



Clinical and Immunological Characteristics of Patients with Odontogenic Maxillary Sinusitis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Inflammatory diseases of the maxillary sinus of odontogenic aetiology have a high prevalence and hold leading positions in the structure of otorhinolaryngological and dental morbidity. High-intensity lesions in all age and social groups, the lack of over the last decade a downward trend in frequency, refractory to traditional drug therapy determine the high medical and social problem significance. To date, the main treatment standard is the surgical removal of the "causal" infection focus, but this stage is not always resolved by complete recovery, in consequence of which the disease acquires a cyclical character. Many authors point out the role of the immune system in chronization of the inflammatory process in the sinuses and the development of exacerbation frequent periods. Treatment of odontogenic sinusitis is more complex and prone to relapses. The main objectives of treatment are differential diagnosis of odontogenic sinusitis and its treatment. In

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this regard, determination of the immunological reactivity state and search for pathogenetically significant disorders in the effector protective link in patients with odontogenic sinusitis becomes especially relevant. The article presents a detailed analysis of the immune status of 60 patients with odontogenic maxillary sinusitis caused by acute periodontitis, radicular cyst, and filling material. Clearly demonstrated the results of the paranasal sinuses x-ray examination and clinical examination of patients. In the course of the research were found significant changes of immunological indicators for several considered criteria. They indicate the presence of pronounced autoimmune shifts in the subjects, which play a key role in aggravating the disease severity and its outcome. This type of research is crucial for the development of improved drug therapy strategies for individuals with odontogenic sinusitis aimed at correcting immune disorders. The aim of the article is research of the immunological molecular changes that occur in odontogenic sinusitis, and to lay the foundation for studying the molecular mechanism of odontogenic sinusitis.

Keywords: Odontogenic maxillary sinusitis; immune status.

1. INTRODUCTION

Currently, along with the high prevalence of paranasal sinuses inflammatory diseases, there is an increase in the number of patients with complicated forms of odontogenic maxillary sinusitis (OMS), which are difficult to treat [1,2]. The progressive course, short remission period, and negative impact on the general somatic status determine the high medical and social significance of this problem and dictate the need to create innovative methods of preclinical diagnostics, promising schemes of complex treatment, and effective measures to prevent the incidence rate increase [3-5].

According to authoritative researchers, low effectiveness of OMS therapy is related to the presence of polyresistant microbial strains, low compliance of patients and late treatment for qualified help [6,7]. At the same time, the widespread tactic of dealing with OMS complications exclusively with antimicrobial drugs does not justify itself [8,9]. As a result, it becomes necessary to switch from a unipolar classical treatment regimen to an integrative treatment model combining the eradication of the bacterial factor and the correction of violations of the effector defense mechanisms [10,11].

In the OMS pathogenesis, the predominant role belongs to microbial contamination occurred within the upper jaw teeth and passed to the maxillary sinus due to their close anatomical proximity [12-14]. Long-term persistence of highly virulent microflora significantly changes the reactivity of the Schneiderian membrane. It leads to the destabilization of local protective reactions, which are manifested in a decrease in the non-specific resistance factors activity and the residents of antral biocenosis composition

displacement [15]. As a result of inflammatory-destructive processes, mucociliary clearance functions are inhibited. It leads to the accumulation of purulent exudate, violation of drainage and aeration of the maxillary sinuses, metaplasia of the simple ciliated epithelium in a scaly stratified epithelium [16]. In addition, prolonged entry of alien agents and tissue breakdown products into the internal environment can initiate immunopathological processes, which are expressed in sensitization to antigens of damaged sinus tissues [17]. All this dictates the need for dentists to revise the traditional views on the cure of patients with OMS and inculcation a stepped approach in clinical practice, which provides for the elimination of the "causal" factor and normalization of changes initiated by it. Substantiation of a complex of etiologically and pathogenetically justified therapeutic measures is possible only if there is a convincing evidence of the specific trigger factors participation, as well as establishing consistent mechanisms for maintaining and modulating the pathological process in the future [18]. In this regard, an important link in the examination of individuals with OMS is determined by the evaluation of the immune status, allowing to identify pathogenetically significant immunological disorders [19].

