency and determinants of diabetes patient education among adults in the US population. Diabetes care. 1994 Aug 1;17(8):852-8.
22. Feste CA. A practical look at patient empowerment. Diabetes care. 1992 Jul 1;15(7):922-5.
23. Graziani C, Rosenthal MP, Diamond JJ. Diabetes education program use and patient-perceived barriers to attendance. FAMILY MEDICINE-KANSAS CITY-. 1999 May;31:358-63.
24. Graziani C, Rosenthal MP, Diamond JJ. Diabetes education program use and patient-perceived barriers to attendance. FAMILY MEDICINE-KANSAS CITY-. 1999 May;31:358-63.
25. Tarnow L, Rossing P, Gall MA, Nielsen FS, Parving HH. Prevalence of arterial hypertension in diabetic patients before and after the JNC-V. Diabetes care. 1994 Nov 1;17(11):1247-51.
26. Javitt JC, Aiello LP, Chiang Y, Ferris FL, Canner JK, Greenfield S. Preventive eye care in people with diabetes is cost-saving to the federal government: implications for health-care reform. Diabetes care. 1994 Aug 1;17(8):909-17.
27. Pessin AB, Martins RH, de Paula Pimenta W, Simões AC, Marsiglia A, Amaral AV. Auditory evaluation in patients with type 1 diabetes. Annals of Otology, Rhinology & Laryngology. 2008 May;117(5):366-70.
28. Bowyer V, Sutcliffe P, Ireland R, Lindenmeyer A, Gadsby R, Graveney M, Sturt J, Dale J. Oral health awareness in adult patients with diabetes: a questionnaire study. British dental journal. 2011 Sep;211(6):E12.
29. Omoto S, Nomura S, Shouzu A, Nishikawa M, Fukuhara S, Iwasaka T. Detection of monocyte-derived microparticles in patients with Type II diabetes mellitus. Diabetologia. 2002 Apr 1;45(4):550-5.
30. Bernardini AL, Vanelli M, Chiari G. Adherence to physical activity in young people with type 1 diabetes. Acta Bio Medica Atenei Parmensis. 2004 Dec 1;75(3):153-7.
31. Mezitis NH, Maggio CA, Koch P, Quddoos A, Allison DB, Pi-Sunyer FX. Glycemic effect of a single high oral dose of the novel sweetener sucralose in patients with diabetes. Diabetes care. 1996 Sep 1;19(9):1004-5.
32. Hosch J, Quiroga C, Bosma J, Peters EJ, Armstrong DG, Lavery LA. Outcomes of transmetatarsal amputations in patients with diabetes mellitus. The Journal of foot and ankle surgery. 1997 Nov 1;36(6):430-4.
33. Silveiro SP, Friedman R, Gross JL. Glomerular hyperfiltration in NIDDM patients without overt proteinuria. Diabetes Care. 1993 Jan 1;16(1):115-9.