The aim of the article is research of the immunological molecular changes that occur in odontogenic sinusitis, and to lay the foundation for studying the molecular mechanism of odontogenic sinusitis

2. MATERIALS AND METHODS

Based on primary screening results, a follow-up group was formed from 60 patients with an

average age of 40.3 ± 2.7 years with a diagnosis of odontogenic maxillary sinusitis (OMS). The causes of the disease were the following: acute periodontitis (20 people), odontogenic radicular cyst (20 people), foreign objects in the maxillary sinus (filling material) 20 people. Reference data were obtained from 30 intact patients with an average age of 42.6 ± 2.3 years, without acute and relapse of chronic somatic diseases formed the control group. Proband of both groups were comparable in gender and as close as possible in the age category. At the initial stage of the study, participants were asked to fill out voluntary informed consent and questionnaires with questions allowed them to assess the functional state of the organism and the presence of comorbidities. Antibiotic therapy, systemic autoimmune, allergic, infectious diseases, and diabetes mellitus were the criteria for exclusion. Peripheral venous blood and fingerstick blood were the study materials. In order to verify the diagnosis, all the subjects of the main group underwent an x-ray examination. It allowed to identify the extent and exact localization of the odontogenic infection focus, the possible spread of the inflammatory process to the neighbouring paranasal sinuses, as well as to determine the periapical tissues of the teeth condition and the presence of radiopaque foreign objects in the sinus. Depending on the indications, we performed orthopantomography on the orthopantomograph "Ortopantomograph OP 100" (Instrumentarium Imaging, Finland) and cone beam computed tomography (CBCT) of the paranasal sinuses using the "PaX-Zenith 3D" tomograph (Vatech, South Korea).

Immunological researches included a comprehensive assessment of the immune status and the use of indicative and analytical methods. Determination of the level of main classes (IgG, IgM, IgA) immunoglobulins in blood serum and C3 -, C4- components of the complement system was performed using a solid-phase "sandwich" - enzyme-linked immunosorbent assay (ELISA) on the immunoassay analyzer "Multiscan FS", (Thermo Scientific, Finland) using the software "Thermo Scientific Scan It" and commercial reagents ("Vector-best", Russia, "Assay Pro", USA). Immunophenotyping of lymphocytes was performed in the reaction of indirect immunofluorescence with monoclonal antibodies ("Spring Bioscience", USA), specific to the surface cluster markers of immunocompetent cells and fluorescein isothiocyanate - labelled antiglobulin antibodies ("Beckman Coulter",

USA). The finished product was analyzed in ultraviolet light under immersion oil using a fluorescent microscope "Mikmed-6" ("LOMO", Russia). The phagocytic activity of neutrophils and blood macrophages were evaluated on a model of polystyrene latex particles ("DIA-M", Russia) absorption with the phagocytic index (PI) and phagocytic number (PN) calculation. The oxygen-dependent metabolism of neutrophils was analyzed according to the indicators of activated and spontaneous nitroblue tetrazolium (NBT) ("Sigma", USA) reduction test. The level of circulating immune complexes was set on a "DU-650" spectrophotometer ("Beckman Coulter", USA). The disease of immune complexes is mediated by the activation of the complement system, the formation of anaphylatoxins C3a and C5a, the involvement of other cells of the immune system, infiltration of the CEC deposition site. These anaphylatoxins C3a and C5a are just marked.

Statistical analysis of the research results was performed using the statistical software package "Statistica" for Windows 8.0. During the comparing the values of studied indicators in different groups the Spearman's rank correlation method was used. Comparison of empirical trait distributions was performed using the Pierson's χ^2 -criterion. The differences between the two independent samples according to the level of quantitatively measured features were evaluated using the nonparametric Mann-Whitney U-test. The reliability of data differences for series with normal distribution was analyzed using the Student's t-test. Differences with $p_{0,05}$ were considered statistically significant.

3. RESULTS AND DISCUSSION

Clinical dental and otorhinolaryngological examination methods were used to assess the condition of patients with OMS. Patients of the main group complained of pain in the infra-orbital and buccal areas, radiating across the entire half of the face, headaches that increased while leaning forward and taking a horizontal position. A feeling of heaviness and congestion in the corresponding half of the nose, nasal breathing disorder, a decrease in the sense of smell up to anosmia, the presence of purulent discharge from the nose with a «sharp» smell were characteristic. Patients with a high frequency indicated discomfort in the teeth of the upper jaw on the side of the lesion, difficulty chewing. The external examination oedema and tissue infiltration in the projection of the maxillary sinus

were revealed, palpation and percussion in the area of the zygomatico-alveolar crest and the anterior surface of the maxillary bone were painful. During the anterior rhinoscopy in the nasal cavity from the inflamed sinus, oedema and hyperemia of the mucous membrane, hypertrophy of the middle and inferior nasal conchae were determined. After the treatment of the ostiomeatal complex tissues with decongestant solutions and the occlusion removal from the natural sinus anastomosis, there was an abundant discharge of "fetid" purulent masses from the nose when the head was tilted forward and towards the intact sinus. In addition to that, the patients with OMS, the cause of which was an acute periodontitis complained of continuous pain in the «causal» tooth, aggravated by exposure to temperature and mechanical stimuli. In some cases, patients indicated a protruding of a tooth feeling from the dentition, noting its sharp soreness with vertical percussion. During the examination of patients with OMS, the cause of which was a radicular cyst in the vestibule of the oral cavity was observed the bulging of transitory fold. Palpation of alveolar process allowed to determine the presence of cortical plate pliability in the projection of cyst with a characteristic "parchment crunch" when pressed (positive symptom of Runge-Dupuytren). There was a lack of bone tissue above the cyst and a symptom of fluctuation among some patients. In 65% (13

people) of cases, the radicular cyst was located in the area of destroyed teeth, 35% (7 people) previously treated endodontically for pulpitis, or periodontitis. The teeth located on the borders of the cyst were displaced.

During the roentgen study results evaluation, it was found that the patients of the main group had the different intensity of the maxillary sinus homogeneous darkening, parietal thickening of the mucous membrane, destruction of the cortical plate in the area of sinus fundus, and a decrease in its pneumatization (Figs 1 - 6). Among the studied patients with a radicular cyst was revealed a focus of bone tissue rarefaction, which was rounded shape with clear, even contours, in which the root of the "causal" tooth was directed (Fig. 4 (A, B)). The periodontal fissure in the apex area was not determined (Fig 4 (A, B)). At the same time, there was a maxillary sinusiformity, thinning and inflammatory resorption of the bone walls. In several cases was registered a domed darkening of the maxillary sinus due to prolapse and growth of odontogenic cyst (Fig. 3 (A, B)). In the group of patients with OMS caused by foreign objects, x-ray images visualized radiopaque fillings that had entered the sinus during root canal obturation (Fig. 1 3). Anamnestic data and results of the control group's probands x-ray examination confirmed the presence of clinically intact paranasal sinuses.

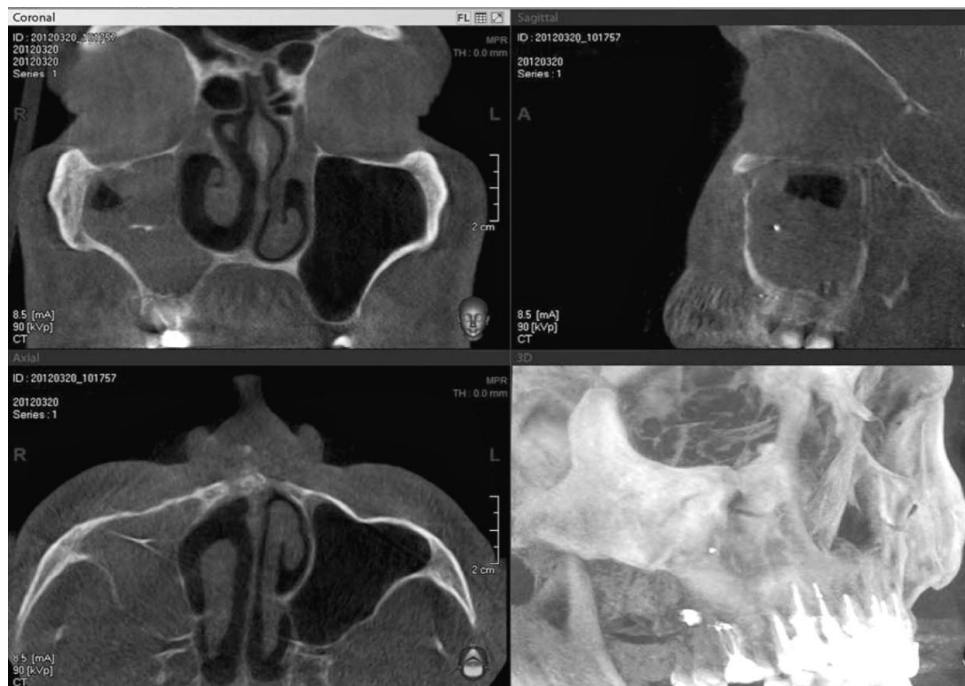




Fig. 1-2. Cone beam computed tomography. Coronal, sagittal and axial reconstruction. In the cavity of the left maxillary sinus against the background of thickening of the mucous membrane is determined by a foreign object – filling material. Cone beam computed tomography

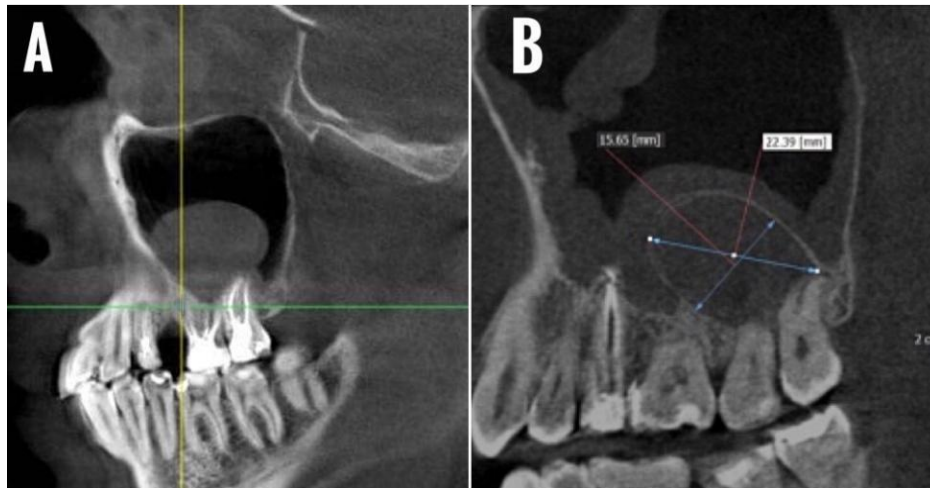


Fig. 3. A, B – Cone beam computed tomography of two patients. Sagittal reconstruction at the level of the maxillary sinus. In the cavity of the left maxillary sinus a domed darkening and destruction of the bone wall in the sinus fundus area are determined due to the growth of an odontogenic radicular cystfundus

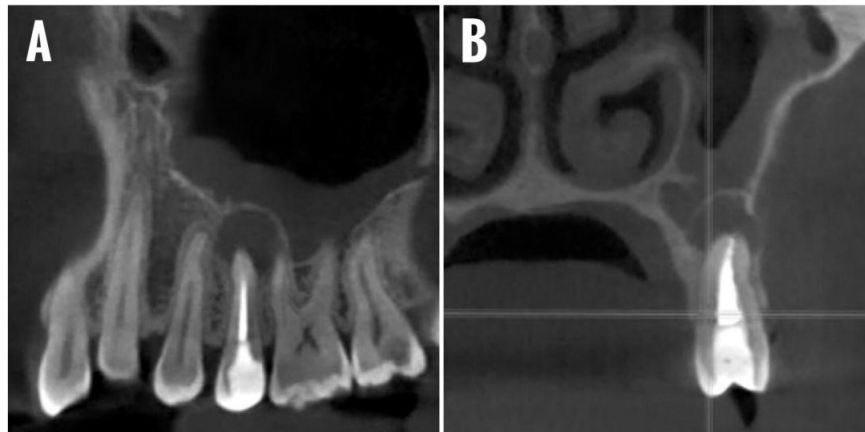


Fig. 4. Cone beam computed tomography. A – Sagittal reconstruction. B – Coronal reconstruction. In the area of tooth 2.5 visualized the focus of the bone tissue rarefaction with rounded shape and clear contours (cyst 9 mm). The «causal» tooth was previously treated endodontically. In the cavity of the left maxillary sinus a thickening of the mucous membrane is determined

Cellular immunity indicators monitoring (Table 1, Fig. 5) revealed a significant decline in the population of common T-lymphocytes (CD_3^+), as well as a subpopulation of T-helper cells (CD_4^+) in the main group of patients. It is regarded as a transient immune-deficient state that spring up as a result of the T-cells redistribution to the focus of inflammation and secondary organs of the immune system [20-22]. Within the same group, there is an increase in the blood content of T-cytotoxic lymphocytes (CD_8^+), effector elements that recognize antigens together with molecules of the main histocompatibility complex type I (MHC I) and destroy defective target cells. In the group of patients registered a statistically significant increase in the NK-cells (CD_{16}^+) level, which have spontaneous cytotoxicity and provide the first lines of defense against genetically alien agents before the specific immune mechanisms inclusion [23]. There was a drop in the immunoregulatory index (IRI) among patients with OMS, which is regarded as an adverse sign indicating defects in reaction to antigens.

As a result of the humoral immunity indicators evaluation (Table 2, Fig. 6), it was noted that

patients with OMS showed marked activation of the B-lymphocyte population (CD_{19}^+) and, at the same time increase in the percentage of cells expressing CD_{72}^+ and capable of developing an active synthesis of antibodies. The detected changes are explained by the prolonged course of odontogenic sinusitis and indicate the intensity of the immune response. Analysis of the main serum immunoglobulins (IgA, IgG, IgM) level (Table 2, Fig. 6) showed that the concentration of IgM in the main group was higher than the acceptable reference values. It indicates the manifestation of an acute inflammatory reaction and the development of antibody-dependent cellular cytotoxicity. IgG indicators were similarly within high values, significantly dominating over the data of the control group, which indicates the intensity of the current odontogenic sinusitis. Within the same group, an increase in the IgA level was registered prevailing over the parameters of intact patients. Pronounced activation of immune system humoral components indicates a special severity of the pathological process, hyperreactivity development, which leads to auto-allergization of the macroorganism[24-26].

Table 1. Indicators of cellular immunity among patients with odontogenic maxillary sinusitis

Indicator	Maingroup (n = 60)	Controlgroup (n = 30)
T-lymphocytes (CD_3^+) %	56.2±0.8*	67.5±0.5
T-helpers (CD_4^+) %	27.3±0.5**	45.1±0.9
T-CTL (CD_8^+) %	33.2±0.7*	24.4±0.6
IRI (CD_4^+ / CD_8^+)	0.9±0.03**	1.87±0.1
NK-cells (CD_{16}^+) %	25.2±0.4**	12.6±0.8

* $p < 0.05$ compared to the control group data; ** $p < 0.01$ compared to the control group data

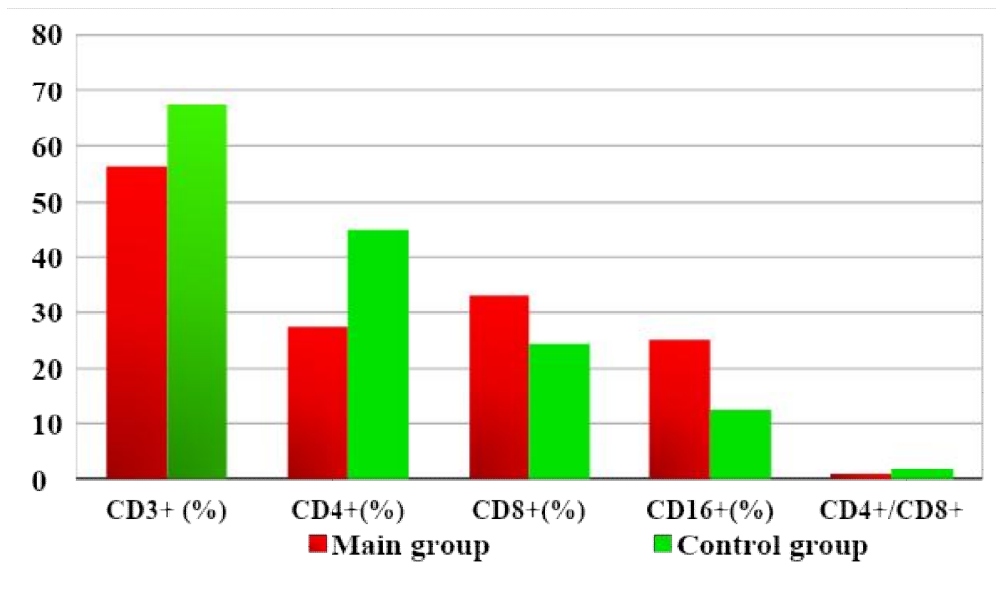


Fig. 5. Indicators of cellular immunity among patients with odontogenic maxillary sinusitis

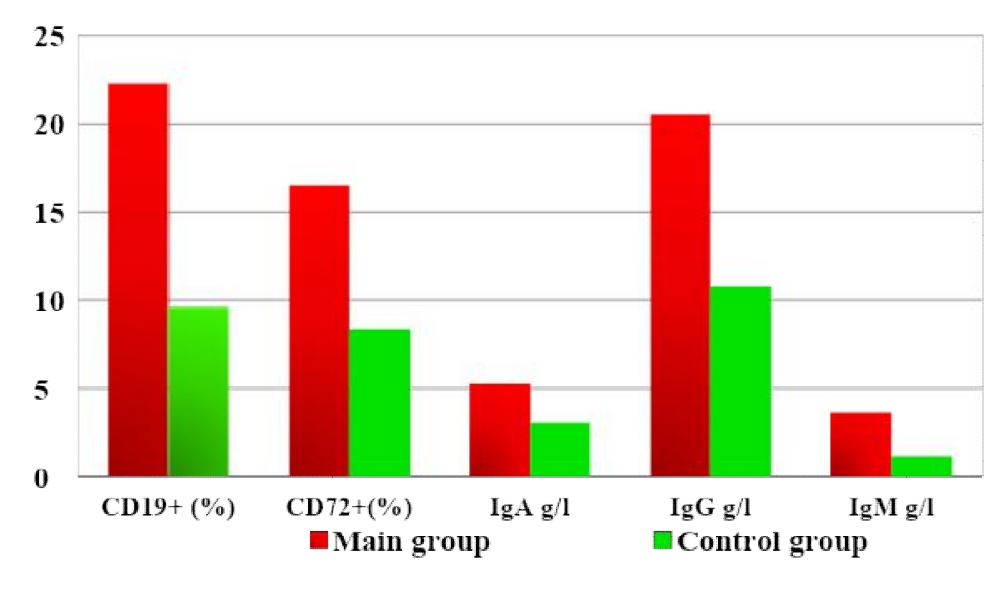


Fig. 6. Indicators of humoral immunity among patients with odontogenic maxillary sinusitis

Table 2. Indicators of humoral immunity among patients with odontogenic maxillary sinusitis

Indicator	Main group (n = 60)	Control group (n = 30)
CD19 ⁺ %	22.3±0.7**	9.6±0.8
CD72 ⁺ %	16.5±1.3**	8.3±0.6
IgA g/l	5.29±0.36*	3.1±0.07
IgG g/l	20.5±0.7**	10.8±0.4
IgM g/l	3.6±0.4**	1.2±0.3

*p<0.05 compared to the control group data; **p<0.01 compared to the control group data

In the course of studying the CIC level in blood serum (Table 3), we observed an indicator excess among patients with OMS relative to the corresponding results of intact individuals. It is probably conditioned the excess production of immunoglobulins and the functional inferiority of mechanisms that provide for the CIC elimination from the organism. As a result of this imbalance, CIC accumulate and have an incomparably greater damaging effect than autoantibodies [27]. A high level of CIC in the main group is a diagnostically and prognostically significant criterion indicating the autoimmune shifts presence, hypersensitivity, developing type III allergic reactions in patients [28].

This fact is also evidenced by changes in the level of components of the complement system in the blood serum, which is a humoral immunity non-specific factor (Table 4, Fig. 7). In the main group, a significant deviation from the parameters of healthy individuals was registered. It is expressed in a significant excess of C₃ and C₄ components in the blood, which indicates activation of the processes of complement-dependent cytolysis. The obtained data may be caused by activation of the complement system along the classical pathway, due to the accumulation of CIC in the organism. As a result of a reactions cascade, a membrane-attacking complex (C₅ - C₉) is formed, causing

microorganisms lysis, as well as necrosis of the maxillary sinus mucosa in areas where the “antigen-antibody” complexes were fixed. Complement system activation due to the formation of immune complexes *in vivo* is a possible cause of tissue destruction [29].

Analysis of the study of phagocytic cells functional activity allowed to conclude that the phagocytic index and phagocytic number of patients with OMS were significantly lower than the similar parameters of the control group. This indicates the inhibition of the absorbing ability of macro – and microphages (Table 5, Fig. 8). The revealed phagocytosis inferiority can play a pathogenetic role in the disorder of CIC evacuation from the organism, their accumulation and settling in tissues, with the subsequent development of inflammatory reactions. During evaluation of the indicators of spontaneous and activated NBT-test (Table 5, Fig. 8), we recorded that among patients of the main group significantly increased the indicators of spontaneous NBT-test. This indicates the activation of the intracellular oxidase antimicrobial defense system of the phagocytes, and decreasing the activated NBT-test indicators, which is regarded as a drop in the functional reserve of oxygen-dependent bactericidal potential.

Table 3. The level of circulating immune complexes in the blood of patients with odontogenic maxillary sinusitis

Indicator	Maingroup (n = 60)	Controlgroup (n = 30)
CIC U/ml	84.7±3.9*	47.3±2.6

**p*<0.01 compared to the control group data

Table 4. The content of complement system components in the blood from patients with odontogenic maxillary sinusitis

Indicator	Maingroup (n=60)	Controlgroup (n=30)
Complement C ₃ g/l	3.54± 0.06*	1.19± 0.04
Complement C ₄ g/l	0.61± 0.007*	0.28± 0.006

**p*<0.01 compared to the control group data

Table 5. Indicators of peripheral blood phagocyte activity among patients with odontogenic maxillary sinusitis

Indicator	Maingroup (n=60)	Controlgroup (n=30)
Phagocyticindex (%)	59.4± 2.8*	72.6± 3.1
Phagocyticnumber (u.)	5.06± 0.07*	10.2± 0.05
Spontaneous NBT-test (%)	31.5±3.37**	11.3±1.6
Activated NBT-test (%)	42.6±3.9**	69.8±5.2

p*<0.05 compared to the control group data; *p*<0.01 compared to the control group data

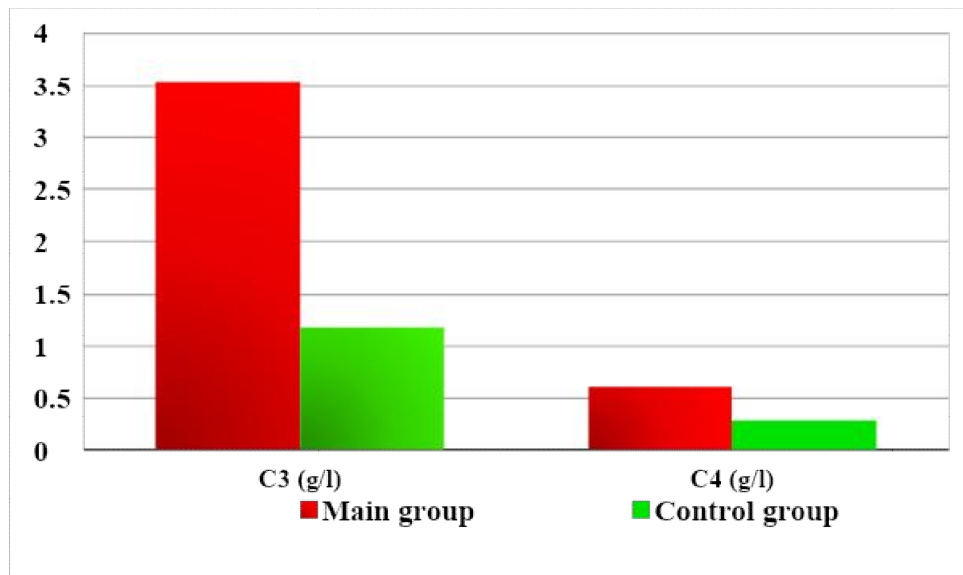


Fig. 7. The content of complement system components in the blood of patients with odontogenic maxillary sinusitis

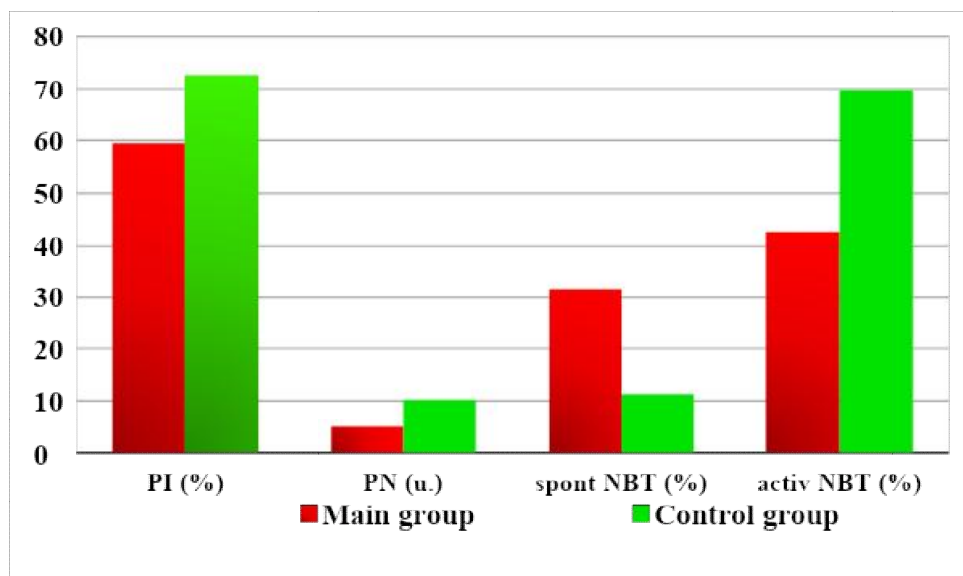


Fig. 8. Indicators of peripheral blood phagocyte activity among patients with odontogenic maxillary sinusitis

4. CONCLUSION

The assessment of the immune status among patients with OMS revealed several significant changes in the innate and adaptive immunity functioning. The study revealed the presence of pronounced CD_8^+ , CD_{16}^+ activation, which is accompanied by the release of cytotoxic substances by the delayed hypersensitivity type,

the antibody-independent cell-mediated cytotoxicity development. At the same time, there is an increase in the population of CD_{19}^+ and IgA, IgM, IgG excessive production, which indicates an aggressive course, the presence of an acute phase and the development of a hyperergic type pathological process. In the main patients group registered a significant load of the CIC and the associated increase in the C_3 and C_4 level

components of the complement system. Such results indicate the presence of autoimmune shifts in patients with OMS and point to the intensity of the inflammatory process. The antibodies produced as a result of autosensitization react with antigens of the damaged sinus tissue and activate the complement system along the classical path. The CIC delay leads to their spread in the organism, which is a potential danger in the form of serious complications developing as immune complex allergic reactions. The study revealed that the accumulation of CIC is associated with functional insufficiency of phagocytic cells. Thus, use of a similar stage of patients examination as an assessment of the immune status opens up new approaches to understanding the role of immune system individual links in the inflammatory process chronization in the sinuses and disease frequent relapse. The violations identified during the research need to be corrected and dictate the necessity of introducing immunotropic pharmacotherapy into the plan of medical treatment. It will reduce the overall treatment duration, decrease the frequency of sinusitis exacerbations, and improve the quality of patients life.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline patient's consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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